What did we learn from historical cohort studies
T.J. Roseboom
AMC, AMSTERDAM, The Netherlands

Poor nutrition during critical periods of early human development has lasting negative consequences for growth, development, and health. This talk summarizes the evidence from studies investigating the effects of prenatal exposure to the Dutch famine on later mental and physical health. The Dutch famine was remarkable in several ways, and its unique features have contributed to the fact that it has most often been used in studies examining the long-term consequences of prenatal undernutrition. The Dutch famine was an acute period of undernutrition that was clearly circumscribed in time and place; it had an abrupt beginning and end and struck a population that was previously and subsequently well nourished. Also, the administration was well organized and records were kept allowing researchers to investigate the consequences of starvation in the decades that followed. All these characteristics make the Dutch famine uniquely suited for such studies, and allow researchers to take a quasi-experimental design to address a question that would otherwise be impossible to answer in a human setting. The effects of famine depended on its timing during gestation and the organs and tissues undergoing critical periods of development at that time. Early gestation appeared to be the most vulnerable period which may not be surprising considering the fact that all organs are laid down within 12 weeks after fertilization. The effects of famine were widespread and affected structure and function of organs and tissues, resulting in altered behavior and increased disease risks, which in turn led to reduced participation in the labor market and increased mortality. The effects of famine were apparent in the absence of any effects on size at birth. Some effects of prenatal undernutrition were more pronounced or even limited to one sex, but generally the effects applied to both men and women. There is preliminary evidence to suggest that the effects of famine may not be limited to those affected prenatally, but were passed on to the next generation, both through genetic programming of the embryonic and placental tissues. Early gestation appeared to be the most vulnerable period which may not be surprising considering the fact that all organs are laid down within 12 weeks after fertilization. The effects of famine were widespread and affected structure and function of organs and tissues, resulting in altered behavior and increased disease risks, which in turn led to reduced participation in the labor market and increased mortality. The effects of famine were apparent in the absence of any effects on size at birth. Some effects of prenatal undernutrition were more pronounced or even limited to one sex, but generally the effects applied to both men and women. There is preliminary evidence to suggest that the effects of famine may not be limited to those affected prenatally, but were passed on to the next generation, both through the maternal and paternal line. Studies in other settings show similar effects and suggest that the findings are not uniquely linked to the characteristics and setting of the Dutch famine, but reflect biologically fundamental processes that describe human plasticity. Adequately feeding women before and during pregnancy will allow future generations to reach their full potential and lead healthier and more productive lives, ultimately leading to healthier and more equal future.

Preconception and embryonic origins of health
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Prenatal growth in the second half of pregnancy and subsequent birth weight have been studied for decades and are shown to be associated not only with pregnancy outcome, but also with health and disease throughout life and even in next generations. The first trimester of pregnancy is highly important with regard to cell multiplication, differentiation and epigenetic programming of the embryonic and placental tissues. These early weeks of pregnancy are most vulnerable in human and therefore it is also not surprising that several pregnancy complications originate during this period, such as congenital malformations, low birth weight and preeclampsia. Although the first trimester represents perhaps the most important period of prenatal development, so embryonic growth as proxy for embryonic health has received relatively little attention both in research and clinical care. New opportunities of three-dimensional ultrasound techniques in combination with the virtual reality (VR) technology of the BARCO I-Space and V-scope visualization software enable depth perception and therefore have tremendously improved the possibilities of visualization of the human embryo. Using this technique in prospectively obtained serial ultrasound scans during the first trimester of pregnancy now revealed associations between maternal age, folic acid supplement use, dietary patterns, smoking and embryonic crown rump length and volume measurements as outcomes of embryonic health. Moreover, being small as an embryo appeared to be associated with an increased risk of being born small for gestational age, but also with an adverse cardiovascular risk profile in childhood. These imaging techniques also enable scoring of embryonic developmental morphology according to the external morphological criteria of the Carnegie stages. Very recently it was shown that a low level of vitamin B12 and high level of homocysteine, as biomarkers of one carbon metabolism involved in epigenetic programming, significantly delay embryonic development. This new knowledge will also contribute to a shift of prenatal
These effects are associated with modulation of hippocampus and hypothalamic paraventricular nucleus (PVN). Transcriptional landscapes in the fetal prefrontal cortex (PFC), changes in the epigenetic (DNA methylation, acetylation) and neuroendocrine levels increase exponentially. This suggests that GCs are potent modulators of brain development, with the brain being particularly sensitive. GCs are maintained at low levels in the fetus until late gestation, when levels increase exponentially. This ‘surge’ in GC is critical for normal maturation of several organ systems including the brain. GCs can become elevated in the fetus as a result of stress (maternal or fetal) or maternal treatment with GCs. The latter occurs in cases of threatened preterm birth (>10% of all pregnancies). Using the guinea pig as a model, we have shown that premature exposure of the fetal brain to GC can lead to profound changes in the epigenetic (DNA methylation, acetylation) and transcriptional landscapes in the fetal prefrontal cortex (PFC), hippocampus and hypothalamic paraventricular nucleus (PVN). These effects are associated with modified hypothalamic-pituitary-adrenal (HPA) function and stress-related behaviours in offspring, and are maintained in to adulthood. Most recently, we have shown that the effects of GCs on epigenetic transcriptional landscapes, HPA function and behaviours extend across multiple generations, and that this can occur via maternal and paternal transmission. These findings have significant implications for clinical practice but also our fundamental understanding of the mechanisms by which the fetal endocrine environment impacts the developing brain.

PA1.01 - Endocrine programming

PA1.01.01

Stress, glucocorticoids and the developing brain

G. Matthews

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The developing fetal brain is highly sensitive to its endocrine environment. Glucocorticoids (GCs) are potent modulators of development, with the brain being particularly sensitive. GCs are maintained at low levels in the fetus until late gestation, when levels increase exponentially. This ‘surge’ in GC is critical for normal maturation of several organ systems including the brain. GCs can become elevated in the fetus as a result of stress (maternal or fetal) or maternal treatment with GCs. The latter occurs in cases of threatened preterm birth (>10% of all pregnancies). Using the guinea pig as a model, we have shown that premature exposure of the fetal brain to GC can lead to profound changes in the epigenetic (DNA methylation, acetylation) and transcriptional landscapes in the fetal prefrontal cortex (PFC), hippocampus and hypothalamic paraventricular nucleus (PVN). These effects are associated with modified hypothalamic-pituitary-adrenal (HPA) function and stress-related behaviours in offspring, and are maintained in to adulthood. Most recently, we have shown that the effects of GCs on epigenetic transcriptional landscapes, HPA function and behaviours extend across multiple generations, and that this can occur via maternal and paternal transmission. These findings have significant implications for clinical practice but also our fundamental understanding of the mechanisms by which the fetal endocrine environment impacts the developing brain.

PA1.01.03

Fetal thyroid hormone exposure

R.P. Peeters

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Thyroid hormone (TH) is essential for normal development of virtually all tissues, especially the brain. Untreated maternal hypothyroidism during pregnancy is associated with an increased risk of adverse pregnancy and child outcomes. Even mild maternal thyroid dysfunction adversely affects child cognitive development resulting in lower IQ scores and an increased risk of autism, ADHD and schizophrenia. During pregnancy, profound changes in thyroid physiology occur, resulting in different reference intervals compared to the nonpregnant state. Therefore, empowering women but also their partner adopting a life course approach from preconception onwards covering the embryonic period may have important implications for not only fertility and pregnancy complications but also for future prevention of non-communicable diseases. Nowadays the reproductive population can easily be reached by (pre)pregnancy eHealth and mHealth platforms providing personalized lifestyle programs integrated in health care. The evidence-based online personal platform ‘Smarter Pregnancy’ (Dutch version www.slimmerzwanger.nl, English version www.smarterpregnancy.co.uk) is an example of mHealth coaching tailored on nutrition and lifestyle to improve preconceptional health and care. This platform already shows beneficial effects on the adoption of adequate intake of folic acid supplements, vegetables and fruits, and to quit smoking and alcohol use in women, but in particular in those couples of whom the male partner is being coached as well. Such technology may offer excellent opportunities and possible great health and health care benefits for current and next generations.

PA1.01.05

Leptin trajectories from birth to mid-childhood and early adolescence cardio-metabolic outcomes: Findings from project Viva

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Background: Leptin is a hormone produced by adipose tissue that promotes satiety, and some evidence suggests that greater....
early life leptin exposure prevents excessive adiposity gain in later life. However, few studies have analyzed longitudinal changes in leptin throughout childhood. In this study, we aimed to identify distinct leptin trajectories in childhood, and to examine their predictors and associations with cardio-metabolic outcomes at early adolescence.

Methods: Among children in the Project Viva cohort born 1999-2002 in Massachusetts, USA, we studied 1360 with leptin measured at least once at birth, early childhood (mean 3.3±0.3 years), or mid-childhood (7.9±0.8 years) for leptin trajectory analysis. At in person research visits, we collected information on maternal characteristics (e.g., pre-pregnancy body mass index [BMI], smoking history), paternal BMI, gestational characteristics (e.g. glucose level, gestational weight gain), and offspring characteristics (e.g. sex, birth weight, gestational age, anthropometry). We assessed markers of cardio-metabolic health including anthropometry, blood pressure (BP), and fasting plasma biomarkers in early adolescence (13.2±0.9 years). We determined childhood leptin trajectories in two stages: 1. As we were interested in effects of early life leptin exposure independent of maternal leptin or child weight, we first regressed each leptin measure (birth, early childhood, and mid-childhood) on maternal 2nd-trimester leptin, child sex, race/ethnicity and birth weight for gestational age z-score (and also child current age and BMI for the early and mid-childhood measures) to estimate leptin independent of these factors; 2. We next included the residuals from these models in latent class growth models to identify trajectories in leptin over time from birth to mid-childhood. Finally, we used multiple regression models to examine associations of other early life exposures with these trajectories and of leptin trajectories with cardio-metabolic outcomes in early adolescence.

Results: The latent class growth models identified three distinct leptin trajectories, which we characterized as “low stable” (n = 1031, 75.8%), “high-decreasing” (n = 219, 16.1%) and “intermediate-increasing” (n = 110, 8.1%) (Figure). After adjustment for confounders, those with higher paternal BMI (ratio of relative risk [RRR] 1.03; 95% confidence interval [CI]: 0.95, 1.11) and maternal gestational weight gain (1.05; 0.97, 1.15) were somewhat more likely to be in the “intermediate-increasing” compared with the “low-stable”. Compared with the “low-stable”, the “intermediate-increasing” trajectory was associated with several markers of adverse cardiometabolic health in early adolescence, including higher adiposity (e.g. BMI z-score for age and sex: 0.63 units; 0.29, 0.97), abnormal metabolic biomarkers (e.g. HOMA-IR: 2.24; 1.26, 3.22), higher metabolic risk scores (0.41; 0.13, 0.70) and greater odds of obesity (odds ratio 2.92; 1.20, 7.11), but lower BP (SBP z-score for age, sex, and height: -0.45; -0.74, -0.17).

Conclusions: In our prospective cohort, we identified three distinct trajectories of leptin from birth to mid-childhood. Even after adjustment for early life BMI, the intermediate-increasing leptin trajectory was associated with higher adiposity and metabolic risk scores yet lower systolic blood pressure at early adolescence. Our findings implies a great opportunity for cardio-metabolic outcomes especially for obesity intervention during early childhood, and future studies are warrant a longer follow-up on the leptin changes in offspring.

Three leptin trajectories identified by latent class growth models.

PA1.01.06
Prenatal air pollution exposure and newborn thyroid function
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Background: Thyroid hormones are critical for normal fetal growth and development. Previous studies have observed that prenatal tobacco smoke (PTS) exposure impacts fetal thyroid function, and recent evidence from a birth cohort in Belgium suggests that 3rd trimester exposure to particulate matter (PM) air pollution may alter cord blood thyroid hormones. However, this has not been investigated in other populations, and additional air pollutants have not been evaluated. Our objective was to examine associations between prenatal exposure to both ambient and traffic-related air pollutants and newborn total thyroxine (TT4) concentrations in the Southern California-based Children’s Health Study (CHS).

Methods: TT4 concentrations in newborn heel stick blood spots were acquired from the California Department of Public Health for 2178 singleton-birth CHS participants. Monthly averages of ambient (PM2.5, PM10, O3, NO3) and traffic-related air pollutants (Freeway NOx, Non-Freeway NOx, and Total NOx) were determined based on inverse distance-squared weighted central monitoring data and the CALINE4 dispersion model, respectively. Pregnancy and trimester-specific averages were calculated for each pollutant. Associations between air pollutants and newborn TT4 concentrations were evaluated using mixed effects linear regression models, adjusted for baby’s age at blood spot collection, gestational and maternal age, maternal parity and education, baby’s sex and race/ethnicity, PTS exposure, and season of birth (fixed effects), and also the community of the participant at recruitment (random effect). We additionally evaluated potential interactions with sex and birth weight.
Results: Prenatal exposure to ambient air pollutants was associated with higher newborn TT4 concentrations. Associations were statistically significant for PM_{10} (P < 0.01), PM_{2.5} (P < 0.01), and O_3 (P = 0.03), with a similar trend for NO_2 (P = 0.13). A 2 SD increase in PM_{10} (equivalent to 22.5 micrograms/m^3), PM_{2.5} (equivalent to 16.5 micrograms/m^3), and O_3 (equivalent to 24.3 ppb) was associated with a 1.1, 0.9, and 0.5 micrograms/dl higher newborn TT4 concentration, respectively. Associations were stronger for late pregnancy PM and O_3 exposures (2nd or 3rd trimester). PTS exposure was also positively associated with newborn TT4 concentrations (P = 0.04); on average, TT4 concentrations were 0.7 micrograms/dl higher in PTS exposed newborns. In contrast, prenatal Freeway, Non-Freeway, and Total NOx exposures were not significantly associated with newborn TT4, and we did not observe significant interactions between sex or birth weight and any of the air pollutants.

Conclusions: In our study population of newborns in Southern California, prenatal exposure to ambient air pollution, particularly in the 2nd or 3rd trimester, was associated with higher TT4 levels, and the magnitude of association for prenatal PM was similar to that for PTS.

PAI.01.07

Maternal thyroid function during pregnancy and offspring depression and anxiety: A study from Avon Longitudinal Study of Parents and Children

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Background: Brain development can be affected by several factors of which iodine and thyroid hormones contribute the lion share. Maternal thyroid dysfunction during pregnancy can affect neurobehavioral disorders in the offspring. We investigated the relationship between maternal thyroid function during pregnancy and offspring depression and anxiety.

Methods: Data were sourced from the Avon Longitudinal Study of Parents and Children (ALSPAC). A total of 4,839 mother-child pairs were included. Thyroid stimulating hormone (TSH) levels, free thyroxine (FT4) and autoantibodies to thyroid peroxidase (TPO-Ab) were assessed during the first trimester of their pregnancy. Child depression and anxiety were assessed using the Development and Well-Being Assessment at age 91 months and 15 years old and were coded according to DSM-IV criteria. The odds of presenting with depression and anxiety were estimated using generalized estimating equations model.

Results: The levels of maternal thyroxine hormone during the first trimester of pregnancy was associated with child depression [OR = 1.21, 95% CI: 1.00-1.44]. An increase of one unit standard deviation distance from the mean level of FT4 during pregnancy increases the odds of child depression at age 15 by 30% after adjusted for TPO-Ab, maternal age, body mass index, gender, birth weight, maternal smoking, maternal depression, gestational hypertension, zinc and iodine intake during pregnancy [OR = 1.30, 95% CI: 1.02-1.65]. There was no relation between maternal levels of TSH, FT4 and TPO-Ab and childhood anxiety.

Conclusions: An increased level of thyroxine from the mean value during the first trimester of pregnancy is associated with increased risk of offspring depression. This finding suggests that the level of thyroxine in early gestation influences fetal brain development which determines neurobehavioral changes later in life.

PAI.01.08

Association between maternal thyroid function in early pregnancy and offspring autistic traits: meta-analysis of three prospective birth cohorts

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Background: During the first 18-20 weeks of pregnancy, optimal fetal brain development depends on the placental transfer of maternal thyroid hormones. Thyroid hormone dependent brain development processes, such as neuronal cell proliferation and migration, have been implicated in the pathophysiology of autism. Previous studies focusing on the association between maternal thyroid function and the risk of autism spectrum disorder in the offspring are scarce and conflicting. Therefore, we assessed whether maternal thyroid function in early pregnancy is associated with offspring autistic traits.

Methods: We analyzed data from three large European, population-based birth cohorts: INMA (Spain), Generation R (The Netherlands) and ALSPAC (United Kingdom). Thyroid stimulating hormone (TSH), free thyroxine (FT4) and thyroid peroxidase antibodies (TPOAbs) were measured before the 18th week of pregnancy. Autistic traits were assessed at age 4-7 years using validated parental questionnaires. Adjusted cohort-specific effect estimates were combined using random-effects individual data meta-analysis.

Results: A total 7,778 mother-child pairs were included of which 1.4%, 3.1%, and 7.5% of children were defined as having autistic traits in the clinical range in INMA, Generation R and ALSPAC, respectively. Maternal FT4 concentrations below the 5th percentile were associated with a 1.5-fold higher risk of offspring autistic traits (95%CI 1.0 to 2.4). Similarly, maternal hypothyroxinemia was associated with a 1.9-fold higher risk of autistic traits (95%CI 1.2 to 3.0). Additionally,
FT4 above the 97.5th percentile also increased the risk on autistic traits by 1.9-fold (95%CI 1.0 to 3.5). Neither maternal TSH concentrations continuously, nor subclinical hypothyroidism were associated with offspring autistic traits.

**Conclusion:** Both low and high maternal FT4 concentrations in early pregnancy are associated with a higher risk of offspring autistic traits. This cross-cohort study indicates that suboptimal FT4 concentrations may have adverse fetal effects and thus that overtreatment with high dose levothyroxine should be prevented.

**PA1.01.09**

**Role of leptin in M1 programming of monocyte-derived macrophages from newborns of obese mothers**

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Offspring from women with pre-gestational obesity (pOB) are at high risk to develop chronic diseases related to an altered immune function. We recently reported that monocytes and macrophages from neonates of mothers with differentially express pro-inflammatory and anti-inflammatory genes compared with cells from offspring of normal weight mothers (pNW), suggesting a functional programming of immune cells by maternal metabolic status. Several studies show that leptin is substantially increased in cord blood plasma from pOB offspring compared to pNW, without significant changes in the levels of pro-inflammatory and anti-inflammatory cytokines. In this context, leptin induces the expression of pro-inflammatory cytokines in macrophages from lean adults. Considering the increased levels of leptin in pOB neonates, we hypothesize that leptin exposure during monocyte-to-macrophage differentiation modifies the expression of pro-inflammatory and anti-inflammatory mediators in neonatal macrophages obtained from pNW women enhancing the development of M1-skewed macrophages. Neonatal monocytes were purified and differentiated into macrophages by the addition of M-CSF (100 ng/mL) in presence or absence of leptin (10 or 100 ng/mL) for 7 days. Macrophages were stimulated for additional 24 hours with E.coli-LPS (100 ng/mL) and recombinant human IFN-γ (20 ng/mL) and the mRNA levels of TNF-α and IL-10 were assessed by qPCR. Parallel experiments were carried out in the monocyte cell line THP-1. Exposing neonatal macrophages to leptin (100 ng/mL) increased the basal levels of TNF-α mRNA (10-fold). Furthermore, when treated with LPS + IFN-γ, the expression of TNF-α showed a 20-fold increase, whilst further increased when exposed to 10 or 100 ng/mL leptin (161-fold and 138-fold, respectively). Conversely, the expression of IL-10 did not change significantly after stimulation with LPS + INF-γ in neonatal macrophages when treated with leptin during differentiation. Similarly, the treatment of THP-1 cells with leptin (10 ng/mL) enhanced the expression of TNF-α in response to LPS (37-fold) with respect to LPS alone (27-fold), whilst the expression of IL-10 in THP-1 stimulated with LPS was lower in cells pre-treated with leptin (186-fold) compared to LPS alone (494-fold). These preliminary results show that leptin enhances the expression of pro-inflammatory cytokines while keeping a low expression of anti-inflammatory cytokines upon stimulation with M1-skewing agents (LPS and IFN-γ). This effect may be involved in the developmental effect of pre-gestational obesity in the mother, with high levels of neonatal leptin, and the postnatal risk of developing chronic diseases. The latter could be due to a leptin-mediated programming of macrophages to a pro-inflammatory M1-skewed phenotype, leading to the establishment of long-term, low-grade inflammation, thus increasing the risk of developing chronic diseases during adulthood in pOB.

**PA1.02 - Pregnancy interventions**

**PA1.02.01**

**Pregnancy interventions, where are we?**

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Associations between a sub-optimal early life environment and longer term adverse health outcomes are now recognised by health care policy makers, but few evidence based preventative intervention strategies are available. One reason lies in the limited number of large and rigorously designed intervention studies designed for long term child/adulthood health outcomes, in contrast to the many cohort and population studies reported. A recent individual patient data meta-analysis (IPDMA) of the numerous lifestyle interventions in pregnant women designed primarily to improve pregnancy outcome (Rogozinska et al 2017), concluded that diet and physical activity recommendations can reduce maternal weight gain and the risk of caesarean section, but that there is little effect on fetal outcomes. It is not yet known if these maternal benefits are sufficient to improve lifelong health in the child, and only a few of the component studies have reported childhood follow-up.
UPBEAT, a randomised controlled trial of an intensive diet and physical activity intervention in obese pregnant women, which contributed to the IPDMA, has analysed the maternal metabolic profile and followed the children to 6 months of age. The intervention which improved maternal diet, and reduced maternal adiposity and gestational weight gain was associated with a healthier maternal metabolome (unpublished), and with reduced adiposity in the infants at 6 months of age (Patel et al., 2017). Whether this effect is sustained remains to be determined, and longer term follow up of the children is underway. Interventions which target those women most at risk of having an obese child are likely to have maximal benefit for mother and child. Strategies for targeted intervention in obese women will be discussed.


PA1.02.03
A little less association, a little more action: a workshop to develop new approaches to implementing and evaluating early life interventions

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The early years of life are considered to be the most important period in determining physical, emotional and cognitive development. Early interventions are recognised as key to improving the life chances for children and reducing inequalities in health and well-being. There is good research evidence about the factors that affect health and development such as parenting practices, diet, physical activity, language and communication skills. However there is a paucity of research into the effectiveness of programmes to address these factors and improve outcomes. Ten years after setting up the Born in Bradford family cohort study we became increasingly frustrated by the limitations of observational research to change practice: many of the health problems that they were researching were getting worse rather than better. In 2015 we were successful in obtaining Big Lottery funding to set up the World Bradford family cohort study we became increasingly frustrated by the limitations of observational research to change practice: many of the health problems that they were researching were getting worse rather than better. In 2015 we were successful in obtaining Big Lottery funding to set up the World

This presentation will describe
1. How we identified effective early life interventions to improve child health and wellbeing that can be tested in the new cohort
2. How we are developing innovative, efficient and pragmatic approaches to evaluation of these interventions using routine data linkage
3. The challenges of integrating large scale, system-wide research and practice.

PA1.02.05
Effects of an antenatal dietary intervention in overweight and obese women on 6-month infant outcomes: follow-up from the LIMIT trial.

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Background: The immediate impact of providing an antenatal dietary intervention during pregnancy on health has been extensively studied, but little is known of the longer-term effects beyond the neonatal period. Our aim was to evaluate the effects of an antenatal dietary intervention in overweight or obese women on early infant outcomes obtained 6-months after birth.

Methods: We conducted follow-up of infants born to women who participated in the LIMIT randomized trial. Live-born infants at 6-months of age, and whose mother provided consent to ongoing follow-up were eligible for inclusion. While pregnant, women were randomized to a comprehensive antenatal dietary intervention or standard antenatal care. The primary study endpoint for the follow-up study was the incidence of infant BMI z-score ≥90th centile for infant sex and age. Secondary study outcomes included a range of infant anthropometric measures, neurodevelopment (assessed using the Ages and Stages Questionnaire), general health, and infant feeding. Analyses used intention to treat principles according to the treatment group allocated in pregnancy. Missing data were imputed and analyses adjusted for maternal early pregnancy BMI, parity, study centre, socioeconomic status, age, and smoking status. Outcome assessors were blinded to the allocated treatment group.

Results: 1,754 infants were assessed at age 6 months (Lifestyle Advice n = 869; Standard Care n = 885), representing 82.1% of the eligible sample (n = 2,136). There were no statistically significant differences in the incidence of infant BMI z-score ≥90th centile for infants born to women in the Lifestyle Advice group, as compared with the Standard Care group (Lifestyle Advice 233 (21.71%) versus Standard Care 233 (21.90%); adjusted relative risk aRR 0.99; 95% confidence interval 0.82 to 1.18; p = 0.88). There were no other effects on infant growth, adiposity, or neurodevelopment.

Conclusions & Relevance: Antenatal dietary intervention did not alter 6-month infant growth and adiposity. Ongoing follow-up will enable assessment of obesity related outcomes in later childhood, and exploration of pathways from maternal obesity to child health.
**PA1.02.06**

Which lifestyle interventions improve gestational weight gain for women of varying educational attainment? IPD meta-analysis from the i-WIP collaboration

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**Background:** Pregnancy outcomes, including gestational weight gain (GWG), are negatively influenced by low socioeconomic status. Lifestyle interventions aim to manage GWG, but few stratify analyses by socioeconomic status. We aimed to identify if socioeconomic status is a prognostic factor for GWG, and to determine the differential effects of lifestyle interventions (diet-alone, exercise-alone or mixed approach) on GWG, according to socioeconomic status.

**Methods:** Data from the International Weight Management in Pregnancy (i-WIP) Network were used, including 21 randomised control trials and 5,183 participants. The PRISMA-IPD Statement guidelines and pre-specified protocol were followed. IPD meta-analyses were performed using one-step generalised linear mixed models. The outcome GWG/week was analysed as per the Institute of Medicine 2009 guidelines (inadequate, adequate, excess) and as kg/week. GWG was analysed according to maternal educational attainment (proxy for socioeconomic status) and type of lifestyle intervention.

**Results:** Regarding GWG, we found that women of lower educational attainment had an increased risk of both excess (OR: 1.182, 95% CI: 1.008, 1.385) and inadequate (OR: 1.284, 95% CI: 1.045, 1.577) GWG. Among women with lower education, diet-alone interventions reduced risk of excess and inadequate GWG (OR: 0.515, 95% CI: 0.339, 0.785; OR: 0.504, 95% CI: 0.288, 0.884, respectively), and reduced GWG/week (kg) (B = -0.055, 95% CI: -0.098, -0.012). Mixed interventions also reduced risk of excess GWG for women of low education (OR: 0.735, 95% CI: 0.561, 0.963). Among women with high education, diet-alone interventions reduced risk of excess GWG (OR: 0.609, 95% CI: 0.437, 0.849), and mixed interventions reduced GWG/week (kg) (B = -0.053, 95% CI: -0.069, -0.037). Exercise-alone interventions did not have an impact on GWG in the total cohort, nor stratified by educational attainment.

**Conclusions:** Pregnant women with low education are at an increased risk of both excess and inadequate GWG, highlighting the need for intervention among these women. Diet-alone interventions seem to be the most appropriate choice for women with lower education, and additional support through mixed interventions may also be beneficial. Women with higher education also benefited from diet-alone interventions. No impact on GWG was observed with exercise-alone interventions. Health care professionals should consider nutrition based interventions as part of baseline maternity care packages, for all pregnant women.

**PA1.02.07**

Exercise during pregnancy to prevent gestational diabetes mellitus and improve outcomes in overweight/obese pregnant women: A randomized controlled trial

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**Background:** The portion of overweight/obese women of reproductive age has increased recently. Being overweight/obese is a risk factor for gestational diabetes mellitus (GDM), and increases the risk of adverse outcome for both mothers and their offspring. Regular exercise has the potential to reduce the risk of developing GDM, however, its efficacy remains controversial. At present, most exercise interventions are implemented on Caucasian women and in the second trimester, and there is a paucity of studies focusing on overweight/obese pregnant women. Thus we aimed to test the efficacy of regular exercise in early pregnancy to prevent GDM in Chinese overweight/obese pregnant women.

**Methods:** This was a prospective randomized clinical trial in which non-smoking women over 18 with a singleton pregnancy and met the criteria for overweight/obese status (BMI < 28 kg/m²; obese, BMI ≥ 28kg/m²) and an uncomplicated pregnancy at less than 12th weeks of gestation were randomly allocated to either exercise group (EG) or a control group (CG). Patients allocated to the EG were assigned to exercise 3 times per week (no less than 30 min/session with a rating of perceived exertion between 12-14) via a cycling program begun within 3 days of randomization until 37 weeks of gestation. Those in the CG continued their usual daily activities. Both groups received standard prenatal care. The primary outcome was incidence of GDM.

**Results:** From December 2014 to July 2016, 300 singleton women at 10 gestational age and with a mean pre-pregnancy BMI of 26.78 ± 2.75 kg/m² were recruited. They were randomized into an EG (n = 150) or a CG (150). (1) Women randomized to the EG had significantly lower incidence of GDM (22.0% vs. 40.6%, p < 0.001). These women also had significantly (2) less gestational weight gain (4.08 ± 3.02 kg vs. 5.92 ± 2.58 kg, p < 0.001) by 25 gestational weeks and at the end of pregnancy (8.38 ± 3.65 kg vs. 10.47 ± 3.33 kg, p < 0.001), and (3) reduced insulin resistance levels (2.92 ± 1.27 vs. 3.33 ± 2.00, p = 0.033) at 25 gestational weeks.
Other secondary outcomes, including (4) hypertensive disorders of pregnancy (17.0% vs. 19.3%; OR, 0.854; 95% CI, 0.434–2.683, \( P = 0.6 \)), (5) cesarean delivery (except for scar uterus) (29.5% vs. 32.5%; OR, 0.869; 95% CI, 0.494–1.529, \( P = 0.6 \)), (6) mean gestational age at birth (39.02 ± 1.29 vs. 38.89 ± 37 weeks gestation; \( P = 0.5 \)), (7) preterm birth (2.7% vs. 4.4%; OR, 0.600; 95% CI, 0.140–2.573, \( P = 0.5 \)), (8) macrosomia (defined as birth weight above 4000 g) (6.3% vs. 9.6%; OR, 0.624; 95% CI, 0.233–1.673, \( P = 0.3 \)) and (9) large for gestational age infants (14.3% vs. 22.8%; OR, 0.564; 95% CI, 0.284–1.121, \( P = 0.1 \)) were also lower in the EG compared to the CG, but without significant difference. However, infants born to women following the exercise intervention had a significantly lower birth weight compared with those born to women allocated to the CG (3345.27 ± 397.07 g vs. 3457.46 ± 446.00 g, \( P = 0.049 \)).

Conclusions: Cycling exercise initiated early in pregnancy is associated with a significant reduction in the frequency of GDM in overweight/obese pregnant women. Furthermore, it did not increase the risk of preterm birth or reduce the mean gestational age at birth.

PA1.02.08
The effect of a lifestyle intervention in obese pregnant women on change in gestational metabolic profiles: findings from UPBEAT

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Background: Obesity in pregnancy is considered to be associated with disturbances in metabolic function which can lead to adverse outcomes for mother and child. Randomised controlled trials (RCTs) in pregnant women have suggested some beneficial effect of lifestyle interventions on maternal gestational weight gain and adiposity, but whether this improves their metabolic profiles is unclear. The UK Pregnancies Better Eating and Activity Trial (UPBEAT), a RCT of a lifestyle intervention in obese pregnant women, was previously shown to improve diet and physical activity, to reduce maternal gestational weight gain and adiposity, but not to prevent gestational diabetes. We used UPBEAT to determine (a) the magnitude of change in metabolic profiles during pregnancy in obese women and (b) the impact of the lifestyle intervention on these profiles.

Methods: UPBEAT recruited and randomised 1555 obese (BMI ≥ 30kg/m²) pregnant women, aged 16 years or older and with a singleton pregnancy between 15+0–18+6 weeks gestation. Detailed targeted metabolic profiling, with quantification of 158 metabolic traits (129 lipid measures, 9 glycerides and phospholipids, and 20 low-molecular weight metabolites) was completed on three occasions (~17-, 28- and 35-weeks of gestation) in the UPBEAT participants using NMR. Random intercept and random slope models were used to quantify metabolic changes in obese women using the control (usual care) group only. The effect of the intervention was determined by comparing rates of metabolic change between women randomised to the intervention or to usual care, using intention to treat analyses (using \( N = 1158 \) women with metabolite data). In all analyses we controlled for the minimising variables used in randomization (BMI, ethnicity, parity, age and clinic centre).

Results: There were adverse changes across pregnancy in most lipoprotein subclasses, lipids, glycerides, phospholipids, several fatty acids and glucose. All extremely large, very large, large, medium, small and very small VLDL particles increased by 2 to 3 standard deviation units (SD), with IDL, and large, medium and small LDL particles increasing by 1 to 2SD, between 16- and 36-weeks. Triglycerides increased by 3 to 4SD, and glucose increased by 2SD, across the same time period, with more modest changes in other metabolites. The intervention resulted in reductions in the rate of change of concentrations of most lipids, phospholipids and triglycerides in extremely large, very large, large and medium VLDL particles. Triglyceride to phosphoglyceride ratio was reduced and there were improvements in fatty acid profiles (increased rates of change in the degree of saturation of fatty acids, and the ratios of linoleic, omega-6, and polyunsaturated fatty acids to total fatty acids, and decreased rates of change in the ratio of saturated to total fatty acids).

Conclusions: These findings demonstrate systematic metabolic disruption in obese pregnant women as their pregnancy progresses. Importantly, we have demonstrated that a lifestyle intervention that effectively improved diet and physical activity in these women resulted in improvements in most VLDL particles and VLDL size. With further follow-up of these participants we will be able to explore the extent to which these improvements in metabolic profiles impact maternal and offspring adiposity postnatally.

PA1.02.09
Exercise before and during pregnancy in maternal obese rats has preventative effects on offspring lipid dysregulation at 650 days age

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Background: Epidemiological and animal studies demonstrate that maternal obesity (MO) predisposes offspring to metabolic...
disorders - excessive weight, adiposity, and dysregulation of lipid metabolism – that increase with age. There is a need for interventions that slow or even reverse these aging outcomes. Exercise is well established to have numerous health benefits; however, the effects of maternal (F0) exercise on the offspring (F1) aging metabolic phenotype are poorly understood. We hypothesized that maternal exercise before and during pregnancy has preventative effects on these outcomes and the benefit persists into late life in male and female F1.

Methods: F0 female Wistar rats are control (C) or obesegenic diet (MO) from weaning through lactation. From 90 days (d) to 120 d (when they were bred) half of each group wheel ran 30 min/day, 5 times/week, providing four groups: control (C), obese (MO), exercised controls (CEx), and exercised obese (MOEx). After weaning all male and female F1 groups ate C diet. We evaluated serum leptin and triglycerides (TG) in males (MOEx). After weaning all male and female F1 groups ate C diet. We evaluated serum leptin and triglycerides (TG) in males (MOEx). After weaning all male and female F1 groups ate C diet. We evaluated serum leptin and triglycerides (TG) in males (MOEx). After weaning all male and female F1 groups ate C diet. We evaluated serum leptin and triglycerides (TG) in males (MOEx). After weaning all male and female F1 groups ate C diet. We evaluated serum leptin and triglycerides (TG) in males (MOEx).

Results: With aging, F1 male and female C group increases in total fat, leptin, and TG between 110 and 650 d were greater in MO F1 than in C. However, maternal exercise prevented these age-related changes in MO F1 at 650 d (Fig 1A-F). Interestingly, maternal exercise even lowered leptin and TG in CEx males.

Conclusions: Our data indicate maternal voluntary exercise intervention prior and during pregnancy has beneficial effects on programming of lipid metabolism in F1 of MO rats.

Epigenetic mechanisms including DNA methylation stably regulate mitotically heritable alterations in gene expression potential. Nutritional influences on developmental epigenetics may be an important mechanism linking early exposures to adult disease. Testing this in humans is complicated, however, because 1) epigenetic marks can vary between different cell types, so measurements in easily obtainable samples (like peripheral blood) may not indicate epigenetic regulation in cell types most relevant to many diseases, and 2) the disease process itself can induce epigenetic changes, so many disease-associated epigenetic aberrations neither caused nor preceded the disease. Exceptional genomic loci called metastable epialleles (MEs) offer unprecedented opportunities to circumvent these obstacles. MEs – essentially epigenetic polymorphisms – are stable interindividual epigenetic variants that are neither tissue-specific nor genetically mediated. We have pioneered a novel approach for discovery of human MEs – DNA methylation profiling across multiple tissues from multiple individuals – and shown that the loci we identify exhibit all the characteristic of MEs in inbred mice, including persistent effects of periconceptional nutrition. Several of the MEs we have identified affect genes implicated in disease. Population studies are underway to determine whether individual variation in DNA methylation at MEs predicts risk of diseases including obesity and specific types of cancer.

PA1.03.03
Epigenetic selection and the DNA methylation signature of prenatal adversity
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DNA methylation (DNAm) patterns associated with early prenatal adversity are often interpreted as signatures of adaptive plasticity. We propose as an alternative explanation that epigenetic reprogramming after fertilization creates stochastic DNAm differences between embryos that affect embryo survival, and show that such ‘epigenetic selection’ provides a more tenable mechanism for DNAm signatures of prenatal adversity than adaptive plasticity. A model of early embryonic DNAm dynamics separates the scenarios by demonstrating that only epigenetic selection will generate a characteristic reduction in variance in DNAm at selected loci in populations exposed to prenatal adversity. We found this predicted variance reduction in DNAm data on a human cohort prenatally exposed to the Dutch Famine. Our hypothesis has implications for the interpretation of the developmental origins of health and disease, and for developing intervention strategies.
PA1.03.05

Low vitamin B12 in pregnancy is associated with adipose derived circulating miRNAs targeting PPARγ and insulin resistance

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Background: Low vitamin B12 (B12) during pregnancy is associated with higher maternal obesity, insulin resistance (IR), gestational diabetes (GDM) and type 2 diabetes (T2D) prevalence at 5 year follow up. However, it is not clear whether these are causally related. B12 is a key co-factor of the DNA methylation cycle (1-carbon metabolism). We hypothesize that B12 plays a role in epigenetic regulation by altering circulating miRNAs (miRs) during adipocyte differentiation and results in an adverse metabolic phenotype.

Methods: Maternal venous blood samples (n=91) and subcutaneous adipose tissue (n=42) were collected at delivery. Human pre-adipocyte cells (Chub-S7) were differentiated in various B12 concentrations (1) Control (B12 = 500nM); (2) LowB12 (B12 = 0.15nM) (3) NoB12 (B12 = 0nM). Serum B12, folate, lipids and plasma 1-carbon metabolites were determined. miR profiling, miR expression and gene expression were measured.

Results: We demonstrated that low B12 in human pregnancy was associated with higher BMI and lipids, and in maternal adipose tissue, increased gene expression of adipogenesis (PPARγ, CEBPα, RXRα) and lipogenesis (FASN, ACC1, perilipin) (Fig1A). Our in vitro human adipocyte model showed that adipocytes differentiated in B12 deficient conditions accumulated more lipids (Fig1B-D), had higher triglyceride levels (Fig1E,F) and increased gene expressions of adipogenesis (Fig1G) and lipogenesis (Fig1H). MiR array screening in adipocytes revealed differential expression of 133miRs (adjusted p < 0.05). We then validated 14miRs related to adipocyte differentiation and function by q-RT PCR. MiRs targeting PPARγ (miR-27b, miR-23a, miR-130b), CEBPα (miR-31), Zfp423 (miR-195a), adipocyte differentiation (miR-143, miR-145, miR-146a, miR-221, miR-222, miR-125b) and IR (miR-103a, miR-107 and miR-29b) were altered in adipocytes and its secretion. In vivo validation in pregnant women with low B12, identified a similar pattern of altered miR expression in human adipose tissue and circulating miR expression in serum. Of the 14 circulating miRs, regression analysis after adjusting for likely confounders (age, parity, folate supplement use, smoking, insulin and glucose) in addition to B12, showed that four miRs (miR-27b, miR-23a, miR-103a, miR-107) associated with BMI. Further multivariate analysis showed that the association of B12 with BMI was mediated by these circulating miRs which targets PPARγ (miR-27b, miR-23a) and IR (miR-103a, miR-107). Finally, the miR-gene-pathway network analysis evidenced that these miRs associated with the genes regulating the signalling pathways such as PPARγ, adipokynine, insulin, Wnt and T2D.

Conclusions: Our study shows that low B12 levels in pregnancy alters adipose derived circulating miRs, which may mediate an adipogenic and insulin resistant phenotype leading to obesity. This is the first study to identify the changes in miR secretion due to micronutrient deficiency and provides new insight that these circulating miRs can act as a novel mode of cell signalling molecules from dysfunctional adipocytes and develop obesity associated adipocyte dysfunction in mothers. This may predispose metabolic disease to both mothers and offspring in later life. These findings need to be replicated in early pregnancy cohort and in longitudinal studies involving offspring data.

Gene expression of adipogenesis and lipogenesis in human maternal adipose tissue and human adipocyte cell line (Chub-S7).

Figure legends:
Figure 1: (A) Gene expression of adipogenic regulators and lipogenesis in human maternal adipose tissue. Control: n=29; LB-Low B12: n=13. Values are mean ± SEM. *P ≤ 0.05; **P ≤ 0.01, ***P ≤ 0.001, p-value compared to control. Oil red O staining of adipocytes in (B) Control, (C) Low B12, (D) No B12 (lipid droplets stained as red). B12 deficient conditions increases (E) lipid accumulation and (F) triglycerides in human adipocytes. Low B12 increases gene expression of (G) adipogenic regulators and (H) lipogenesis in human adipocyte cell line (Chub-S7). All experiments were performed as n=6; Control: LB-Low B12, NoB-NoB12. Values are mean ± SEM. *P ≤ 0.05; **P ≤ 0.01, ***P ≤ 0.001, p-value compared to control.
PAI.03.06

Prenatal air pollution exposure and genetic and epigenetic variation in mitochondrial DNA are associated with infant growth

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Background: Mitochondria are the cellular organelles that serve as central regulators of metabolism and oxidative stress. Dysfunctional mitochondria have been implicated in a variety of diseases and are important in fetal development. Mitochondria also contain the machinery required to epigenetically modify mtDNA and affect its transcription, suggesting that these modifications may have the ability to affect disease risk.

Methods: We investigated whether prenatal exposure to air pollution caused alterations in mtDNA methylation in cord blood and whether mtSNPs modified such relationships in 181 newborns in the Maternal and Child Health Study. We also examined whether differences in mtDNA methylation level were associated with birth weight and infant growth trajectories in a subset of infants who were followed by phone and had medical records abstracted until 6 months old (n = 52). Traffic related air pollution (TRP) and ambient air pollution (AAP) exposures were estimated based on participants’ residential addresses reported at study entry using California Line-Source Dispersion Model (CALINE4) or routine air monitoring data collected daily in California and available from the U.S. Environmental Protection Agency’s Air Quality System, respectively. DNA was extracted from cord blood and methylation measured using Pyrosequencing in three mtDNA regions: the RNR1 transfer RNA phenylalanine (MT-TF), 12S ribosomal RNA (MT-RNRI) and D-loop control region. mtDNA methylation was also measured in a subset of sorted CD4+ and CD14+ cells (N = 89) to evaluate cell type specific differences. Sixteen mitochondrial SNPs (mtSNPs) were genotyped using the Sequenom iPLEX Gold MassArray technique. Multiple linear mixed models were used to evaluate the associations between prenatal air pollution, percent mtDNA methylation and infant growth.

Results: A 1 SD (2 ppb) increase in prenatal non-freeway NOx was associated with 0.16 (95% CI: 0.00, 0.31) higher MT-RNRI methylation in whole blood but not in CD14+ or CD4+ cells. Living near major roads during pregnancy was also associated with higher MT-RNRI methylation in whole blood, consistent with the CALINE4 modeled non-freeway NOx findings. In contrast, a 1 SD (1 μg/m3) increase in PM2.5 was associated with a 0.13 (95% CI: -0.03, -0.24) lower MT-RNRI methylation and a 0.45 (95% CI: 0.08, 0.81) higher D-Loop methylation only in CD14+ cells. A 1 SD (3 ppb) increase in O3 was also associated with a 0.53 (95% CI: 0.01, 1.05) higher D-Loop methylation in CD14+ cells when adjusting for PM2.5. One mtSNP, T16189C, modified the association between prenatal air pollutants and mtDNA methylation in MT-RNRI and the D-Loop. This mtSNP also modified the association between mtDNA methylation levels and infant birth weight. A one SD increase in MT-TF methylation was associated with a 115 gram (95% CI: -226, -5) lower birth weight in subjects carrying the C allele and a 42 gram (95% CI: -29, 113) increase in birth weight in subjects carrying the T allele (p = 0.03).

Conclusion: Prenatal air pollution exposures, either alone or in combination with mtDNA SNPs, may alter mtDNA methylation and influence child growth.

PAI.03.07

Maternal obesity induces epigenetic changes in baboon fetal liver that regulate pathways thought to play important roles in regulating lifespan

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Introduction: Maternal obesity (MO) increases offspring cardiometabolic disease and shortens lifespan (PMID: 23943697) as a result of developmental programming, defined as a response to a specific challenge to the mammalian organism during a critical developmental time window that alters the trajectory of development with persistent effects on offspring phenotype. To anticipate altered aging trajectories it is of interest to determine changes in fetal life capable of altering the rate of aging. We have developed a baboon model of MO in which MO was induced prior to pregnancy by a diet rich in fat and sucrose. Controls (CON) ate normal baboon chow. We hypothesized that MO would alter fetal baboon liver molecular mechanisms considered key to regulating metabolic pathways that affect longevity.

Methods: Gene array and microRNA (miRNA; small RNA Seq) abundance analyses were performed on near-term fetal baboon livers (CON = 6, MO = 5) and subjected to pathway analyses to identify coordinated fetal liver molecular response to MO.

Results: 933 genes were differentially expressed between control and MO livers: 350 up-regulated and 583 down-regulated. MO fetal livers showed down-regulation of the proteasome and oxidative phosphorylation (Table 1), TCA cycle and glycolytic pathways (not shown), and inversely expressed miRNAs targeting genes in these pathways, supporting MO induction of epigenetic changes that dysregulate pathways central to cellular metabolism in MO fetal livers.

Conclusion: MO fetal livers revealed dysregulation of the proteasome, oxidative phosphorylation, TCA, and glycolysis.
pathways. There was evidence of epigenetic changes in that miRNAs exhibited inverse expression with genes regulated by the miRNAs in these pathways. This is the first observation of fetal nonhuman primate liver miRNA changes that, if they persist in later life, would result in alteration of mechanisms such as the proteasome and oxidative phosphorylation, which are considered potential candidates driving aging processes.

**Funding:** OD P51 OD011133 to Southwest National Primate Center; HD 21350.

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Differentially expressed microRNAs inversely expressed with gene targets in key KEGG pathways.

**PA1.03.08**

Cadmium-associated differential methylation throughout the placental epigenome: an EWAS across two US birth cohorts

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**Background:** Maternal cadmium (Cd) exposure during pregnancy has been associated with impaired fetal growth, pregnancy complications, and cognitive deficits in early childhood, all of which may set the stage for health and/or cognitive issues throughout the life-course. The underlying mechanisms driving this toxicity are unclear. The placenta acts as a partial barrier, limiting direct fetal exposure to Cd via sequestration throughout pregnancy. However, given the critical developmental functions of the placenta and toxic effects of Cd, this sequestration may not be without consequence to fetal development. We aimed to investigate Cd-associated variations in placental DNA methylation, their associations with gene expression potential, and their potential roles in Cd-associated reproductive toxicity.

**Methods:** We investigated placental whole genome methylation in relation to placental Cd concentrations with linear models in the New Hampshire Birth Cohort Study (NHBCS, n = 343) and the Rhode Island Child Health Study (RICHS, n = 141). We performed an EWAS analysis adjusted for tissue heterogeneity using a reference-free method, aggregated cohort-specific results via inverse variance weighted fixed effects meta-analysis, and examined whether differentially methylated CpGs were associated with gene expression. Lastly, we performed functional enrichment analyses and tested for associations between gene expression and standardized birth metrics.

**Results:** We identified 17 Cd-associated differentially methylated CpG sites with meta-analysis p-values < 1e-05, two of which were within a 5% false discovery rate (FDR). Methylation levels at 9 of the 17 loci were associated with increased expression of 6 cis genes (5% FDR): TNFAIP2, EXOC3L4, GAS7, SREBF1, ACOT7, and RORA. Furthermore, higher placental expression of TNFAIP2 and ACOT7, and lower expression of ROR4, were associated with lower birth weight z-scores (p-values < 0.05) while ACOT7 expression was also associated with decreased birth length and head circumference (p-values < 0.05). The top 250 hits from the meta-analysis were enriched for KEGG pathways including cell adhesion molecules and tight junctions, multiple cancer pathways, G-protein and nitric oxide signaling, and cytotoxicity (5% FDR).

**Conclusion:** We identified novel differentially methylated loci associated with placental Cd concentrations, and evidence of DNAM-expression associations at multiple epigenetic loci involved in inflammatory signaling and cellular outgrowth. The expression levels of genes involved in inflammatory signaling (TNFAIP2, ACOT7, and ROR4), were also associated with growth metrics at birth. Furthermore, the biological pathways identified in our KEGG enrichment analyses are consistent with many of the Cd-associated mechanisms of toxicity that have been examined via animal and/or in-vitro models, but have yet to be thoroughly studied in human pregnancy.

**PA1.03.09**

Methylome changes associated with prenatal tobacco smoke exposure in sorted cord blood CD4+ cells

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**Background:** Prenatal tobacco smoke (PTS) exposure has been associated with alterations in newborn DNA methylation patterns at both the global and gene-specific level. However, studies evaluating the impacts of PTS exposure on gene-specific DNA methylation have largely utilized candidate gene or methylation array approaches, which cover only a small fraction of CpG sites within the human genome. Furthermore, the majority of these studies have evaluated DNA methylation patterns in cord blood, which consists of a mixture of different cell types, each of which have distinct DNA methylation profiles. Our objective was to evaluate whether PTS exposure alters whole genome DNA methylation patterns, measured by
whole-genome bisulfite sequencing (WGBS), in sorted CD4+ cord blood cells from the Southern California-based Maternal and Children’s Health Study (MACHS).

Methods: 10 PTS-exposed MACHS Hispanic white newborns were identified and matched to 10 PTS-unexposed MACHS Hispanic white newborns, according to gestational age and also maternal age, BMI, and history of diabetes. Cord blood cells were sorted for these 20 participants, and high-resolution, whole genome DNA methylation levels were obtained using WGBS in sorted CD4+ cells. The average coverage on CpG sites was 6X. WGBS data was mapped to Human Genome Build 19, using the Wildcard ALignment Tool (WALT). The MethPipe package was used to calculate average CpG methylation levels and bisulfite conversion rates, which were close to 99% for all CpGs. Differentially methylated (DM) CpGs and differentially methylated regions (DMRs) were identified using the Regression Analysis of Differential Methylation (RAD-Meth) software, which utilizes beta-binomial regression. DMRs were filtered for those containing 5 or more significant DM CpG sites. Regression models were adjusted for baby’s sex and whether or not the mother worked during pregnancy. Annotation of genomic regions was conducted using the “Goldmine” package in R.

Results: After adjusting for multiple comparisons, we identified 3673 DM CpG sites and 56 DMRs (FDR-adjusted p-value < 0.01). DMRs spanned from 84 to 491 base pairs, with an average methylation difference of ±18%. The largest methylation differences for these DMRs were -45% and +42%. Of the identified DMRs, 26.8%, 30.4%, 30.4%, 7.1%, and 5.3% were found to overlap promoter, intergenic, intron, 3’ end, and exon regions, respectively. We plan to conduct pathway analyses to determine if specific gene networks are impacted by PTS exposure. We will additionally evaluate whether any of the DM CpG sites and regions have been identified in previous studies of PTS exposure.

Conclusions: Using WGBS, we identified 3673 CpG sites and 56 regions that were DM by PTS exposure in sorted cord blood CD4+ cells.

PA1.04- Kidney outcomes
PA1.04.01
Early kidney development and later life consequences
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The association between stress experienced during fetal and early post-natal development and an increased risk of later-life high blood pressure and kidney disease is now well accepted. In part this association is modulated by impairment of nephrogenesis leading to a low nephron number and a kidney that over time is less able to compensate in the setting of injury or increased metabolic demand. Other factors, including programming of cardiovascular disease, diabetes and vascular reactivity all contribute to the programmed phenotype of premature chronic kidney disease and even death. Thus far most attention has focused on low birth weight (defined as a birth weight < 2.5 Kg) and preterm birth (birth before 37 weeks of gestation) as the major clinical markers of intrauterine stress. In humans associations exist between low birth weight or preterm birth and low nephron numbers; low nephron numbers and higher blood pressures; low birth weight or preterm birth and higher blood pressures; low birth weight or preterm birth and chronic kidney disease. Evidence is growing suggesting that being small for gestational age (birth weight < 10th percentile), being high birth weight or being born in a pregnancy complicated by pre-eclampsia, maternal overweight/obesity or maternal diabetes are also risk factors for fetal programming of blood pressure and kidney disease. Other maternal exposures such as chronic illness, infections or medication exposure during pregnancy are risk factors for low birth weight and preterm birth and may also predict future risk in the offspring. Given that 15% of babies born annually are of low birth weight and 11% are born preterm, millions of babies are at risk of future chronic disease. Awareness of the programmed risk should begin at birth and simple preventive measures should be implemented early. The risk for low birth weight and preterm birth differ between low- and high-income countries. In low-income countries maternal malnutrition, short stature, poverty, lack of family planning, suboptimal education for girls, child marriage, teenage pregnancies, anaemia and poor antenatal care are important. In high-income countries older maternal age, more maternal chronic illness, lower socio-economic status and greater use of assisted reproduction technology predominate. Importantly a mother who herself was born of low birth weight or preterm has herself an increased risk of delivering a low birth weight or preterm infant as well as experiencing pre-eclampsia and gestational diabetes. The consequences of developmental programming therefore can cross generations. The World Health Organisation has now embraced A “Life Course Approach” to the prevention of chronic diseases, stressing the importance of optimizing maternal health before conception and throughout pregnancy, optimizing early childhood nutrition, avoiding obesity and promoting healthy life-styles as achievable strategies to interrupt the programming cycle. Given the many social/structural factors that impact maternal, fetal and child health that extend beyond the health system, achievement of the Sustainable Development Goals will also be important in the quest to achieve true primary prevention of high blood pressure and kidney disease in future generations.

PA1.04.03
Early childhood: A critical period for kidney function throughout life
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Beyond the critical role of the perinatal period in determining future cardiorenal health, each person’s growth and development during early childhood also is crucial in setting individual risk, all important for future good health or future health challenges. Much emphasis has been placed on perinatal events in determining chronic kidney disease, and less on the influence of childhood events beyond the neonatal period. Nephrogenesis is completed by term birth in the human; thus, intrauterine events may affect the child’s perinatal history. For example, a person born premature or with low birthweight for postmenstrual age who grows at a rate commensurate with his or her initial relative size is less likely to develop hypertension, cardiovascular disease and type 2 diabetes than someone whose trajectory is one of quicker-than-anticipated growth. However, there is less known about the rate of childhood growth and kidney function and structure. We do know that premature babies receive many potentially nephrotoxic medications while in the newborn intensive care unit, which makes them more vulnerable than those born at term without difficulty. We are starting to understand that exposures in early childhood will be particularly important for future kidney health for persons at risk, owing to their perinatal history. For example, the presence of an adverse early childhood milieu, related not only to nutrition, but also to the home environment, socioeconomic status, parental health and education and the wider economy, may have profound legacy effects on general health and on kidney health. Further, there is increasing evidence that still other factors impact future kidney disease. Humans interact with macro- and micro-organisms of many types. Indeed, the microbiome is very important in future health and may influence the level of chronic inflammation, which can have a profound influence on the kidney and the vasculature. Experimental data support these contentsions, while strong clinical data are evolving. What seems clear, presently, is that certain children are at higher risk for suffering kidney injury as they mature. Given known risks, it will be increasingly important to institute programs during childhood that may help to prevent chronic kidney disease, presently affecting (conservatively) as much as 10% of the world population.

PA1.04.05

A new approach to chronic kidney disease through the application of principles of evolutionary biology: tradeoffs and life history theory

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Background: There is a growing epidemic of progressive chronic kidney disease (CKD), which now affects 10% of the global population, resulting in millions of deaths annually. Reduction in nephron number leads to early hyperfiltration and hypertrophy of remaining nephrons, but later nephron loss through atrophy and fibrosis. Current research in CKD is based on the concept of “maladaptation” by nephrons following injurious stimuli. Angiotensin inhibitors remain the only generally available therapy to slow progression of CKD, and they do not stop the process. A new paradigm is needed to explain the changing response of the kidney to injury over the life cycle.

Methods and Results—Literature review: A new discipline was developed in the 1990s by G.C. Williams and R. Nesse, now recognized as evolutionary medicine. Williams proposed that natural selection of deleterious genetic effects is the result of antagonistic pleiotropy, whereby a gene has survival benefit through reproductive age, but detrimental effects afterward. Rather than framing the nephron response to injury as maladaptive (physiologic adaptation), viewed in the context of evolutionary tradeoffs and life history theory, the process can be considered as molded by selection for reproductive success (evolutionary adaptation). The physiology of the mammalian nephron is counterintuitive: high blood flow and filtration of 180 liters of plasma daily is matched by tubular reabsorption of 99% of the filtrate, requiring high energy expenditure. This is a result of millions of years of evolution, with adaptation from a marine to freshwater environment. Adaptation to terrestrial life required subsequent evolution of the distal nephron to provide urine concentration and sodium conservation. The evolutionary tradeoff for the nephron: a hyperosmolar environment at the brink of hypoxia, vulnerable to ischemic or toxic injury. Human mortality is high in embryonic development, during which the kidney is susceptible to developmental anomalies driven by genetic and epigenetic factors (Figure); most CKD in children is caused by congenital anomalies. Mortality decreases to a nadir, then increases again, driven largely by environmental factors after reproductive years. Natural selection operates through the reproductive years, then becomes less influential. The normal 10-fold variation in nephron number at birth is the result of developmental plasticity, determined by natural selection. Mismatch of the renal phenotype to the environment develops in adulthood in infants of low birth weight, and subjected to Western diet which also promotes diabetes, the primary cause of CKD in adults. Before the age of 40, energy is directed to renal maintenance and repair, enhancing selection for reproductive success and a low incidence of kidney failure. The steep increase in kidney failure thereafter results from loss of nephrons through senescence with superimposed environmental factors. These reflect a reduction in energy commitment to repair/regeneration as selection pressure decreases.

Conclusions: Future research in CKD would benefit from the study of tissue ecosystems and diversified animal models in the context of evolved differences between species (not just their genetic homologies). Combining genomics across large sample sizes of life histories, systems biology could reveal evolutionary insights into maladaptation in CKD, and potential new interventions.
Relative contribution to CKD of environment, natural selection, and genetic/epigenetic factors as determinants of mortality throughout the life cycle.

PA1.04.06

Early longitudinal kidney growth patterns and glomerular filtration rate at school-age


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Background: Suboptimal kidney development in early life may be associated with an increased risk of kidney disease in later life. We aimed to identify specific kidney growth patterns during fetal life and infancy associated with impaired kidney function in childhood.

Methods: In a population-based prospective cohort study among 614 mothers and their children, combined kidney volume was measured by ultrasound at the ages of 30 weeks of gestation, and 6, 24 and 72 months. At the age of 6 years, estimated glomerular filtration rate (eGFR) was calculated from blood creatinine and cystatin C concentrations.

Results: Children with small combined kidney volume during fetal life which persisted at 6 years had lower eGFR compared to children with persistent large combined kidney volume (differences eGFRcreat -0.64 SD (95% CI -0.95 to -0.33) and eGFRcyst -0.39 SD (95% CI -0.71 to -0.07), respectively). Longitudinal analyses showed that children in the lowest tertile of eGFRcreat and eGFRcyst had smaller combined kidney volume from fetal life onwards, compared to children in the highest tertile (all p values < 0.01). Conditional regression analyses showed that early childhood kidney growth, independent from previous kidney growth, was positively associated with eGFRcreat and eGFRcyst (all P values <0.05).

Conclusion: Smaller combined kidney growth during both fetal life and early childhood is associated with lower eGFR at school-age.

PA1.04.07

Deficiency in retinoic acid leads to inborn nephron deficit in offspring exposed to diabetes in utero

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Background: Diabetes mellitus is a global health crisis. Besides adversely affecting the individual, maternal diabetes can cause long-term negative consequence in the offspring. There is growing evidence that offspring of mothers with type 1 diabetes are more prone to develop hypertension and chronic kidney disease in adulthood. Epidemiological and experimental animal studies show that prenatal programming of hypertension and chronic kidney disease is related to low nephron mass. It is therefore important to understand the mechanism by which nephron generation is perturbed in embryos exposed to maternal diabetes, so as to develop in utero therapy to restore nephrogenesis. During mammalian embryogenesis, all-trans retinoic acid (RA), synthesized from vitamin A obtained from maternal circulation, is crucial for nephrogenesis. A positive correlation between maternal circulatory vitamin A levels and fetal nephron number has been demonstrated. In studying a mouse model of type 1 diabetes induced by streptozotocin, we find that serum vitamin A concentrations are lower in pregnant diabetic mice than non-diabetic mice. We therefore hypothesize that there is RA deficiency in the kidneys of embryos exposed to maternal diabetes, which leads to reduced nephron number.

Methods: Streptozotocin-induced diabetic or non-diabetic female ICR mice were mated with non-diabetic male ICR mice. At gestational day 12, the embryonic kidneys, at early stage of development, were collected for various measurements,
including RA synthesis and RA concentrations using a highly sensitive RA reporter cell line, and the mRNA expression levels of RA target genes by real-time qRT-PCR. Nephron number at birth was counted by physical dissector/fractionator combination of peanut agglutinin-stained glomeruli. To determine whether hyperglycemia is the critical factor in the maternal diabetic milieu that perturbs RA homeostasis in the embryonic kidney, an in vitro model was established by culturing kidney explants in vitro in high glucose conditions. Varying concentrations of RA were added to the culture to test whether high glucose-induced impairment of nephrogenesis could be corrected.

Results: In the developing kidneys of embryos of diabetic mice, there was a significant decrease in RA synthesis and RA concentrations. The expressions of several RA target genes including Ret, which is important for modulation of nephron number via regulating ureteric branching morphogenesis, were significantly downregulated. At birth, neonates of diabetic mice exhibited 30% deficit in nephrons in comparison to neonates of non-diabetic mice. Perturbation of RA homeostasis and signalling with reduced ureteric branching and nephrogenesis were similarly found in kidney explants cultured in a high glucose medium. Notably, co-addition of RA could stimulate ureteric branching and restore nephrogenesis.

Conclusions: Together, our findings show that maternal diabetes inhibits RA synthesis and causes a deficiency of RA in the embryonic kidney, which perturbs RA signalling in the control of the expression of key genes, including Ret, for nephrogenesis. This mechanism contributes, at least in part, to reduced nephron endowment in the offspring. These findings will pave the way for the design of in utero therapeutic intervention to promote nephrogenesis and prevent inborn nephron deficit in the offspring exposed to diabetes in utero.

Methods: Kidneys were collected at postnatal day 21 (PN21) from male Sprague-Dawley rats exposed to a maternal low (LPD; 8%) or normal (NPD; 20%) protein diet from 3 weeks before pregnancy until weaning. At PN21, a cohort of rats exposed to maternal LPD or NPD, were then fed either a normal (NFD, 6% fat) or high (HFD, 21% fat) fat diet until 6 months, at which time body composition (dual energy x-ray absorptiometry), proteinuria (albumin to creatinine ratio), podocyte number per glomerulus (immunofluorescence, optical clearing and confocal microscopy - WT1 + nuclei indicated podocytes) and renal pathology were assessed.

Results: At PN21, LPD offspring had significantly lower body (40%) and kidney (50%) weight, nephron number (30%) and podocyte number per glomerulus (13%; NPD 152±7, LPD 133±7, (mean ± SD), P <0.001) than NPD offspring. At 6 months, LPD offspring fed a NFD (LPD/NFD) had undergone significant catch-up growth, weighing just 15% less than NPD/NFD offspring. Podocyte number did not change between PN21 and 6 months in either NPD/NFD or LPD/NFD offspring. Despite lower nephron and podocyte number in LPD/NFD offspring at 6 months, NPD/HFD offspring weighed 13% more and had a 35% greater fat mass than LPD/HFD offspring. Surprisingly, at 6 months, NPD/HFD offspring had lost 13% of their podocytes compared with NPD/NFD offspring. In contrast, there was no podocyte loss in LPD/HFD offspring compared to LPD/NFD offspring. At 6 months, both NPD and LPD offspring fed HFD exhibited proteinuria and focal and segmental glomerulosclerosis (FSGS), glomerular pathology indicative of podocyte depletion and CKD. Both NPD and LPD offspring fed a HFD had significantly fewer podocytes per glomerulus per kg bodyweight (26% in NPD/HFD offspring and 14% in LPD/HFD offspring) than offspring fed a NFD for 6 months.

Conclusions: This study shows for the first time that podocyte number can be developmentally programmed. Both birth weight and postnatal weight influenced podocyte number. Postnatal body weight gain plays a significant role in podocyte loss and development of renal pathophysiology. Whether podocyte number per glomerulus/kg bodyweight can indicate risk for renal pathophysiology in humans should be investigated.

Cardiorenal and metabolic pregnancy adaptations in females born small on a high fat diet and benefits of endurance exercise training

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Intrauterine growth restriction programs adult cardio renal and metabolic diseases, which are exacerbated with "second hits"
such as pregnancy and obesity in females born small. Importantly, exercise is reported to have a positive effect in those born small. This study determined if a high fat diet (HFD) exacerbates the known adverse cardiorenal and metabolic adaptations to pregnancy in rats born small and whether exercise before and during pregnancy is more beneficial in preventing these complications than exercise during pregnancy alone. Uteroplacental insufficiency resulting in growth restriction was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery on embryonic day 18 (E18) in Wistar-Kyoto rats. Female offspring consumed a Chow or HFD (23% fat) from 5 weeks and were mated at 20 weeks. Female rats were exercised on treadmills for 4 weeks before pregnancy and throughout pregnancy or during the last two thirds of pregnancy only. Systolic blood pressure was measured by tail cuff and non-fasted glucose tolerance test was performed at E18. At E19, rats were individually placed in a metabolic cage to collect urine and plasma was taken by tail vein to calculate estimated glomerular filtration rate (eGFR). At E20, rats were anaesthetised with intraperitoneal injection of Ketamine (100mg/kg) and Llium Xylazil-20 (30mg/kg) and plasma, pancreas and skeletal muscle were collected. Control and Restricted rats consuming a HFD were significantly heavier with higher plasma leptin concentrations compared to Chow-fed rats irrespective of exercise interventions. No changes in pre-pregnancy systolic blood pressure were observed in all groups. Restricted Chow-fed rats, and both Control and Restricted females on a HFD had an adverse cardiovascular adaptation to pregnancy with a greater reduction in systolic blood pressure during late gestation (p < 0.05). Importantly, both exercise interventions prevented the adverse cardiovascular adaptation (p < 0.05). Sedentary Control females on a HFD had adverse renal function (+50% eGFR; p < 0.05) and this was not affected by exercise. Compared to Control, Restricted females that remained Sedentary had adverse renal function (+56% eGFR; p < 0.05), which was not exacerbated by HFD, but was prevented by exercise. HFD exacerbated the pregnancy induced glucose intolerance in Restricted females (+18%; p < 0.05) and importantly exercise before and during pregnancy prevented this development and exacerbation of glucose intolerance (p < 0.05). Control and Restricted females on a HFD who exercised before and during pregnancy had increased pancreatic β-cell mass (+36%; p < 0.05). No differences in skeletal muscle mitochondrial biogenesis markers (peroxisome proliferator-activated receptor gamma coactivator 1-α and citrate synthase activity) were detected across the groups. Metabolic dysfunction was not impacted by exercise in pregnancy alone. In summary, pregnant females born small are at a greater risk of cardiorenal adaptations during pregnancy. Females born small also have exacerbated glucose intolerance when consuming a HFD; this was prevented by the lifestyle intervention of exercise, potentially due to improved β-cell mass. Although cardiorenal dysfunction was prevented by exercise both prior to and during pregnancy as well as during pregnancy alone, only exercise initiated before conception and continued during pregnancy prevented metabolic dysfunction.

PA1.05 - Dynahealth Consortium
PA1.05.01
Lifecourse origins of healthy ageing - The DynaHEALTH project
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The relationships between glycaemic health, psychosocial factors and healthy aging, including freedom from non-communicable diseases, may be conceptualised in several different ways. It is an integral part of DynaHEALTH to develop these concepts and operationalize them into corresponding analytical study designs compatible with the available data in the consortium. A very large body of evidence, gathered from multiple complementary fields spanning from genetic epidemiology to social sciences has established the hypothesis of causal pathways linking the developmental period to the risk of unhealthy and inactive ageing. Multiple knowledge gaps remain in order to understand and integrate the factors contributing to the mediation of poor cardiometabolic health from the fetal period onwards. Critically, the entanglement between the healthy ageing and the psychosocial gradient imposes challenges to researchers and the social and healthcare systems by eliciting important vicious circles complicated by trans-generational factors. The DynaHEALTH project consortium is harnessing part of the wealth of prospective data collected in Europe from 1934 onward and empowering scientific skills in Data science to i) operate life-course models for biopsychosocial health affecting the path from early adiposity to co-morbid patterns of non communicable disease; ii) design econometric equations; iii) analyse the metabolic, epigenetic and brain markers and their predictive power and iv) provide ways to exploit the scientific research into tools and recommendations targeted to healthcare providers and their clients.

After two years of inspiring work in the project, the consortium is reaching a stage of primary discovery to pilot new biostatistical tools and molecular markers on the backbone of a robust life-course model to explore the lifecourse origins of healthy aging. This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 633595.

PA1.05.03
Prenatal depressive symptoms and offspring brain morphology: a pediatric neuroimaging study
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During the reproductive years, a significant proportion of women experience depressive and anxiety disorders. Approximately,
8–15% of women suffer from clinically relevant depressive or anxiety symptoms during pregnancy. There is a large number of studies demonstrating that untreated depression and anxiety have a negative impact on the offspring. For example, untreated depression during pregnancy has been repeatedly associated with low birth weight, preterm birth, and a broad range of physiological and psychological problems later in life. These include problems involving affect, cognition, interpersonal relationships, and neuroendocrine functioning; and these suggest that prenatal maternal depression influences neurodevelopment. However, the underlying neurobiological mechanisms have remained unclear. To better understand the possible underlying neurobiological effects of prenatal maternal depression on offspring, structural and functional neuroimaging could be used. Nevertheless, very limited information is available about the potential association of maternal depression during pregnancy and offspring brain morphology and connectivity. Further, little information is present on whether the course of maternal depressive symptoms is important, or whether there is a specific period of vulnerability. In this presentation, we will provide an overview of the current literature on maternal depressive symptoms and child development with a focus on neurodevelopmental outcomes. Furthermore, recent results of analyses on prenatal depressive symptoms and childhood brain development will be presented. Finally, trajectories of maternal depressive symptoms from pregnancy until childhood will be presented to explore how the course of maternal depressive symptoms influence child brain development.

This project was performed as part of the DynaHEALTH project and has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 633595.

PAI.05.05

DNA hypomethylation of placental growth factor and decreased SAM:SAH ratio in placental tissue of preeclampsia-complicated pregnancies


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Background: The pathophysiology of preeclampsia is largely unknown. Aberrant DNA methylation might be involved in the etiology of preeclampsia (PE). Serum placental induced growth factor (PlGF) levels are decreased during second trimester pregnancy. We hypothesize that placental levels of PlGF DNA methylation are lower in PE pregnancies. In addition, we measured global methylation by long-interspersed nuclear element-1 (LINE-1) and S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) levels in placental tissue. Methods: Placental tissue of 22 PE pregnancies (11 early onset PE (EOPE) and 11 late onset PE (LOPE)) and 60 controls (25 uncomplicated controls and 35 complicated controls including 20 fetal growth restriction and 15 preterm births) was collected from a nested case-control study in The Rotterdam Periconceptional Cohort. DNA was isolated from placental tissue and was treated with sodium bisulfite. Methylation of LINE-1 and PlGF genes was analyzed by Sequenom Epityper and SAM and SAH were measured by LC-ESI-MS/MS. Results: Placental SAM levels and SAM:SAH ratio were significantly lower in placental tissue of PE pregnancies compared to uncomplicated and complicated controls (Beta = -0.30 and Beta = -0.29 respectively, P < 0.05). PlGF DNA hypomethylation was observed in PE casus versus controls (Beta = -0.30, P = 0.005). Stratification according to onset of PE showed that these effects were more pronounced in EOPE (Beta = -0.42, Beta = -0.46 and Beta = -0.47 respectively for SAM, SAM:SAH ratio and PlGF DNA methylation, P < 0.05). No significant differences were observed for SAH and LINE-1 DNA methylation. Conclusions: Placental PlGF gene is hypomethylated in preeclampsia. Together with disturbed SAM:SAH ratio this underlines the possible role of aberrant placental DNA methylation in the pathophysiology of PE, which needs to be further addressed.

PAI.05.06

Metabolomics in Gestational Diabetes mellitus: transgenerational correlations and impact of maternal phenotypes on offspring metabolites

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Background: Children, who were exposed to either gestational diabetes mellitus (GDM) or obesity while in utero, are at increased risk for obesity later in life. Additionally, other maternal phenotypes, such as current BMI or gestational weight gain, could affect the metabolism of their offspring. In order to identify offspring metabolite changes correlating with maternal phenotypes or metabolites we correlated the metabolic profiles of healthy offspring several years postpartum with the metabolic profiles of their mothers with GDM and other maternal phenotypes. Methods: Targeted metabolomics (137 metabolites) was performed in 75 mothers with GDM and their offspring, participating at the Postpartum Outcomes in Women with Gestational Diabetes and their Offspring (POGO)-study. Mean age at time of analysis was 40.6 ± 5.0 years in mothers and 6.7 ± 2.2 years in offspring. Plasma samples were collected from mother-offspring pairs at 0, 30 and 120 min during a 75g oral glucose tolerance test. Transgenerational correlations of metabolites were calculated, adjusting for gender, BMI and age of the children, and BMI and age of the mothers. A correlation network was built for visualization (Figure). Correlations
between phenotypes and offspring metabolites were significant if their p-value was less than 0.05 after correcting for multiple testing using the Bonferroni method.

**Results:** Transgenerational correlation networks revealed a clear separation between maternal and offspring fasting metabolites, with few connections across generations. Of these, three identical metabolites correlated significantly between mothers and offspring within the network (H1, \( p = 1.03 \times 10^{-7} \); taurine, \( p = 2.68 \times 10^{-6} \); acetyl-ornithine, \( p = 3.83 \times 10^{-13} \)). Furthermore, we identified significant correlations of offspring fasting SM C20:2 with maternal gestational weight gain (\( p = 7.40 \times 10^{-5} \)) and of offspring fasting PC aa C36:3 and PC aa C38:3 with maternal BMI (\( p = 3.04 \times 10^{-4} \) and \( p = 3.09 \times 10^{-4} \), respectively). Maternal smoking during pregnancy was not correlated with offspring metabolites. The offspring AUCs of metabolites over the glucose challenge were not significantly correlated with gestational weight gain, maternal BMI or maternal smoking during pregnancy.

**Conclusions:** We conclude that maternal phenotypes have an impact on the metabolic profiles of their offspring and that these changes can be seen up to several years postpartum. Furthermore, the metabolites affected by gestational weight gain or current BMI suggest pathways which could lead to later obesity in the currently lean and healthy offspring.

Transgenerational correlation network of fasting metabolites of mothers with GDM and their offspring.

**PA1.05.07**

The association between duration of breastfeeding and type 2 diabetes in adulthood: influence from potential confounders

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**Background:** Although a number of observational studies suggest that breastfeeding protects against the development of type 2 diabetes later in life, there are inconsistencies across studies, potentially due to differences in study size and adjustment for potential confounders. Moreover, most studies are limited to comparison of breast-fed versus bottle-fed infants. Therefore, the aim of this study was to examine the association between duration of breastfeeding and type 2 diabetes in adulthood in a cohort with a wide range of potentially confounding variables.

**Methods:** We included 4,786 individuals from the Copenhagen Perinatal Cohort born 1959-61 in Denmark. The duration of any breastfeeding as assessed by a physician interviewing the mothers at the infant’s 1-year examination was divided into quartiles (\( \leq 1, >1-2, >2-4, >4 \) months). Type 2 diabetes status (age \( \geq 30 \) years) was obtained from the National Patient Register (n = 171). Hazard ratios (HR) and 95% confidence intervals for the association between duration of breastfeeding and type 2 diabetes were estimated by Cox proportional hazards regressions without and with adjustment for sex, birth weight, maternal body mass index, maternal diabetes during pregnancy, maternal smoking during the third trimester and parental social status and education.

**Results:** In the unadjusted analysis, there was a significant and inverse trend between quartiles of duration of breastfeeding and risk of type 2 diabetes in adulthood (\( P = 0.01 \)). In unadjusted analyses, compared with infants breastfed for 1 month or less, among infants breastfed for >2-4 months there was a non-statistically significant, albeit inverse, association with type 2 diabetes (HR = 0.84 [0.56-1.26]). In unadjusted analyses, compared with infants breastfed for 1 month or less, infants breastfed for > 4 months had a 40% reduced risk of type 2 diabetes (HR = 0.60 [0.38-0.96]). However, after adjustment for potential confounders this was attenuated to a 29% reduced risk (HR = 0.76 [0.47-1.23]) and was no longer statistically significant.

**Conclusion:** When a range of type 2 diabetes risk factors are considered, breastfeeding is not associated with adult type 2 diabetes. Although breastfeeding has a modest but non-significant protective effect against this disease, the results suggest that it is likely an indirect indicator of diabetes risk factors, highlighting the potential effects of unknown or poorly measured confounders. In addition, mediation by later life risk factors should be considered.

**PA1.05.08**

Life-course accumulation of socioeconomic adversities and obesity: a 46-year follow-up of the Northern Finland Birth Cohort


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**Background:** Social inequalities in morbidity and mortality continue to be a public health concern. Whilst the association
between adulthood socioeconomic position (SEP) and obesity is well-established, the extent to which adverse social circumstances during childhood influences risk of later obesity is less clear. Recent research has focused on the accumulation hypothesis in which the cumulative effects of socioeconomic disadvantage across the life-course impacts upon adult health status. Additionally, the pathway to a particular adult SEP may be associated with differential risk of obesity.

**Aim:** We are using life-course modelling to investigate the influence of socioeconomic factors in childhood and adulthood on the later onset of obesity. In addition, we aim to identify life-course SEP trajectories, and compare those reaching the same final SEP to ascertain importance of pathways.

**Methods:** We used longitudinal data from the Northern Finland Birth Cohort 1966 (n = 3,763). Those with missing data at any of the time points were excluded. SEP was assessed using latent factors at three time points: peri-natal, 31 and 46 years. Material and psychosocial measures relating to family, working life and education at each time point were combined using factor analysis in order to reflect a more comprehensive measure of SEP. At the peri-natal stage, parental information was used to represent SEP of the offspring. Total factor scores were divided into tertiles representing low (0), intermediate (1) and high (2) SEP at each time point in the life-course. A cumulative score was derived as a sum of SEP at each time point ranging from 0 to 6 (lowest to highest SEP score at all three time points).

The next step in modelling life-course SEP is to apply group-based trajectory modelling. We will use the PROC TRAJ macro in SAS to test for latent SEP trajectories. SEP factor scores will be used as a continuous variable within a censored normal model. We will follow the general recommendations of selecting the model with smallest absolute Bayesian Information Criterion value that also meets the standards of additional diagnostics. Multivariate regression will determine associations between SEP trajectories and BMI at age 46 years.

**Results and Conclusion:** At all time points, we observed significantly higher mean BMI at age 46 years in those categorised as low SEP. Furthermore, there was a graded linear relationship between accumulation of socioeconomic exposure and BMI. Participants with a score of 0 had significantly higher BMI at age 46 years than those with a score of 6 (Table 1). Additionally, peri-natal SEP was significantly related to BMI at age 46 years, independently of SEP at ages 31 and 46 years. These results emphasise the adverse long-term impact of accumulated socioeconomic disadvantage from childhood to adulthood. We have derived a comprehensive life-course measure of SEP representing a combination of material and psychosocial adversities. The independent association with SEP in childhood supports the need for interventions to reduce inequalities in early life. Further research is needed to understanding the underlying mechanisms by which social circumstances, particularly in early life, influence adult obesity.

Mean BMI at age 46 years by SEP tertile at each stage of the life-course. ANOVA was used to assess differences between mean BMI at age 46 years.

**PA1.05.09**

Genetically determined later puberty impacts lowered bone mineral density in childhood and adulthood

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**Background:** Later puberty is associated with lower areal bone mineral density (aBMD), and both are known risk factors for osteoporosis later in life. However, the relationship between puberty-associated genetic variants and aBMD during development, and the potential causal relationship between puberty and aBMD, remain uncharacterized.

**Methods:** We constructed sex-specific polygenic risk scores (GRS) consisting of genetic variants associated with later puberty (Female GRS, n = 333 age at menarche-associated variants; Male GRS, n = 49 age at voice break-associated variants). The sample consisted of European-descent children in the Bone Mineral Density in Childhood Study, a longitudinal cohort with up to seven assessments (n = 1419) between the ages of 5-20 years. These GRS were tested for associations with age- and sex-specific aBMD Z-scores at the lumbar spine (LS), femoral neck (FN), total hip, and distal one-third radius, accounting for clinical covariates using sex-stratified linear mixed models. Two-sample Mendelian randomization (MR) was used to test for a causal relationship between pubertal timing and aBMD in the BMDCS and in adults using publicly available data from the GEfos consortium.

**Results:** The sex-specific puberty-delaying GRS were associated with lower pediatric LS-aBMD in girls and boys, even after adjusting for height and pubertal stage (beta (SE) = -0.088 (0.034); P=0.0097 and beta (SE) = -0.068 (0.033), P=0.039, for girls and boys, respectively). In the MR framework, the puberty-delaying genetic instruments supported a causal association with lower LS-aBMD in adolescent girls (beta (SE) = -0.18 (0.063), P=0.0046) and in adults of both sexes (women: beta (SE) = -0.072 (0.016), P=9.21 × 10^-6; men: beta (SE) = -0.12 (0.033), P=0.0003) as well as lower FN-aBMD in adults (women: beta (SE) = -0.074 (0.014), P=9.44 × 10^-8; men: beta (SE) = -0.11 (0.028), P=7.04 × 10^-5).
Conclusions: Pubertal timing and bone density during skeletal development share a genetic basis, and the genetic determinants of pubertal timing impact bone in a site-specific manner with potential implications for later life skeletal health. A clearer understanding of the complex interactions between sexual maturation and BMD is important for developing personalized recommendations for optimizing bone health over the lifespan, but further studies are needed to assess the impact of puberty loci on fracture risk and to identify causal genes at key loci.

LM1.01.01
How to write a successful grant
B. Koletzko¹,²,³,⁴

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Writing grant applications is an essential part of research and a skill in itself. Every scientific researcher faces the challenge of putting research ideas to paper and presenting them in the most optimal way, targeted at the funding agency and the specific funding call text. In this workshop, Professor Berthold Koletzko will try to give insights in how to approach writing a successful grant application and will discuss tips and tricks, based on his extensive experience. Professor Koletzko is Professor of Paediatrics at the Ludwig-Maximillians-Universität in Munich, Germany. His research is funded by the European Commission, the European Research Council, the German Research Council, and other public funding bodies. He is coordinator of the EU FP7 project Early Nutrition. He also serves as member of the Grant Review Board Medicine and as Chair of the Clinical Trial Grant Review Board of the German Research Council.

LM1.02 - Oral slam session: Maternal and fetal health
LM1.02.01
Assessment of adaptive cerebrovascular changes in fetuses of diabetic mothers on two-dimensional obstetrics ultrasound
N. Mohammed¹, R. Nuruddin², M. Yakoob², S.I. Azam², S. Khan³, S. Butt¹

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Background: Hyperglycemia in pregnancy (HIP) exposes fetuses to high glucose levels. The subsequent fetal hyperglycemia and hyperinsulinemia may lead to the possible consequences of hyperglycemia-induced-insulin-resistance in the fetal brain. We hypothesize that this pathophysiological phenomenon could be associated with increased resistance in middle cerebral artery (MCA) blood flow velocity waveform and therefore, a proxy of fetal brain insulin-resistance.

Objective: To assess the difference in middle cerebral artery (MCA) pulsatility index (PI) between HIP and euglycemic pregnancies (EP).

Methods: For this cross-sectional study, we identified 86 HIP and 80 EP carrying appropriate-for-gestational-age singleton fetus. HIP group consisted of 55 subjects with gestational-diabetes-mellitus (GDM) and 31 with pre-pregnancy-diabetes-mellitus (PPDM). We excluded fetuses with congenital abnormalities and mothers with conditions such as Rh-iso-immunization and hypertensive-disorders-of-pregnancy. All fetuses had serial ultrasound-scan for growth and MCA, umbilical artery (UA) and uterine artery (UtA) blood flow velocity studies performed during the third-trimester. Doppler studies performed within 2 weeks of delivery were chosen for analysis. Groups were compared by two-tailed independent sample t-test or Mann-Whitney U test, where appropriate.

Results: Compared to EP mothers, mothers with HIP were older (years) [Mean 30.4 (SD 5.0) versus 32.3 (SD 4.8) P = 0.01]. Gestational age (GA) at registration for antenatal check-up and at delivery (weeks) were similar for both the groups [Mean 14.1 (SD 4.3 vs 14.8 (SD 4.9) P = 0.3] and [Mean 37.2 (SD 1.41) vs 37.2 (SD 1.44) P = 0.8] respectively. The GA (weeks) at the performance of the last third-trimester ultrasound scan was also not significantly different between the two groups [Mean 35.3 (SD 1.0) vs 35.7 (1.1) P = 0.06]. The birthweight centile of neonates born to HIP mother were significantly higher [52.1 (SD 25.6) vs 43.1 (SD 26.3) P = 0.03]. MCA PI was found to be significantly higher in fetuses of HIP as compared to EP [1.84 (SD 0.2) vs 1.78 (SD 0.3) P = 0.02], Median MCA Peak Systolic Velocity was also significantly elevated in HIP [52.7 (SD 2.7) vs 51.7 (SD 2.3 P = 0.02)]. Umbilical artery (UA)/Uterine artery (UtA) ratio and MCA/UtA ratio was found to be higher in HIP as compared to EP group [1.08 (SD 0.20) vs 0.97 (SD 0.19) P = 0.02] and [2.34 (SD 0.47) vs 2.01 (SD 0.65 P = 0.02), respectively. Those subjects who were on insulin therapy were found to have a significantly elevated MCA PI [1.90 (SD 0.19)] as compared to those on oral hypoglycemic agent [1.78 (SD 0.24) P = 0.02].

Conclusion: HIP is associated with elevated fetal MCA PI, MCA/UtA and UA/UtA ratio. Those subjects who are on insulin treatment have demonstrated significantly elevated MCA blood flow velocity waveform as compared to those on oral medication. High resistance in MCA blood flow could be suggestive of chronic-hypoxia and an adaptive fetal cerebrovascular reorganization in response to compromised intrauterine environment. Association between MCA vascular-remodeling and neuro-cognitive impairment in early childhood needs further evaluation.
**LM1.02.02**

**Associations of gestational diabetes and glucose levels with ultrasound scan assessed fetal growth in South Asian and White European women.**

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¹University of Bristol, BRISTOL, United Kingdom; ²Bradford Institute for Health Research, Bradford Royal Infirmary, BRADFORD, United Kingdom

**Background:** Intrauterine exposure to gestational diabetes (GDM) is associated with perinatal complications, including excess fetal growth and macrosomia. Diagnostic oral glucose tolerance testing (OGTT) for clinical detection of GDM is performed at 24-28 weeks' gestation (wkGA) because there are detectable increases in insulin resistance at this time. However, results from a study of predominantly White European women, has shown that fetal growth acceleration occurs between 20 and 28 wkGA in those subsequently diagnosed with GDM. Whether this is the same for South Asians who have greater risk of GDM and greater infant adiposity, is unknown. Our aim was to determine the associations of GDM and gestational glucose levels with fetal growth in women of South Asian and White European origin.

**Methods:** We used data from 10 105 (4296 South Asian and 5809 White European) women with a singleton pregnancy and without pre-existing diabetes in the Born in Bradford (BiB) birth cohort study who completed a 75-g OGTT at 26-28 wkGA. Ultrasound measurements of fetal head circumference (HC), femur length (FL) abdominal circumference (AC) and estimated fetal weight (EFW) and corresponding anthropometric measurements at birth were collected as per routine clinical care and the BiB study protocol. Best fitting growth curves were identified using second-degree fractional polynomials and associations with GDM and fasting and 2h post-load glucose levels were analysed using multilevel models, adjusting for maternal and pregnancy related characteristics. We evaluated the timing at which differences in fetal size were first apparent and potential interactions with ethnicity.

**Results:** 805 (8.0%) of pregnancies were complicated by GDM and this prevalence was higher among South Asian (10.3%) than White European (4.8%) women. Diagnosis of GDM was preceded by an increase in all fetal parameters except FL. At 26 wkGA, predicted differences (95% CI) in mean HC, AC and EFW comparing women with and without GDM were 1.2 mm (0.6-1.9), 1.8 mm (0.9-2.7) and 14.9 g (5.6-24.3), respectively. In women who were not diagnosed with GDM a linear relation with fetal size from 20 wkGA, especially in South Asian women. These findings highlight the importance of developing novel diagnostic tools for identifying women at risk of hyperglycaemia earlier in pregnancy.

**Conclusions:** Fetal growth acceleration starts prior to routine GDM diagnostic testing, with gestational glucose levels showing a linear relation with fetal size from 20 wkGA, especially in South Asian women. These findings highlight the importance of developing novel diagnostic tools for identifying women at risk of hyperglycaemia earlier in pregnancy.

**LM1.02.03**

**Association of maternal and cord blood adipokines with offspring adiposity in project Viva: Is there an interaction with child age?**

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**Background:** Higher leptin and lower adiponectin correlate with adult and childhood adiposity, but it is unclear how exposure to these adipokines during gestation relates to offspring growth. We aimed to investigate the relationship between maternal and cord adipokines and offspring adiposity across childhood to early adolescence, as well as interactions with child age.

**Methods:** In mother-child pairs in the Project Viva cohort (Massachusetts, USA), we measured adipokines in mothers at 2nd trimester (n = 1106) and in cord blood at birth (n = 657). We measured offspring adiposity indices at early childhood (mean 3.3 ± SD 0.3 years), mid-childhood (7.9 ± 0.8 years) and early adolescence (13.2 ± 0.9 years). To assess our main hypothesis that maternal and cord blood adipokines were associated with offspring adiposity measures and such effects were age-dependent, we fit mixed linear models as a function of child age at outcome measurement. This method accounts for the correlation between repeated measures on the same individual at different ages. We further adjusted models for maternal pre-pregnancy body mass index (BMI), age at enrollment, smoking history, college degree (yes or no), and gestational weight gain (GWG) at exposure; paternal BMI; child sex and race/ethnicity; and the other adipokine at exposure.

**Results:** Leptin levels in 2nd trimester were higher among mothers who were overweight or obese before pregnancy (30.0 vs. 15.6 ng/dl normal/underweight), had excessive GWG (24.5 vs. 15.0 ng/dl adequate GWG), and smoked during pregnancy (24.4 vs. 19.7 ng/dl nonsmokers). Offspring born to mothers with the highest (vs. lowest) quartile of leptin had lower BMI...
z-score (-0.49 units, 95% CI: -0.72, -0.26), waist circumference
(-2.6 cm, 95% CI: -3.7,-1.5) and sum of subscapular and triceps
skinfolds (SS + TR) (-2.8 mm, 95% CI: -4.1,-1.4) in early life.
Children of mothers in the lowest (vs. highest) adiponectin
quartile had lower early life BMI z-score (-0.27 units, 95% CI:
-0.48, -0.05), waist circumference (-1.7 cm, 95% CI: -2.7,
-0.6), hip circumference (-1.4 cm, 95% CI: -2.6, -0.2) and sums of
SS + TR (-1.8 mm, 95% CI: -3.1, -0.5) after adjusting for
covariates. The association between maternal adipokines and
offspring adiposity growth was not constant as the children age, as
effect estimates for higher leptin and lower adiponectin became
less negative with increasing offspring age. Results were similar for
cord blood leptin but largely null for cord blood adiponectin.
Furthermore, maternal and cord blood highest (vs. lowest)
quartile of leptin was associated with lower offspring early adoles-
tent total lean mass index (-0.9 kg/m²; 95% CI: -1.4, -0.4) and
(-0.7 kg/m²; 95% CI: -1.3, -0.03), respectively.

Conclusions: Our findings showed that higher maternal and
cord leptin, and lower maternal adiponectin, were associated with
lower offspring adiposity from childhood to early adolescence,
independent of maternal BMI and GWG. However, the strength
of the associations were not constant over time, which suggests a
weakening of the programming effect of adipokine exposure
during gestation on offspring adiposity as children age.

LM1.02.04
Association of fetal fractional limb volume at 20 and 30
weeks gestation with newborn body composition
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Wadhwa2
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Irvine, IRVINE, CA, United States of America;3University of
Pittsburgh, PITTSBURGH, PA, United States of America

Background: Fetal fractional limb volume has recently been
proposed as a useful measure for predicting fetal and newborn
size and growth. However, the association of fractional limb
volume measures with newborn body composition is poorly
understood. The aim of this study was to determine whether
fetal fractional limb volume is prospectively associated with
newborn body composition.

Method: In a prospective, longitudinal study of 93 low-risk
pregnancies, fetal ultrasonography was performed at approxi-
ately 20 and 30 weeks gestation. Fractional arm volume and
fractional thigh volume were measured as cylindrical limb volume
based on 50% of total diaphysis length (to eliminate the proximal
or distal end of the diaphysis, where the soft tissue boundaries are
poorly visualized) using 4D View software. The acquired partial
limb volume was divided into 5 subsections of equal length, and
the contour in each subsection was traced manually in an axial
view. Birth weight percentile was determined using the 2000
United States Natality dataset. Newborn body composition
(body fat percentage) was quantified by whole body Dual Energy
X-Ray Absorptiometry (DXA) imaging. The associations of
fractional limb volume with birth weight percentile and with
newborn body fat percentage were determined by multiple linear
regression, controlling for key covariates (maternal age, parity,
socioeconomic status, race/ethnicity, pre-pregnancy BMI,
maternal gestational weight gain, gestational diabetes, gestational
age at birth, infant sex, postnatal age at DXA scan, and mode of
infant feeding). Partial correlational analysis was used to deter-
mine the relative contribution of fractional limb volume measures
in explaining variation in newborn body fat percentage.

Results: Fractional arm volume was 2.51 ± 0.45 cm³ and
12.8 ± 2.02 cm³ at 20 weeks and 30 weeks gestation, respec-

tively. Fractional thigh volume was 4.99 ± 1.19 cm³ and
29.1 ± 4.92 cm³ at 20 weeks and 30 weeks gestation, respec-
tively. Fractional limb volume at 20 weeks gestation was not
associated with birth weight percentile or newborn body fat
percentage. Fractional arm volume and fractional thigh volume
at 30 weeks gestation were moderately correlated with birth
weight percentile and they explained 6.5% and 4.1% of varia-
tion in newborn body fat percentage (table 1).

Conclusion:Fetal fractional arm volume and fractional thigh
volume at 30 weeks gestation explained a modest portion of the
variation in newborn body fat percentage. Because fractional
limb volume is an indicator of soft tissues that contain not only
fat mass but also lean mass and bone, the additional con-
sideration of other fetal measures that can better differentiate
these compartments may be warranted.

Table 1. Partial correlations coefficients of the associations of fractional limb volume with
birth weight percentile and newborn body fat percentage

<table>
<thead>
<tr>
<th></th>
<th>Birth weight percentile</th>
<th>Newborn body fat percentage</th>
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<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>P value</td>
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<tr>
<td>20 weeks gestation</td>
<td></td>
<td></td>
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<tr>
<td>Fractional arm volume</td>
<td>0.164</td>
<td>0.219</td>
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<tr>
<td>Fractional thigh volume</td>
<td>0.097</td>
<td>0.443</td>
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<tr>
<td>30 weeks gestation</td>
<td></td>
<td></td>
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<tr>
<td>Fractional arm volume</td>
<td>0.506</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fractional thigh volume</td>
<td>0.394</td>
<td>&lt; 0.001</td>
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</table>

Table 1: Partial correlations coefficients are adjusted for maternal age, parity, pre-pregnancy BMI, maternal gestational weight gain, gestational diabetes, gestational age at birth, and postnatal age at DXA scan.

LM1.02.05
Feasibility of three-dimensional power Doppler ultrasound and Virtual Reality measurements of (utero)placental vascularization as non-invasive biomarkers of (utero)placental health
Erasmus MC, ROTTERDAM, The Netherlands
Background: Worldwide, every year millions of women suffer from subfertility and/or placenta-related pregnancy complications, such as pre-eclampsia, low birth weight and preterm birth. These adverse outcomes are also associated with the health of mothers and offspring later in life. We hypothesize that preconceptional uterine vascularization and early first trimester utero(placental) vascularization are determinants of endometrial receptivity and placental health respectively. If it is feasible to reliably and noninvasively measure indices of the utero(placental) vascularization in vivo, new opportunities will be provided for early prediction, prevention and treatment of subfertility and placenta-related adverse outcomes. The current state-of-the-art technology for the evaluation of utero(placental) vascular morphology is three-dimensional power Doppler ultrasound (3D PD US). To enable use of the third dimension, i.e. depth, we have developed an in-house novel, innovative technology that displays volumetric ultrasound datasets as holograms, using the Barco I-Space CAVE™-like virtual reality (VR) system (Barco NV, Belgium). Recently, a VR desktop system based on the technical principles of the I-space has been implemented to enable clinical application of VR. Therefore, this study aims to develop a feasible and reliable method to assess preconceptional and early first-trimester utero (placental) vascular volumes using three-dimensional power Doppler ultrasound (3D PD US) on two Virtual Reality (VR) systems.

Methods: In 35 women, either preconceptional (n = 5) or in pregnancy at 7 (n = 10), 9 (n = 10) or 11 (n = 10) weeks of gestation, 3D PD US images of the utero(placental) vascularization were obtained. Preconceptional uterine vascular volume (UVV) and first-trimester placental vascular volume (PVV) and embryonic vascular volume (EVV) were measured by two observers on two different VR systems i.e., the I-Space and the VR desktop. Intra- and inter-observer agreement and intersystem agreement were assessed by intra-class correlation coefficients (ICC) and absolute and relative differences.

Results: Median UVV preconceptional was 1.8 cm³ [range: 1.0;5.5]. Throughout the first trimester of pregnancy, median PVV increased being 0.4 cm³ [range: 0.1;1.0] at 7 weeks of gestation, 4.5 cm³ [range: 1.6;9.2] at 9 weeks of gestation and 7.0 cm³ [range: 1.9;16.2] at 11 weeks of gestation. Overall, utero(placental) vascular measurements were feasible and accurate with good to excellent intra- and inter-observer agreement as well as VR inter-system agreement with most ICC >0.8 and relative differences <20% throughout the entire gestational age range. Inter-observer agreement of PVV at 11 weeks gestation was suboptimal (ICC 0.7, relative difference 50%).

Conclusions: Preconceptional and early first-trimester 3D PD US utero(placental) vascular volume measurements are feasible and accurate using VR. Future cohort studies are needed to further validate these measurements and assess their eligibility as potential biomarkers for endometrial receptivity and placental health. Ultimately, utero(placental) vascular volumes could be part of a strategy towards more accurate and personalized prediction, prevention and treatment of subfertility and placenta-related complications from the earliest moments in pregnancies onwards.

Figure 1: Three-dimensional power Doppler ultrasound images of utero(placental) vascular volumes preconceptional and in pregnancy at 9 weeks of gestation visualized by Virtual Reality (VR)

LM1.02.06
Role of placental, amniotic and cord blood microbiome in the colonisation of the infant gut: a systematic review


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Background: There is increasing evidence for the potential role of the gut microbiome in human health with decreased diversity recognised as a key characteristic of a range of diseases. It is important to understand how the microbiome develops and possible strategies to stimulate a health promoting microbiota. The bacterial colonisation of the infant gastrointestinal tract is a key stage in the process, and maternal and infant events may be important determinants of the diversity and composition of the gut microbiome.
Objective: Maternal anxiety during pregnancy can negatively affect fetal neurodevelopment, predisposing the offspring to a higher risk of behavioral and emotional problems later in life. The current study investigates the association between maternal anxiety during pregnancy and child affective picture processing using event-related brain potentials (ERPs).

Method: Mothers reported anxiety during the second trimester using the anxiety subscale of the Symptom Checklist (SCL-90). At age 4 years, child affective picture processing (N = 86; 44 girls) was measured by recording ERPs during passive viewing of neutral, pleasant, and unpleasant pictures selected from the International Affective Pictures System. The late positive potential (LPP) – an ERP component reflecting individual differences in affective processing – was used as child outcome.

Results: We found a positive association between maternal anxiety during pregnancy and LPP amplitudes for neutral pictures in the middle (-.243, p = .025) and late time window (r = -.272, p = .011) at the anterior electrode location, indicating that children prenatally exposed to higher levels of maternal anxiety show a stronger neural response to neutral pictures. These associations remained significant after adjusting for maternal postnatal anxiety and gestational age at birth. No significant results were observed for pleasant or unpleasant pictures.

Conclusions: Our study provides neurophysiological evidence that children prenatally exposed to higher maternal anxiety devote more attentional resources to neutral pictures, but not to unpleasant or pleasant pictures. Possibly, these children show enhanced vigilance, resulting in a lower threshold for appraising threat in seemingly neutral stimuli. Although useful in dangerous environments, this enhanced vigilance may predispose children prenatally exposed to higher maternal anxiety to developing behavioral and/or emotional problems later in life.

LM1.02.07

Prenatal exposure to maternal anxiety and emotion processing at age 4 years: an event-related potential study

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¹Wayne State University, NIH/NICHD, DETROIT, United States of America; ²Maastricht University, MAASTRICHT, The Netherlands; ³VU Medical Center, AMSTERDAM, The Netherlands; ⁴KU Leuven, LEUVEN, Belgium

Group-average (N = 86) LPP amplitudes to the neutral pictures of children exposed to low (blue line; N = 69) and high (orange line; N = 17) anxiety, for the...
Positive maternal mental health during pregnancy associated with specific forms of adaptive development in early childhood

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1Singapore Institute for Clinical Sciences, SINGAPORE, Singapore; 2K Women’s and Children’s Hospital, SINGAPORE, Singapore; 3National University of Singapore, SINGAPORE, Singapore; 4Queen Mary University, LONDON, United Kingdom; 5Sackler Program for Epigenetics & Psychobiology at McGill University, MONTREAL, Canada

Background: The quality of prenatal maternal mental health, from psychological stress, depressive symptoms, to anxiety and other non-psychotic mental disorders profoundly affects fetal neurodevelopment. Despite the compelling evidence for the broad influence of maternal emotional well-being, the existing literature focuses almost exclusively on the effects of stress or symptoms of depression or anxiety, and does therefore not capture the full range of mental well-being. Health is a continuum that is not defined by merely an absence of illness or disability. Positive mental health has been shown to be a distinct construct from absence of symptoms of mental illnesses which predicts future mental and physical health. Despite the evidence for the influence of positive mental well-being on health there is, to our knowledge, no research examining the possible effects of positive antenatal mental health on the development of the offspring. While large-scale birth-cohort studies emphasize the importance of maternal mental health problems, measures of positive mental health in the study design are rarely considered. While such measures are used to screen for symptoms of mental disorders, it may nevertheless be possible to detect aspects of positive mental health through latent variable modelling.

Methods: This study was part of a prospective birth cohort study, Growing Up in Singapore Towards Healthy Outcomes (GUSTO). The sample (n = 1066) included women who conceived naturally, did not have any medical conditions before or during pregnancy, and gave birth to full-term babies with normal birth weight. Three mental health measures (i.e., Beck Depression Inventory II [BDI-II], State-Trait Anxiety Inventory [STAI] & Edinburgh Postnatal Depression Scale [EPDS]) were administered during 26-week pregnancy during the participants’ clinic visit. The responses to the measures’ items were used in bifactor latent modelling. Mothers rated their child on the Infant Toddler Socio-Emotional Assessment (ITESA) questionnaire at 12-months-old and the Quantitative Checklist for Autism in Toddlers (QChat) at 18-months-old. At 24-month, and the Bayley Scales of Infant and Toddler Development third edition (Bayley) was used to assess the child’s development in the domains of cognition, language, motor skills, socio-emotional behaviors and adaptability.

Results: A seven-factor bi-factor model best fitted the data. This included a general factor and six sub-factors. Two of the sub-factors were related to positive mental health – Positive Mood (FD = 0.94; ωH = .51; H=0.87) and Positive Self (FD = 0.89; ωH = .43; H=0.65). The reliability indices suggest that positive mental health construct can be reliably extracted from screening tools for depression and anxiety. A heatmap illustrates the significant association of positive antenatal mental health with some behaviors in children, specifically those associated with sociability, communication and parentally-rated competence.

Conclusion: In conclusion, this study demonstrates the feasibility of using common psychiatric disorders screening tools to examine the effect of positive mental health. Moreover, the effects of positive mental health are likely to be specific and different from the lack of mental disorders. A deeper understanding of positive mental health will allow for more comprehensive understanding of fetal and child development.
LM1.02.09
Can obesity in early childhood be influenced by lifestyle interventions during pregnancy? A systematic review of the literature.

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King’s College London, LONDON, United Kingdom

Background: Childhood obesity is rapidly becoming a global pandemic, in 2015 more than 41 million children <5 years were affected by overweight or obesity. In the UK, over a fifth of children aged 4-5 years are classified as overweight or obese. There is an increasingly convincing body of evidence that obesity in children may have its origins in early life, specifically adverse exposures during in-utero development. Cohort studies have highlighted the association between childhood obesity and increased maternal body mass index (BMI) and excessive gestational weight gain. Furthermore, observational studies suggest that manipulation of maternal diet and/or physical activity in the antenatal period has the potential to influence offspring growth and development and this has been shown in experimental animals and their offspring. The maternal population is therefore a target for prevention of childhood obesity, and this has led to a number of randomised controlled trials focusing on lifestyle in pregnancy. However, any lasting causal effect on childhood obesity from these trials is currently unknown. The objective of this systematic review was to determine whether antenatal lifestyle interventions in pregnant women, aimed at modifying diet and/or physical activity, lead to a reduction in measures of offspring obesity in early childhood.

Methods: A systematic review of the literature was completed from 1st January 1990-31st March 2017 in MEDLINE, Embase, and CENTRAL for antenatal interventions with subsequent offspring follow-up publications. A hand search of reference lists and cited articles of relevant reports and review articles was also completed. Electronic searches identified 3361 titles and a further three trials were identified through hand searches. Of these 145 duplicates were removed, 32 abstracts were eligible for full-text review, KD and JMO independently screened the relevant articles, extracted the data and assessed risk of bias.

Results: Seven antenatal lifestyle interventions with offspring follow-up data were identified. Four trials included women from all BMI categories and three trials included obese women only. The antenatal interventions were heterogeneous in terms of intervention design, intensity and outcome measures. For the seven offspring follow-up publications children aged 6 months–7 years, measures of obesity in the offspring (n = 1689) included, weight, BMI, weight-for-length z-scores, skinfold thicknesses and circumferences. Two studies, focusing on obese women only, reported reduced measures of adiposity from 6-12 months (n = 787). The remaining five studies, two from infancy (n = 500) and three (n = 402) from early childhood found no effect on measures of obesity.

Conclusion: For the offspring follow-up studies, there was heterogeneity in methods and variations in reported outcomes and studies were limited due to high rates of attrition. Measures of obesity up to 12 months of age have been shown to be reduced by lifestyle interventions during pregnancy in obese women, however we are unable to draw a conclusion on the influence antenatal interventions have on measures of obesity in early childhood.

LM1.02.10
Maternal circulating cotinine concentration in pregnancy and offspring weight and body mass index (BMI) in the first 36 months


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Introduction: Cotinine is an objective biomarker widely used to quantify exposure levels to active tobacco smoking and environmental tobacco smoke (ETS). Whilst there is good evidence that maternal self-reported smoking during pregnancy is associated with decreased birthweight, there is now increasing evidence for an associated increased risk of overweight in childhood. This study aimed to examine the relationship between maternal cotinine concentrations in pregnancy and child weight and BMI changes from birth to 36 months of age.

Methods: There were 970 mother-child pairs identified from the GUSTO birth cohort. Cotinine levels in maternal plasma collected at 26-28 weeks of gestation were measured by LC/MS/MS with a detection limit (LOD) of 0.17 ng/mL. Offspring weight and length were obtained at birth and at age 3, 6, 9, 12, 15, 18, 24 and 36 months. All subjects were categorized into 4 groups by cotinine levels and history of ETS exposure; Group 1: cotinine below LOD and no exposure to ETS
(n = 511); Group 2: cotinine below LOD but self-reported ETS (n = 284); Group 3: cotinine concentration 0.17-13.99 ng/mL (n = 139); Group 4: cotinine concentration equal to or above 14 ng/mL (n = 36), which is consistent with active smoking. Age- and sex-specific z-scores for weight and BMI were calculated using the WHO 2006 reference. The associations of maternal circulating cotinine with 1) offspring weight (Fig. A) and BMI (Fig. B) at each time point were estimated using multivariable regression and 2) weight (Fig. C) and BMI (Fig. D) changes from birth to 36 months was analyzed using linear mixed effect models.

Results: Compared with Group 1, maternal circulating cotinine ≥ 14ng/mL (Group 4) was associated with a reduction of 180.8 (95% CI -309.87, -51.68) grams in birthweight and 0.44 (95% CI -0.86, -0.01) kg/m² in BMI at birth, after adjusting for infant sex, gestational age at birth, ethnicity, maternal age, education level, parity and maternal BMI in the 1st trimester. However, across 3 to 36 months, there were no statistically significant differences in z-scores for weight and BMI between Group 1 and Group 4. In contrast, offspring in Group 3 had a higher z-score for BMI at 6 months [β 0.25 (95%CI 0.01, 0.49)], 15 months [β 0.36 (95%CI 0.13, 0.59)], 18 months [β 0.33 (95%CI 0.33 (0.07, 0.59)], 24 months [β 0.34 (95%CI 0.08, 0.59)] and 36 months [β 0.40 (95%CI 0.15, 0.66)] compared with Group 1, amounting to an average increase of 0.16 (95%CI 0.0002, 0.32) kg/m² from birth to age 36 months. Over the 36 months, there was significantly faster weight gain in Group 4 offspring and an increasingly higher BMI in Groups 3 and 4, compared to Group 1.

Conclusions: These findings suggest that increased prenatal cotinine exposure is associated with faster weight gain and greater BMI in offspring during early childhood, even at relatively low cotinine levels consistent with mere ETS exposure without active smoking. Whether in utero programming is a contributory factor to this phenomena in addition to post-natal confounding lifestyle factors remains to be elucidated.

The associations of maternal circulating cotinine with Offspring weight and BMI.

Effect of maternal exercise during obese pregnancy on the cardiovascular health of male mouse offspring


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Background: The prevalence of obesity amongst women of childbearing age has increased dramatically over the past few decades. Recent studies in the UK suggest that over half of women are now overweight or obese during pregnancy. This is of concern as obesity during pregnancy is associated with short and long term consequences for both mother and child. Studies in humans have suggested that individuals born to obese mothers are at increased risk of cardio-metabolic disease and death from cardiovascular disease. Studies in animal models provide strong evidence that these effects are mediated by non-genetic programmed mechanisms. It is critical that suitable interventions are identified to prevent this epigenetic propagation of obesity and cardio-metabolic dysfunction from mother to child. Exercise is one potential intervention strategy. This study therefore aimed to investigate the effect of exercise during obese pregnancy on the cardiovascular health of the offspring.

Methods: A diet-induced obesity mouse model was used where female dams are maintained on an obesogenic diet (high fat and sugar) for approximately six weeks prior to pregnancy. For the exercise intervention, daily treadmill exercise (5 days/week) was started one week before mating and continued until gestational day 17 of pregnancy in obesogenic diet fed mice. Offspring of these dams were compared to the offspring of control-fed dams. Both groups of offspring were weaned onto standard laboratory chow fed ad libitum. Male offspring were studied at 8 weeks of age. Cardiomyocyte area was assessed by manually circumscribing cell borders of mid-cardiac sections stained by wheat germ agglutinin. Expression of genes implicated in pathological cardiac hypertrophy were measured by RT-PCR. Blood pressure was measured non-invasively through tail-cuff photoplethysmography.

Results: Offspring born to obese dams (ObeseOff) displayed pathological cardiac hypertrophy, demonstrated by increased heart weight (p < 0.001) and cardiomyocyte area (p < 0.05) alongside re-expression of fetal genes including atrial natriuretic peptide (Nppa) (p < 0.001) and β-myosin heavy chain (myh7) (p < 0.05). Maternal exercise prevented all measured markers of cardiac hypertrophy in the offspring. ObeseOff had increased systolic blood pressure compared to control offspring (101 ± 2.2 versus 131 ± 6.2 mmHg) (p < 0.01). This was not corrected by maternal exercise intervention.

Conclusions: Maternal exercise prevented the development of cardiac hypertrophy in offspring exposed to maternal obesity. However, offspring blood pressure remained elevated suggesting that pressure overload did not drive the structural changes in the heart. These findings demonstrate that maternal exercise...
during an obese pregnancy has therapeutic effects on the cardiovascular health of the offspring; however further work is needed to understand the underlying mechanisms.

LM1.03 - DOHaD Australia and New Zealand symposium

LM1.03.11

The Importance of Birth Cohorts in DOHaD Research (an Australian and New Zealand Perspective)

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This Symposium, hosted by the DOHaD Society of Australia and New Zealand, will highlight the critical role that longitudinal, and in some cases, transgenerational, birth cohorts have played (and continue to play) in DOHaD Research in Australia and New Zealand. The Symposium will feature presentations on several of the prominent birth cohorts from the region, including:

The Raine cohort and the intergenerational cycle of obesity
The role of long-term cohort studies for evaluating the impacts of ART/IVF
The Adelaide Women’s Health Study
The Aboriginal Birth Cohort
the PETS (twin cohort study)
Growing Up In New Zealand Study

The symposium will comprise of short presentations by each of the speakers, with a focus on the role that each cohort/study has played in supporting the DOHaD concept, and providing evidence regarding critical windows/potential interventions. This will be followed by a panel discussion with all speakers, encouraging audience participation/discussion.

We look forward to welcoming you to the Symposium.

LM1.03.01

Aboriginal Birth Cohort Study

G. Singh

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Background: Aboriginal Australians fare worse than other Australians on almost every measure of physical and mental health. A greater burden of disease is evident at both ends of the life course, with higher rates of preterm birth and low birth weight babies at the start of life and higher rates of chronic diseases such as diabetes, cardiovascular and renal disease at the end of life. The core objective of the Australian Aboriginal Birth Cohort (ABC) is to examine the effect of early life events and conditions on later health in this high risk population.

Methods: The ABC is recognised as the largest and longest running prospective birth cohort of Indigenous Australians. A total of 686 babies born to Aboriginal mothers (a representative sample of the 1238 eligible babies) recruited at Royal Darwin Hospital (RDH), between January 1987 and March 1990. Subsequent follow-up has occurred at Wave-2 (mean age 11.4 years: 85% of living participants), Wave-3 (mean age 18.2 years: 71% of living participants) and Wave-4 (mean age 25.4 years: 71% of living participants). To date there have been 39 deaths, therefore 647 people are available for future follow-up. Core data obtained at each follow-up includes anthropometry (weight, height, head, mid upper arm, waist circumferences, fat percentage), socioeconomic measures, renal (size and function), metabolic, cardiovascular and haematological biomarkers. Additional markers were included. At Wave-2, puberty stage and respiratory function were collected. Wave-3 saw expansion to include oral health, lifestyle and emotional status, iodine status with thyroid ultrasound, long term immunity to Hepatitis B vaccination at birth, cognitive and novel cardiovascular markers. In Wave-4, in addition to the above, nutritional intake, stress and inflammatory markers were added.

Results: Fetal Growth Restriction (FGR) rates were high (25%) and major risk factors were maternal smoking, undernutrition and age <20 years. At 11, 18 and 25 years participants who had been FGR at birth were still shorter and lighter than non-FGR babies. Although undernutrition is still present at 25 years in this population, the rates of overweight are rising. The high risk combination for chronic disease, of FGR with later obesity, was rare in this cohort. The prevalence of chronic disease markers at adolescence and young adulthood was low. In cross-sectional analyses, current weight and not birth weight has been the predominant determinant of early biomarkers of chronic disease. Predictors of chronic disease risk factors, particularly as they relate to chronic kidney disease will be discussed in greater detail.

Conclusions: Although the prevalence of chronic disease markers at adolescence and young adulthood was low, these are increasing with age. Current weight continues to be the predominant determinant of biomarkers of chronic disease. The major strengths of the study are the availability of reliable gestational age, the direct standardised collection of comprehensive health data obtained via face-to-face health checks by a core group of trained researchers and excellent retention rates despite logistical challenges.

LM1.03.03

Growing up In New Zealand Study

S. Morton

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Background: New Zealand is regarded as a “great place to raise kids”, but international rankings of child health tell a different story. New Zealand children rank bottom of 24 OECD countries for non-intentional injury, infant mortality and immunisation rates. Hospitalization rates for respiratory and skin infections are twice those of Australian children. Overall population statistics hide large health inequalities, with Māori and Pacific children most vulnerable to a poor start to life.
Method: Growing Up in New Zealand is the contemporary longitudinal cohort study that tracks the health and development of 6853 NZ children from born in 2009 and 2010, in the context of their diverse families and their wider social environments. The longitudinal study was explicitly established to provide population relevant evidence to inform new cross-sectorial policies that could improve population wellbeing and reduce inequalities in health and development from birth. Information is currently available from children, families and routine record linkage over their first five years of life. Factor analysis and stepwise multivariable regression were used to examine the capacity of twelve routinely available antenatal maternal factors to define population sub-groups of NZ children most vulnerable to poor health and development from before they were born. Risk factors included teenage motherhood, lower socioeconomic status, partnership status for mothers, antenatal maternal depression and maternal smoking.

Results: Risk factors for vulnerability clustered with no single risk factor being sufficient alone to efficiently identify vulnerable population sub-groups of pregnant mothers. Three common clusters occurred however which together explained just less than 50% of the population distribution of all factors. Using longitudinal exposure data over the first 1000 days of life we noted that cumulative exposure identified vulnerability more efficiently than any single time point, and also that Māori and Pacific mothers and children experienced the greatest cumulative burden of adversity. Exposure to a greater cumulative exposure in the perinatal period in particular was associated with lower birth weight, reduced breastfeeding duration more childhood infections and admissions to hospital as well as with more likelihood of abnormal behaviours in the pre-school period.

Conclusions: Identifying vulnerable children effectively from before their birth using clusters of routinely available maternal risk factors offers an opportunity to optimise life course wellbeing and give all NZ children the best start in life. Using multi-disciplinary population relevant evidence on a cohort of almost 7000 NZ pre-school children it is clear that cumulative exposure to disadvantaged environments from before birth leads to some population subgroups in New Zealand falling behind before they can even begin life’s race. Additionally the information from the cohort about “what works” for children who are resilient in the face of this cumulative adversity can provide us with novel ways to support all NZ children and families better right from the start.

Studies of the role of epigenetics in the early life origins of disease using a twin cohort
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Background: The Peri/postnatal Epigenetic Twins Study (PETS) is a unique cohort of 250 mothers and their twins. Women were recruited from three Melbourne hospitals midway through their second trimester, which enabled measurement of maternal shared and fetal nonshared factors at multiple time points. We collected multiple biospecimens at birth (cord blood, cords, placenta and buccal tissue) and repeat samples when twins were 18 months of age (blood and buccal swabs) and 6 years of age (blood, buccal swabs, saliva, tooth plaque, stools). Our aim is to use the power of twins to shed light on the early life origins of chronic diseases, for example, using a within-monozygotic-twin pair design to study the role of nonshared environment - the largest component of variation of NCDs – in DOHaD. Specifically we are investigating the effect of environment in the first 1000 days of life on epigenome and microbiome complexity and on specific outcomes including oral health, BMI, blood pressure, and neurodevelopmental disorders in children.

Methods: We performed both gene-specific and genome-wide analysis of the epigenetic mark of DNA methylation in multiple cell types using Sequenom MassArray Epityper and Illumina Infinium arrays. Data were regressed against multiple shared maternal factors (e.g. IVF, folate intake, gestational diabetes) and placenta weights, specific to each twin. We analysed microbiomes using 16S rRNA sequencing.

Results: Twin pairs exhibited a wide range of within-pair epigenetic discordance at birth, which overlapped with that observed between unrelated individuals. Using gene-specific analysis we found that that certain gene ontologies are consistently variably methylated within pairs in all tissues, and that genetic and intrauterine environmental influence on DNA methylation varied throughout the genome. Using regression analysis, we identified genes whose expression and methylation levels correlated with birth weight in MZ pairs. These were enriched in functions related to nutrient metabolism and response to environmental agents. We also found an associations between placental weight and gestational diabetes and DNA methylation at birth and tissue-specific association with other factors. Similarly to the epigenome, the largest component of variation in the plaque microbiome, was nonshared environment.

Conclusions: Our data support the idea that genetic, shared (maternal) and nonshared (placental) environmental factors impact on the developing epigenome and microbiome, with the largest component being nonshared environment. They also suggest that multiple early environments may be epigenetically reprogramming genes involved in metabolism, which may provide a mechanism for the early origins of cardiometabolic disease.

Fertility in the fast lane: 21st Century technologies and reproductive outcomes
M. Davies
Robinson Research Institute, ADELAIDE, Australia

Technological innovation has transformed patterns of fertility globally, with improved perinatal outcomes. However, the
same period has seen older age at birth, increased use of assisted reproductive technologies, and epidemics of adverse lifestyle factors such as obesity.

Research on the impact of these factors on the reproductive health of contemporary women and the future health of their children is fragmented, giving rise to poorly focussed and inefficient interventions. This presentation integrates a series of overlapping cohort studies drawn from the same population base to develop a synthetic lifecourse cohort to identify environmental factors that contribute to impaired fertility, adverse pregnancy outcomes after infertility treatment, and the consequences of treatment for the enduring health of the offspring.

We have identified the impact of work-place conditions, specifically night shift, on female reproductive health and need for infertility treatment; the contribution of maternal factors, such as obesity to growth trajectories and child obesity and subsequent PCOS; and the contribution of assisted reproductive technologies such as IVF to adverse outcomes for mother and child including low birth weight, low gestational age, neonatal death, cerebral palsy, and birth defects.

**LM1.03.09**

**The Western Australia Pregnancy Cohort (Raine Study) and the Intergenerational Cycle of Obesity**

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**Background and Methods:** Between 1989 and 1991, 2900 pregnant women volunteered to be part of the study and were randomized to receive a single prenatal ultrasound scan at 18 weeks pregnancy or 4 scans at 18, 24, 28 and 38 weeks gestation. 2868 babies were born within the study and were examined on the first or second day after birth by a child health nurse. The families then continued with follow-up assessments of their babies. Follow-ups have occurred with these children at 2, 5, 8, 10, 13, 17, 18, 20 and 22 years-old including anthropometry and blood pressure each time. Ultrasound, DXA and MRI measures of adiposity were undertaken at 17, 20 and 22 years-old respectively. Illumina Infinium HumanMethylation450 BeadChip analysis was undertaken on 1192 individuals at 17 years-old. Between 2014–2017, generation 1 (parents of the Raine Study participants) were invited for assessments including a DXA scan, blood pressure, anthropometric testing, and accelerometry. Currently, generation 3 (children of the Raine Study participants) are being invited for metric testing, and accelerometry. Currently, generation 3 assessments including a DXA scan, blood pressure, anthropometry and blood pressure each time. Ultrasound, DXA and MRI measures of adiposity were undertaken at 17, 20 and 22 years-old respectively. Illumina Infinium HumanMethylation450 BeadChip analysis was undertaken on 1192 individuals at 17 years-old. Between 2014–2017, generation 1 (parents of the Raine Study participants) were invited for assessments including a DXA scan, blood pressure, anthropometric testing, and accelerometry. Currently, generation 3 (children of the Raine Study participants) are being invited for assessment.

**Results:** Investigations from the Raine Study showed for the first time in a western population that both extremes (low and high) birth weight were risk factors for cardio-metabolic disease (U-shaped relationship), confirming that fetal programming occurs in a modern, Western human population. The effects of early life environmental risk factors (such as pre-pregnancy maternal obesity, gestational weight gain, hypertension/pre-eclampsia, and duration of breast feeding) have been demonstrated in the Raine Study. A further critical window for potential intervention that has been heavily investigated in the Raine Study is that of adolescence. In adolescence, the role of smoking, passive exposure to smoking, physical activity levels, alcohol, dietary fructose, depressive and aggressive behaviors, and oral contraception have been demonstrated to affect cardio-metabolic risk. Gender was frequently shown to affect response to these environmental influences. For example females, but not males, who were exposed to passive smoke or smoked themselves had lower HDL-cholesterol at 17 years-old. Genetic and epigenetic influences on fetal programming have also been explored, with contribution to identification of new SNPs and CpGs associated with obesity, and further understanding that preeclampsia and cardiovascular risk share genetic risk factors. Current focus is on dissecting out the interplay between fixed genetic influences, epigenetics and the early life environment on subsequent obesity, using higher order – omics data.

**Conclusions and Discussion:** These data from the Raine Study have contributed to providing evidence for critical windows and potential interventions. The data provides detail pertaining to stratification (for example, by sex) of responses of environment upon obesity-related disease. This generates hypotheses for optimizing and targeting interventions. An important future direction for the Raine and other cohort studies is in contribution to individual participant data (IPD) meta-analyses. The Raine Study is a partner of the LIFE-CYCLE project (EU Horizon2020) (2017-2021), which includes European, UK and Australian pregnancy and child cohort studies combining data on over 250,000 children and their parents. It aims to provide robust evidence on the early life stresses which may affect health trajectories throughout life.

**LM1.04 – DOHaD Africa symposium**

**LM1.04.01**

**International Society of Developmental Origins of Health and Disease: Launch of the DOHaD Africa Chapter**

S.A. Norris

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Africa faces multiple burdens (infectious and noncommunicable diseases). From substantial evidence linking maternal and nutrition exposures that occur during pregnancy and infancy to adult health and disease, the aim of the DOHaD Africa Chapter is to: (i) increase the exposure of DOHaD science across the continent; (ii) see more African researchers contributing to DOHaD; and (iii), applying a DOHaD framework to aid the achievement of the Sustainable Development Goals, and assist in improving health across generations.
To increase DOHaD research and its application in Africa, we need to mobilise multisectoral partners, utilise existing data and expertise on the continent, and foster a new generation of young African scientists engaged in DOHaD. This session marks the launch of the Chapter with information around the Chapter, and invited presentations addressing the value of DOHaD science for Africa, and the importance of integrating maternal mental health into the DOHaD scientific agenda.

**LM1.04.08**

**Association between maternal and household socioeconomic status with birth and infant growth outcomes in sub-Saharan Africa: a systematic review and meta-analysis**

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**Background:** Preterm birth (PTB) and infant malnutrition remain the leading cause of death of children under five years of age in sub-Saharan Africa (SSA), with almost half (49%) of these deaths occurring within the first year of life. If the critical period of growth and development is identified in the first 1000 days of life (from the conception to two years of life), the critical period of life where a majority of deaths appears still between the birth to one year of life. Maternal undernutrition has an impact to the nutritional status of fetus, newborns and infants. Socioeconomic status (SES) has been shown as a determinant of overall health status (maternal and child); however, little is known on the relationship between maternal and household SES and both birth outcomes and infant growth during the first two years. There is no consensus about how to evaluate the SES in different context and, any study has focused on both these outcomes regarding the particular first year of life. This systematic review (SR) and meta-analysis assesses the association between maternal socio-demographic characteristics and household SES under two years of life in sub-Saharan Africa, and the following outcomes: Preterm Birth (PTB), low birth weight (LBW), small for gestational age (SGA), stunting, wasting and underweight. Socioeconomic factors will include: maternal education, employment, marital status, household assets, household size and income.

**Methods:** A SR protocol was developed apriority, and registered on Prospero. Three electronic databases (PubMed, Scopus and Science direct) were used for looking for published citations. The combination of keywords was identified at the same time the SES (maternal education, maternal occupation, income, marital status, household wealth), the form of outcomes (low birth weight, small for gestational age, preterm birth, stunting, wasting, underweight) and Africa. All identified citations were imported into Endnote reference manager and assessed by two independent reviewers (NBC, MD). Eligibility criteria include all studies published from 1990, dealing with association between pre-specified maternal or household SES and outcomes and, leading in sub Saharan African countries. Then, full texts of included relevant studies were retrieved. The quality of their body evidence is systematically assessing by the Agency for Healthcare Research and Quality (AHRQ) approach. Pre-defined relevant SES and outcome data were extracted by NBC and MD, and are being summarized, synthesized and statistically combined using a meta-analysis. This SR will be reported according to the (PRISMA) guideline.

**Results:** The search identified 1969 citations, [Scopus = 1051 (53.4%), Pub med = 816 (41.4%), Science direct = 102 (5.2%)], of which 1141(58%) duplicate references where excluded, 828(42%) citations were screened for final inclusion into the review.

**Conclusion:** The results of the review are to follow.

**LM1.04.10**

**Proposal to investigate the iodine status and thyroid function of South African pregnant women and the impact on their offspring**

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**Background:** During pregnancy requirements for iodine is increased due to increased maternal thyroid hormone production and several other factors. In South Africa pregnant women are not routinely screened and monitored for iodine status, possibly because iodization of household salt is mandatory. Therefore data on iodine status among pregnant women are scarce. Throughout pregnancy, iodine is crucial for the synthesis of maternal thyroxine, which is transferred to the foetus in early gestation and is essential for foetal growth and brain development. Deficiency during this crucial period may lead to irreversible brain damage, and also low birth weight in infants. We will assess iodine status including thyroid hormone function throughout gestation, and further determine associations with offspring growth and development from birth until late adolescence. This study will be nested within a larger birth cohort study (Future Impact Today), aimed at investigating the impact of early environment on the short and long-term outcomes of health and wellbeing.

**Methods:** The proposed research will be designed as a longitudinal observational cohort. Pregnant women (before 14 weeks gestation) and later their newborn infants (n = 3000), will be recruited from two areas in the Free State Province, South Africa. These areas will allow for urban and rural comparisons. Data on iodine intake and thyroid functioning will be collected and analysed in seven stages: (1) Antenatal (during each trimester); (2) Birth; (3) Follow up after delivery; (4) Early childhood– 2 to 6 years; (5) Late childhood– 7 to 10 years; (6) Early adolescence– 11 to 15 years; and (7) Late adolescence– 16 to 20 years. Spot urine samples will be collected from pregnant women and offspring for assessment of urinary iodine concentration (UIC). For thyroid
Fetal exposure to PCBs and alteration of DNA methylation in umbilical cord found in birth cohort in Japan

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Background: In the previous studies, we have reported that environmental contaminants such as polychlorinated biphenyils (PCBs) were detected in maternal blood, umbilical cord and cord blood (Fukata et al., 2005). PCBs are concerned to affect human reproductive and developmental health because of their endocrine-disrupting effects (Mori & Todaka, 2011). A birth cohort study, Chiha Study of Mother and Children’s Health (C-MACH), focusing on environmental health effects on fetuses and involving multomics analysis has been conducted since 2014 (Sakurai et al, 2016). As European birth cohorts using a meta-analysis indicated a negative relationship between PCB exposures with birth weight (Govarts et al, 2012), in C-MACH also, it was revealed that the maternal PCB exposure caused low birth weight of newborns (Eguchi et al, 2017). It is possible that the fetal PCB exposure might inhibit the healthy growth of fetuses through epigenetic alteration (Fukata and Mori 2004). However, the association between maternal PCB levels and fetal DNA methylation tendency has not been studied well. In this study, we investigated the relationship between PCB levels in maternal serum and DNA
methylated tendency in cord tissue (a part of fetus) using 450K-methylation array analysis.

**Methods:** In this study, cohorts from C-MACH participants were used for investigating PCB levels in maternal serum and DNA methylation tendency of cord tissue. Human serum samples (23 maternal sera: sampling at a gestational age of 32 week) and paired cord tissue (n = 23) were collected from participants (Sakurai et al. 2016). Informed consent was obtained from the participants. DNA methylation analysis was performed as previously described (Tachibana et al. 2017). The DNA methylation profiles of the umbilical cords were determined using the Infinium Human Methylaion450 BeadChip (Illumina). The methylation levels at each CpG quantified with average β values were calculated using GenomeStudio 2011.1 (Module M Version 1.9.0; Illumina). This study was approved by the Biomedical Research Ethics Committee of the Graduate School of Medicine, Chiba University (ID 451, 462 and ID 502).

**Results:** The average age, pre-pregnancy body mass index (BMI), parity, and serum PCB concentrations in mothers of the participants were 32.4 years old (standard deviation [SD]: 3.58), 20.6 (SD: 2.54), 1.09 (SD: 1.35) and 0.36 ng g⁻¹ wet wt (SD: 0.18), respectively. In this prediction model, DNA methylation levels of six CpG sites in cord tissue (cg20778915, cg10967430, cg04072301, cg12564102, cg04444959, and cg08695418) were related with PCB levels in the maternal serum. Methylation tendency of cg20778915, cg12564102, cg04444959 and cg08695418 were positively and cg10967430 and cg04072301 were negatively related with maternal PCB levels.

**Discussion and conclusions:** These methylated sites might affect angiogenesis, glycolysis, and myoblast differentiation, indicating maternal PCB levels might be related to their offspring’s DNA methylation tendency. It is possible that these six sites might be biomarker of negative health effects on the next generation.

**LM1.05.05**

Understanding of DOHaD concepts in Japanese pregnant women studied using a standardised questionnaire for international comparison

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**Background:** Evidence to support the DOHaD theory accumulates, and preemptive medicine for prevention of non-communicable diseases (NCDs) is needed. In Japan, there is growing concern that high proportions of thin women in their twenties and thirties, and of low birth weight infants may lead to an increase in NCDs in the future. This research is part of a collaborative research: International Comparative Project on Understanding of DOHaD, between University of Auckland and Fuji Women’s University. The purpose of this study is to obtain basic data on understanding of DOHaD concepts in pregnant women in Japan.

**Methods:** The targets are all pregnant women (about 300/year) in Ishikari-shi (population approximately 59,000), Hokkaido, Japan. When they notified the municipal office of their pregnancy and received maternal and child health handbooks, they were asked to answer a questionnaire. The questionnaire consists of ten statements utilizing Likert attitude scales and contains the statements that the food a mother eats during pregnancy affects the health of the baby during the pregnancy, the first two years of their life, throughout childhood, or adulthood. The response choices were Strongly Agree, Somewhat Agree, Don’t know, Disagree, and Strongly Disagree. The survey using the questionnaire started from June 2016 and is still in progress.

**Results:** From June 2016 to March 2017, thirty-four pregnant women answered the questionnaire and the response rate was 17.4% (the total number of pregnant women was 195). The pregnant women recognized that a mother’s nutrition during pregnancy impacts the health of her fetus. However, they have limited awareness of the association between early-life nutrition and later-life NCD risk. Furthermore, they perceived that nutrition until two years of life has less impact on life-long health than on childhood health.

**Conclusion:** Japanese pregnant women in this study consider a mother’s nutrition during pregnancy to be a much less important influence on lifelong health than on health during fetal period. Dissemination of DOHaD concepts to the Japanese society and introduction of DOHaD education to a wide range of health professionals may be warranted.

**LM1.05.07**

A maternal diet with moderately high-fat modulates adipose gene expression of glucose, lipid metabolism in the offspring

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**Background:** Maternal dietary modifications determine the susceptibility to metabolic diseases in adult life. We investigated the effect of maternal moderately high-fat diet on gene expression of adipose tissue in her offspring. **Methods:** Female 6-weeks-old mice were fed either normal chow diet (ND: 10 kcal% fat) or high-fat diet (HFD: 45 kcal% fat) for 4 weeks before mating and throughout pregnancy. Gene array experiments were performed in the visceral fat tissue of the male offspring mice.

**Results:** At 10-week-old, the weight was not different between the ND and HFD offspring. However, systolic blood pressure was significantly higher in the HFD offspring than in the ND
offspring. Although glucose tolerance was significantly lower in the HFD offspring than in the ND offspring, insulin tolerant test did not show significant difference among two groups. Re-feeding test for offspring from the HFD group showed more insulin resistant in lipid metabolism compared with that in the ND group. Database for Annotation, Visualization and Integrated Discovery analyses indicated that all differentially expressed genes of the offspring between the two groups were mapped to some pathways. Not only lipid pathways including free fatty acid and cholesterol, but also carbohydrate pathways including glycolysis and gluconeogenesis were modified by high-fat diet pregnancy mouse model.

Conclusions: A maternal high-fat diet before and during pregnancy can modulate adipose glucose, lipid homeostasis, and gene expression in lipid signaling pathway.

LM1.05.09

Undernourishment in utero as well as endoplasmic reticulum stress alleviation affects lipid profile of the mice fatty liver

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Background: Recently we reported that the undernourishment in utero primes hepatic steatosis under obesogenic diet and alleviation of Endoplasmic Reticulum (ER) stress by a chemical chaperon improved the adversity in mouse model (Sci Reports; 16867, 2015). Hepatic steatosis was reported to be related to the defects in metabolic pathways that involve hepatic accumulation of Lipid Droplets (LD) however the underlying pathophysiology is unknown. To evaluate the mechanism underlying we aimed to study the cell size and ratio of lipid deposition in the hepatocytes of undernourishment in utero and performed Liquid Chromatography Mass Spectrometry (LCMS) to identify defect in metabolic pathways.

Method: The study included sampling of blood and liver of CN57Bl mice (n = 16) aged 22 weeks, pups (group A; n = 8) obtained from dams with free access to food with normal nutrition (NN) and pups (group B; n = 8) from dams with 40% caloric restriction with undernutrition (UN). After weaning (up to 8 weeks) pups were fed high fat diet (HFD) through 22 weeks and from 17 weeks onward we have subdivided both group to vehicle (Veh) and Tauoursodeoxycholic acid (TUDCA, a chemical chaperon of ER stress) administrated group. Then we randomly selected 4 pups per each group and measured liver weight (gm), liver weight-bodyweight ratio (%), Triglyceride content (mg/gm tissue), total Triglyceride (mg) were measured. Slides were stained with Hematoxylin and Eosin (HE) and Oil Red O stain and using WinRoof software we have calculated (in 3.88mm² field per slides) the mean size (μm²) of the hepatocyte, percentage of the area of lipid deposition per cell size (%) and area of lipid deposition per cell numbers (μm²/cell number). LCMS was done by Q Exactive Benchtop Orbitrap LC-MS/MS System (Thermo fisher).

Result: In UN in utero pups Liver weight, liver weight-bodyweight ratio, Triglyceride content and total Triglyceride amount (P < 0.0001) was significantly elevated. Moreover UN in utero induced enlargement of hepatocyte size (group A [NN] vs group B [UN]; mean size = 1745 ± 187 (SD) μm², 2250 ± 147μm², p < 0.01, respectively) and increase lipid deposition by 63.7% (group A [NN] vs group B [UN] 35.4 ± 12.8%, 46.4 ± 7.8%, p < 0.01). Intriguingly administration of TUDCA improved the condition by reduction of cell size by 19.33% (P > 0.05) and lipid deposition by 82.2% (P < 0.001) (group B[UN-Veh] vs group B[UN-TUDCA]). LCMS analysis showed that UN in utero increased 9 lipid metabolites, 7 of them were significantly reduced by TUDCA treatment; however 2 of them further increased with all the improvement of total triglyceride deposit. On the other hand UN in utero also caused reduction of 14 lipid metabolites all of which were increased by TUDCA administration. Their direction of changes was totally opposite to the changes of triglyceride deposit, suggesting the dynamic changes of lipid composition during the deterioration as well as improvement of hepatic fat deposit induced by undernourishment in utero or ER stress alleviation. Conclusion: Undernourishment in utero significantly enlarged hepatocyte and aggravated intercellular lipid deposition in later life, concomitant with dynamic changes of lipid composition, presumably via integration or alleviation of local ER stress.

LM1.05.11

Japan Environment and Children’s Study (JECS) - Study design and present status

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Background: With increasing public concern over environmental effects on children’s health and development, recent political initiatives have encouraged research on children’s environmental health. Especially a series of the G7/8 Environmental Ministers’ Meetings have emphasized the importance of international cooperation on securing safe environment for children and future generations. The G7 Environment Ministers’ Meeting held in Toyama, Japan in May 2016 reaffirmed their commitment to the better understanding of chemical risks on children’s health and development. Taking this movement into consideration, many children’s studies have been conducted worldwide. In Japan, the Ministry of the Environment started a nationwide 100,000-scale birth cohort study named
Japan Environment and Children’s Study (JECS) in 2011. JECS is designed to evaluate the effect of the environment on children’s health and development. This presentation aims to report the study design and the present status of JECS.

**Methods and Results:** Expecting mothers were recruited for JECS in 15 Regional Centers located nationwide. The Main Study involves all the 100,000 participants. The Sub-Cohort Study is formed with 5,000 children extracted from the Main Study. The health outcomes are measured primarily through questionnaires and medical record transcriptions, while medical examination and clinical blood testing are also performed. JECS priority health outcomes are: Reproduction and pregnancy complications; congenital anomalies; neuropsychiatric/developmental disorders; allergy and immune system disorders; and metabolic and endocrine system dysfunctions. In JECS, the environment is defined broadly such as global/ambient environment including chemical substances and physical conditions, built environment, behaviours/habits, socio-economic factors, family/community support and genetic factors. The exposure assessment is conducted through chemical analyses of biospecimens collected from the participants (pregnant women, their children and the children’s fathers), questionnaires, environmental monitoring and modelling/computer simulations. The biospecimens include blood, urine, umbilical cord blood, breast milk and hair. For the Sub-Cohort Study, more extensive methods of measurement for both environmental factors and health outcomes are employed, such as ambient air monitoring, a neurodevelopmental test, pediatricians’ examinations and blood tests. Maternal whole blood samples of the mid-late trimester period from all participants were analyzed for mercury, lead, cadmium, manganese and selenium. Nicotine metabolite, i.e. cotinine, was measured in maternal urine samples from all participants as well. Completed was the collection of outcomes related to pregnancy, birth and congenital anomalies. In March 2014, the three-year recruitment was completed, achieving the target of 100,000 registration of pregnant women. As of July 2017, children have become 3-6 years old, and more than 90% of the participants are being followed.

**Conclusions:** JECS is successfully in progress, and expected to identify environmental factors that affect children’s health and development. The mission of JECS is to provide scientific basis to decision makers who design better chemical risk management strategies.

**PA1.06 – Genetics of DOHaD**

**PA1.06.01**

*Mendelian Randomisation in a DoHaD context: what does this mean?*

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Mendelian randomisation (MR) has become increasingly popular as an analytical technique in epidemiology given the relative efficiency of the method and the chance of asserting causality in otherwise complex epidemiological problems. In simple form, a genetic proxy for a risk factor of interest is used to re-estimate observational associations between that risk factor and a health outcome. Despite the relative lack of analytical power and the complexities of genetic effects, the potential benefits of a randomly assigned well measured risk factor proxy are substantial and can lead to causal estimates where other approaches cannot. In a developmental origins model, MR can play a role and be a tool for unpicking the importance of early life factors in shaping later life outcomes. I will describe three scenarios where this is pertinent, but also where there are complications to the application of MR that need to be considered. The three scenarios follow: (i) using genetic predictors of environmental risk factors for the foetus in utero, (ii) using genetic predictors for birthweight on applied genetic epidemiology (and potentially MR) and (iii) analysis of the impact of adult derived genetic predictors or cardiovascular risk in early life. These examples each have the ability to comment on the importance of early life events. In utero exposures can be modelled causally in light of later life outcomes, though have the complications of parental genotype correlation; birthweight predictors from genomewide association study analyses exit, but have complex meaning when considering developmental trajectory; adult genetic predictors are manifest in early life, but note the lack of temporal consistency in genetic effects. Together these will give an illustration of what MR means in a DoHaD context and advance the potential, but also the complications of MR application.

**PA1.06.03**

*Assessing causality in associations between maternal adiposity and perinatal birth outcomes in mothers and offspring: A Mendelian randomization approach*

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**Background:** Observational studies consistently suggest that maternal obesity is related to a number of adverse perinatal outcomes. However, which of these are causal and which are due to confounding is unclear. We aimed to carry out Mendelian randomization (MR), which uses genetic variants robustly associated with the exposure of interest as instrumental variables (IV), to determine the causal effect of maternal BMI on a number of obstetric and perinatal outcomes.

**Methods:** Data from the Avon Longitudinal Study of Parents and Children and the Born in Bradford cohort (White European individuals only) were used (N = 3,554 to 9,480 for different outcomes). First, multivariable regression associations between maternal BMI and each outcome were examined adjusting for a range of potential confounders. Second, we used
97 established genetic variants that have been shown to be robustly associated with BMI in a weighted allele score in inverse variance IV analyses to obtain causal estimates of maternal BMI on each of the outcomes. We used MR-Egger and weighted median IV analysis in sensitivity analyses to explore potential bias due tohorizontal pleiotropy. For outcomes where offspring genetic predisposition for BMI was likely to play a role, MR analyses were adjusted for offspring genotype.

Results: In standard multivariable analysis, a 1 standard deviation (SD = 4.95 kg/m²) increase in maternal BMI was associated with a 0.12 SD (95% CI 0.10-0.14) increase in offspring birthweight, 1.64 (95% CI 1.57-1.75) greater odds of gestational hypertension, 1.34 (95% CI 1.25-1.43) greater odds of induced labour and 1.36 (95% CI 1.28-1.46) greater odds of macrosomia. In MR analyses using the 97 variant genetic risk score, a 1 standard deviation increase in maternal BMI was associated with a 0.16 SD (95% CI 0.04-0.28) increase in offspring birthweight, 1.84 (95% CI 1.12-3.03) greater odds of gestational hypertension, 1.55 (95% CI 1.07-2.23) greater odds of induced labour and 2.05 (95% CI 1.12-3.82) greater odds of macrosomia. Results from MR Egger regression and weighted median were generally consistent and did not suggest strong bias by pleiotropy. We also found multivariable regression evidence for positive associations of maternal BMI with birth ponderal index, caesarean delivery, combined pre-eclampsia and gestational hypertension, and membrane rupture before onset of contractions, and inverse associations with Appgar score and breastfeeding. MR estimates for these were all statistically consistent, but the 95% confidence intervals were wide and included the null. In multivariable analyses, maternal greater BMI was associated with shorter gestation age and greater risk of preterm birth, whereas the opposite was true for MR analyses. In these two studies we had insufficient data on gestational diabetes to explore associations with it.

Conclusions: Our findings support a causal effect of increased maternal BMI on several important adverse obstetric and perinatal outcomes with greater BMI generally resulting in poor perinatal health. Our MR analyses are underestimated and we are currently working with more studies in a large consortia to better address this research question.

PA1.06.04
Genome-wide association study identifies three novel genetic determinants of dental maturation
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Background: Advanced or delayed physiological age may influence significantly health and disease processes. Physiological age can be estimated using several parameters including dental age (DA). Previous meta-analyses studying “Number of Teeth at 15 Months” (NT15M) and “Age at First Teeth Eruption” (AFTE) have identified 15 loci. We performed a genome-wide association study (GWAS) meta-analysis to identify genetic determinants in children of school age.

Methods: Discovery GWAS of DA was performed in the Generation R study, a multiethnic pregnancy cohort in Rotterdam, The Netherlands. We included 2,793 children with mean age 9.82 (SD = 0.34) years. DA was determined from dental panoramic radiographs using the Demirjian method. Participants were genotyped with the HumanHap 610K platform, imputed to the 1000GP reference panel. Analysis was adjusted for age, sex, height, BMI and 20 genomic principal components; genome-wide significance (GWS) was set at P < 5 × 10⁻⁸. Replication of signals associated with DA was pursued using summary level results from the published GWAS meta-analysis of the ALSPAC and NFBC1966 studies (n = 12,012) studying NT15M and AFTE. Fisher’s combined probability test weighted by sample size, implemented in METAL, was used for the combined meta-analysis.

Results: Top signals mapped to 16q12.2 (IRX5: P = 1.1 × 10⁻⁷) and 17p11.2 (SREBF1: P = 9.1 × 10⁻⁸) loci associated with advanced DA. Significant evidence for replication of both GWAS signals was observed in the previous NT15M meta-analysis (IRX5: P = 2.7 × 10⁻⁵ and SREBF1: P = 0.001). In the combined meta-analysis, the top-associated marker in the IRX5-region reached GWS (P = 2.1 × 10⁻⁸). Also, alleles of these markers associated with higher DA were nominally associated with earlier teeth eruption in the AFTE meta-analysis (IRX5: P = 1.5 × 10⁻⁵ and SREBF1: P = 0.002). Furthermore, after genome-wide meta-analysis we identified variants in three novel loci: 16q12.2 (IRX5: P = 3.4 × 10⁻⁸), 7p15.3 (IGF2BP3: P = 2.87 × 10⁻⁸) and 14q13.3 (PAX9: P = 3 × 10⁻⁸).

Conclusion: We describe here three novel loci associated with dental development. These findings provide further understanding into the process of dental maturation in children from early infancy to late school age. Further, these novel loci implicate diverse pathways related to BMI, lipid metabolism, growth hormone/insulin-like growth factors and craniofacial development.

PA1.06.05
Transgenerational programming of methylation and gene expression in the prefrontal cortex (PFC) by glucocorticoids
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**Introduction:** Prenatal exposure to excess glucocorticoids increases risk for neurodevelopmental disorders. Previous research has shown that prenatal glucocorticoid exposure results in offspring that are hyperactive in a stressful environment, and that this behavioral phenotype is transmitted over multiple generations. The PFC is implicated in programming stress reactivity and behavior, and has previously been shown to be affected by prenatal glucocorticoids. We hypothesized that prenatal synthetic glucocorticoid (sGC) exposure programs gene transcription and methylation in the PFC across three generations following paternal transmission.

**Methods:** Pregnant guinea pigs received 3 courses of betamethasone (Beta; 1mg/kg) or saline in late gestation. F1 and F2 male offspring were mated with non-experimental females to generate F2 and F3 offspring. Animals were sacrificed at postnatal day 40, and the PFC was micro-punched from F1(C; n = 4, Beta; n = 4), F2(C; n = 4, Beta; n = 4), and F3(C; n = 4, Beta; n = 4) and RNA/DNA extracted. RNA was submitted for RNA-seq and data analyzed using standard bioinformatics. Methylation analyses were performed using bisulfite converted DNA paired with pyrosequencing of proximal transcription start site regions of target genes. In silico transcription factor binding analyses were undertaken using SABiosciences’ DECODE tool.

**Results:** In F1, 1148 genes were significantly (P < 0.001, FDR < 0.05) differentially expressed following prenatal Beta. Of these, 442 genes were significantly up-regulated, and 706 genes down-regulated. In F2 offspring, 432 genes were significantly (P < 0.001, FDR < 0.05) differentially expressed between Veh and Beta, with 255 genes up-regulated, and 177 genes down-regulated. In F3, 438 genes were significantly (P < 0.001, FDR < 0.05) differentially expressed following prenatal Beta. Of these, 258 genes were significantly up-regulated, and 180 genes down-regulated. 22 genes were significantly differentially expressed across all three generations. 16 out of the 22 significantly differentially expressed genes contained MEF2C binding site within 30kb of transcription start site. Mef2c expression was significantly (P < 0.001, FDR < 0.05) upregulated in F1 offspring, significantly (P < 0.001, FDR < 0.05) downregulated in F2 offspring, and trending towards significantly (P = 0.009, FDR = 0.15) increased in F3 animals. Methylation analyses revealed significant (p < 0.05) changes in methylation that significantly (p < 0.05) correlated in gene expression changes across the generations.

**Conclusions:** This is the first evidence of transgenerational programming of gene expression and methylation in the PFC via antenatal sGC. Further, we identified 22 genes that are differentially expressed across all 3 generations, the majority of which contain a MEF2C binding site within cis-regulatory distance of the transcription start site. Mef2c expression and function can be regulated by glucocorticoids. These findings provide insight into the heritable changes in gene expression affected by prenatal sGC exposure. Further, these data have identified key genes for future investigation as drug and intervention targets.

**PAI.06.06**

**Associations of genetic variants for birth weight with fetal growth measures in the Generation R Study.**

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**Background:** Recent large genome-wide association studies (GWAS) have identified 60 common genetic variants (SNPs) associated with birth weight. A number of these genetic variants are also associated with adult height, blood pressure and type 2 diabetes. Birth weight is the result of fetal growth, but a particular birth weight can be the result of different prenatal growth patterns. To further disentangle the effects of the known birth weight variants on fetal growth at different time points, we studied whether a combination of these genetic variants is associated with fetal growth measures throughout pregnancy.

**Methods:** In a population-based prospective cohort study, GWAS data and fetal growth measures were collected among 5374 singleton live-born children. Information on 59 out of the 60 SNPs were available in our population. A weighted genetic risk score was calculated for each child, based on the number of birth weight increasing alleles for each of the 59 SNPs, weighted by their reported effect sizes. Fetal ultrasound data (gestational age adjusted standard deviation scores (SDS)) were collected in the second and third trimester, and included estimated fetal weight, femur length and head circumference. At birth, we measured weight, total body length and head circumference (SDS). We used multivariable linear regression to study the association of the risk score with each growth measure in the second and third trimester and at birth, with adjustment for sex and ancestry. The association of the genetic risk score with longitudinal growth patterns will be studied using linear mixed models.

**Results:** The weighted genetic risk score was not associated with any of the fetal growth measures in the second trimester. Each additional average risk allele in the risk score was associated with an increase of 0.02 SDS (standard error (SE): 0.003) in estimated fetal weight, an increase of 0.01 SDS (SE 0.003) in head circumference and an increase of 0.01 SDS (SE 0.003) in femur length in the third trimester (all p values < 0.004). Strong associations were observed at birth, with an increase in weight of 0.04 SDS (SE 0.003), in head circumference of 0.02 SDS (SE 0.005) and in body length of 0.03 SDS (SE 0.004) per additional average risk allele (all p-values < 0.0001).

**Conclusions:** Our data suggest that the known genetic variants for birth weight exert their effect on fetal growth in late pregnancy.
Genetic variants and fetal weight. Graphic representation of the association between the genetic risk score (number of weighted risk alleles, x-axis) and weight (estimated fetal weight in second and third trimester and birth weight, in gestational age adjusted SDS, right y-axis), adjusted for sex and ancestry. The lines represent the regression of the mean outcome measure values on the categories of the weighted risk score. The number of individuals in each category is shown in the blue histogram (left y-axis).

PA1.06.07

Genome-wide analysis of H3K27ac reveals differential activity of regulatory regions in placentas of pregnancies affected by fetal growth restriction

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Background: Epigenetic dysregulation in the placenta is suggested to be critical to the disturbed placental development and function underlying the majority of pregnancies affected by fetal growth restriction (FGR). At this moment, no epigenetic marks other than methylation profiles have been studied in of FGR placentas. In this study, we explored whether FGR placentas exhibit specific profiles of histone 3 lysine 27 acetylation (H3K27ac). With this approach, we aimed to identify previously unstudied alterations in promoter and enhancer activity and its effect on corresponding gene expression profiles, to provide novel information on candidate genes and pathways involved in the development and maintenance of FGR.

Methods: For this study we collected placentas obtained after Caesarian sections for severe FGR with an estimated fetal weight < p3 (FGR, n = 5) and controls with uncomplicated pregnancies (n = 4). Using ChIP-seq we catalogued the differential H3K27ac occupancy of DNA regulatory regions in FGR compared to controls and used RNA-seq to identify up- and downregulated genes. Next, we identified genes in the close vicinity to the differentially acetylated regions and performed gene ontology and functional pathway analysis. In addition, we performed transcription factor binding motifs (TFBM) enrichment analysis in open chromatin regions overlapping with differentially acetylated regions.

Results: Analysis of H3K27ac shows 366 hyperacetylated and 604 hypoacetylated regions in FGR of which the 500 most variable regions clearly segregate the FGR and control group in the unbiased PCA analysis (Figure). We identified the hyperacetylated sites to be mostly associated with hypoxia-dependent and immune system-related pathways and hypoacetylated sites to be associated with angiogenesis and immune activation. In the subsequent RNA-seq we found 581 upregulated genes and 528 downregulated genes in FGR. Within the upregulated genes we found 34 genes to overlap with genes in close vicinity of hyperacetylated sites which included genes known to be involved in placental pathology (LEP, FLT1, HK2, ENG, FOS). Functional analyses showed these genes are mainly related to the HIF-1-alpha transcription factor network. In addition, we found 26 overlapping genes within the downregulated transcripts and hypoacetylated sites which we could group as genes encoding secreted soluble factors and extracellular matrix protein and being involved in growth hormone receptor signaling (examples: CSH family, GH and FRZB). Upregulated TFs with enriched H3K27ac of their TFBM are SP1, ARNT2, HEY2 and VDR.

Conclusion: In this study we show that FGR placentas carry specific H3K27ac profile in key regions related to the placental function. Our combined CHIP-seq and RNA-seq analysis reveals genes, molecular pathways and processes likely involved in pathogenesis and/or maintenance of FGR.

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PA1.07 - Biological clock

PA1.07.01

Developmental Origin of Health and Disease (DOHaD) and the circadian clock: later life health effects of gestational circadian rhythm disturbance in mice

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Background: The mammalian circadian clock imposes near 24-hour (circa-dies) rhythmicity on physiology, metabolism and behavior, and allows organisms to anticipate daily recurring environmental changes (i.e., light-dark cycle). To keep pace with the day-night cycle, the clock is daily synchronized by light. Epidemiological and animal studies have associated chronic circadian rhythm disturbance (CRD) in adults (as encountered during shift work and jet lag) with a variety of diseases, including cancer, metabolic syndrome and cardiovascular disease. According to the Developmental Origins of Health and Disease (DOHaD) theory, fetal programming permanently shapes the body’s structure, function, and metabolism. In this scenario gestational environmental factors (e.g., nutritional insults), interacting with the genes, contribute to later life disease. Using an animal experimental approach, we have investigated whether gestational CRD leaves epigenetic marks on the fetal genome that remain present throughout life and that touch upon circadian performance, physiology and metabolism, and as a direct consequence, affect the vulnerability to later-life disease.

Methods: Pregnant C57BL6 mice were subjected to either a constant 12 hr light:12 hr dark (LD 12:12) cycle (control) or to repeated (i.e., once every 3 days) 8 hr phase advanced (eastward) or delayed (westward) jet lag, WJL (LD 12:12). At the day of delivery, dams and their offspring were kept again under a constant light-dark cycle. Offspring was followed in time for the occurrence of health effects.

Results: In the first weeks after birth, both EJL and WJL offspring showed a reduced weight gain, resulting in a life-long reduction in body weight. At the age of 3 months, circadian performance was assessed in male offspring. EJL offspring displayed a faster circadian clock. Furthermore, EJL offspring adjusted more rapidly to an 8 hr phase delay, while, oppositely, WJL offspring took less time to overcome an 8 hr phase delay. Strikingly, analysis of the bones (i.e., femur) of 6-month-old male offspring by microcomputed tomography revealed reduced trabecular and cortical bone mass in EJL offspring. Especially in the diaphysis, endocortical volume, perimeter and moment of inertia (a proxy for bone strength), were significantly reduced, whereas cortical thickness was elevated. Analysis of the cardiovascular system of 9-month-old female offspring revealed left ventricle hypertrophy in the EJL offspring. Epigenetic analysis of the livers of control, EJL and WJL offspring revealed markedly differentially DNA methylation patterns in the livers of EJL and WBL offspring, as compared to control offspring.

Conclusions: We have shown that circadian rhythm disturbance in pregnant female mice by a chronic jet lag affects the development of the circadian system and predisposes to health effects in adult life.

PA1.07.05

Impact of postnatal light conditions on development and later life health


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Background: The circadian clock significantly impacts health during the life course. Human and animal studies showed that genetic defects, clock genes and circadian disruption by chronic jet lag or long-term shift work increase the risk of disease, e.g., metabolic syndrome, cardiovascular disease and cancer. Importantly, studies of preterm infants have shown that light conditions in the Neonatal Intensive Care Unit (NICU) exert short-term (e.g., recovery and weight gain) and long-term (i.e., sleep alterations) effects, with cycling light favorable over constant light or (near) dark conditions. Yet, the impact of abnormal postnatal light conditions on development and on later-life health remain largely unexplored. As a consequence, predictive markers for health risk in relation to the early life light environment are currently missing.

Animal studies have shown that postnatal light conditions permanently modulate circadian clock performance, pointing to a programming effect on the developing circadian system. In line with this is the observation that otherwise arrhythmic Cry1/Cry2 double KO mice develop a normal circadian rhythm when exposed to continuous light during the first weeks after birth. This finding leads us to hypothesize that light conditions during early development leave epigenetic marks on circadian performance that remain present throughout life and touch upon physiology and metabolism. As a direct consequence, this may affect the vulnerability to later-life disease.

Methods: In the present study, we investigated whether aberrant postnatal light conditions contribute to later life adverse health effects. During the first four weeks of life, newborn C57BL6 mice were subjected to either a constant 12h light:12h dark cycle (control), constant darkness (dark) or constant light (light). The animals were monitored from three weeks of age.
Mice from the light group showed a reduced weight gain, resulting in a reduced body weight throughout life.

**Results:** Circadian performance was assessed at the age of three months. We observed that the animals housed under constant light during the first four weeks of life have a longer circadian period, indicative of a later chronotype, and display an altered response to changes in the light-dark cycle. We are currently analyzing heart function and pathology, as well as bone structure.

**Conclusions:** This study shows that exposure to aberrant light conditions early in life affects the development of the circadian system. This finding is in line with the Developmental Origins of Health and Disease (DOHaD) theory, which proposes that early-life programming by (adverse) environmental factors predisposes to non-communicable disease in adult life.

**PA1.07.04**

Developmental Origin of Health and Disease (DOHaD) and the circadian clock: epigenetics pre- and early postnatal circadian rhythm disturbance in mice


Erasmus MC, ROTTERDAM, The Netherlands

**Background:** The mammalian circadian clock imposes near 24-hour (circ-a-dies) rhythmity on physiology, metabolism and behavior, and allows organisms to anticipate daily recurring environmental changes (i.e. light-dark cycle). To keep pace with the day-night cycle, the clock is daily synchronized by light. Epidemiological and animal studies have associated chronic circadian rhythm disturbance (CRD) in adults (as encountered during shift work and jet lag) with a variety of diseases, including cancer, metabolic syndrome and cardiovascular disease. According to the Developmental Origins of Health and Disease (DOHaD) theory, fetal programming permanently shapes the body’s structure, function, and metabolism. In this scenario gestational environmental factors (e.g. nutritional insults), interacting with the genes, contribute to later life disease. Using an animal experimental approach, we have investigated whether gestational CRD leaves epigenetic marks on the fetal genome that remain present throughout life and that touch upon circadian performance, physiology and metabolism, and as a direct consequence, affect the vulnerability to later-life disease.

**Methods:** Pregnant C57BL6 mice were subjected to either a constant 12hr light:12hr dark (LD 12:12) cycle (control) or to repeated (i.e. once every 3 days) 8-hr phase advanced (eastbound jet lag, EJL) or delayed (westbound jet lag, WJL) LD 12:12 cycles. At the day of delivery, dams and their offspring were kept again under a constant light-dark cycle. Offspring was followed in time for the occurrence of health effects.

**Results:** In the first weeks after birth, both EJL and WJL offspring showed a reduced weight gain, resulting in a life-long reduction in body weight. At the age of 3 months, circadian performance was assessed in male offspring. EJL offspring displayed an faster circadian clock. Furthermore, EJL offspring adjusted more rapidly to an 8 hr phase advance, while, oppositely, WJL offspring took less time to overcome an 8 hr phase delay. Strikingly, analysis of the bones (i.e. femur) of 6-month-old male offspring by microcomputed tomography revealed reduced trabecular and cortical bone mass in EJL offspring. Especially in the diaphysis, endocortical volume, perimeter and moment of inertia (a proxy for bone strength), were significantly reduced, whereas cortical thickness was elevated. Analysis of the cardiovascular system of 9-month-old female offspring revealed left ventricle hypertrophy in the EJL offspring. Epigenetic analysis of the livers of control, EJL and WJL offspring revealed markedly differentially DNA methylation patterns in the livers of EJL and WJL offspring, as compared to control offspring.

**Conclusions:** We have shown that circadian rhythm disturbance in pregnant female mice by a chronic jet lag affects the development of the circadian system and predisposes to health effects in adult life.

**PA1.07.06**

Maternal melatonin or agomelatine therapy prevents programmed hypertension in male offspring of mother exposed to continuous light

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**Background:** Environmental disturbance of the circadian rhythm is associated with the development of hypertension. Hypertension can originate from early-life insults, whereas maternal melatonin therapy can be protective in a variety of models of programmed hypertension. Because melatonin controls circadian clock and melatonin deficiency causes hypertension, we hypothesize that melatonin or melatonin receptor agonist agomelatine can prevent programmed hypertension in adult offspring induced by maternal exposure to continuous light. We further employed the whole-genome RNA next-generation sequencing (NGS) to quantify the abundance of RNA transcripts in the offspring kidney from maternal exposure to continuous light. We further employed the whole-genome RNA next-generation sequencing (NGS) to quantify the abundance of RNA transcripts in the offspring kidney from maternal exposure to continuous light, melatonin, or agomelatine.

**Methods:** Female Sprague-Dawley pregnant rats randomly divided into four groups: controls, rats exposed to continuous light, exposed to continuous light plus treated with agomelatine (50mg/day i.p.), and exposed to continuous light plus treated with 0.01% melatonin in drinking water throughout pregnancy and lactation period. Three of each group were sacrificed at birth for NGS study. Blood pressure (BP) was measured in conscious rats by an indirect tail-cuff method (BP-2000; Visitech Systems, Inc., Apex, NC). Male offspring (n = 10/group) were sacrificed at 12 weeks of age.

**Results:** The major findings can be summarized as follows: (1) exposure of the mother to continuous light induced
programmed hypertension in adult offspring, which maternal agomelatine or melatonin therapy prevented; (2) continuous light exposure in pregnancy caused 718 renal transcripts to be modified in the developing offspring kidney; (3) continuous light exposure impaired melatonin synthesis and signaling in the developing kidney, but not persisted into adulthood; (4) genes that belong to the RAS, sodium transporters, AMPK pathway, and circadian rhythm were potentially involved in the continuous light exposure induced programmed hypertension; (5) maternal agomelatine therapy decreased Acr expression but increased Agr2 and Mat1; (6) maternal melatonin therapy prevented the increases of Scl9a3, Scl12a3, and Atp1a1 expression induced by maternal continuous light exposure; and (7) in continuous light exposure-induced programmed hypertension, the components of RAS, sodium transporters, and AMPK pathway were differentially regulated by agomelatine and melatonin therapy, to reprogram the development of hypertension.

Conclusions: In conclusion, early agomelatine or melatonin therapy provides protection in male offspring of mothers exposed to continuous light against programmed hypertension. Maternal agomelatine and melatonin therapy reprogram the RAS and sodium transporters differentially to prevent maternal exposure to continuous light-induced programmed hypertension. By providing new information of candidate pathways on BP regulation whose effects can be modified by agomelatine or melatonin, our NGS results are of significance to the development of novel interventions in the prevention of programmed hypertension in children exposed to maternal night shift work and circadian disruption.

PA1.07.07
Premature birth and circadian preference in young adulthood: evidence from two birth cohorts
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Background: A later circadian preference (being a “night owl”) and preterm birth (<37 weeks of gestation) are associated with many similar risk factors and adverse outcomes, such as elevated blood pressure, impaired glucose regulation, poorer physical fitness and lower mood. This raises the question whether circadian preference could be a mediating mechanism for the association observed between preterm birth and these adverse health outcomes. Interestingly, the limited research in the area suggests that prematurity, instead of being associated with eveningness, in fact seems to be associated with an earlier chronotype. We set out to objectively measure whether this is observed across the whole gestation range.

Methods: We studied the circadian rhythm among 594 young adults (mean age 24.3 years, SD 1.3) from two cohorts; the Arvo Ylppö Longitudinal Study and the ESTER [Preterm Birth and Early-Life Programming of Adult Health and Disease] study. We compared participants born early preterm (<34 weeks, n = 83) and late preterm (34 - <37 weeks, n = 165) with those born at term (n = 346). We also compared very low birth weight (VLBW, <1500g) participants with term controls. We obtained objective sleep data with actigraphs. The participants wore the actigraphs for a mean period of 6.8 (SD 1.4) nights. Our primary outcome was mid sleep point during weekdays and weekend. Mid sleep point is the half-way time between falling asleep and waking up, and is considered to represent circadian preference. We also investigated subjective circadian preference with the Morningness-Eveningness Questionnaire (MEQ) in 688 (n = 138/221/329) ESTER participants. The MEQ consists of 19 questions, which estimates the respondent to be of a “morningness”, “eveningness” or “intermediate” chronotype, based on the Morningness-Eveningness Score (MES). We analyzed the data from the actigraphs and the MES with three incremental linear regression models, and analyzed distribution of chronotype class with Pearson χ².

Results: There were no consistent differences across the study groups in mid sleep point. Mean differences and 95% confidence intervals for mid sleep: early preterm weekdays 0:11:47 (-0:08:34 to 0:32:08), early preterm weekend 0:04:14 (-0:19:45 to 0:28:13), late preterm weekdays -0:10:28 (-0:26:16 to 0:05:21) and late preterm weekend -0:01:29 (-0:20:36 to 0:17:37). There was no difference in circadian preference between VLBW-participants and controls either.

The distribution of chronotype in the MEQ among all participants was 12.4% morningness, 65.4% intermediate and 22.2% eveningness. The distribution of subjective chronotype class did not differ between the three gestational age groups (p = 0.975). The linear regression models did not show any influence of gestational age group or VLBW status on the MES (all p > 0.5).

Conclusions: We found no consistent differences between adults born early or late preterm and those born at term in circadian rhythm or preference. The earlier chronotype observed in those born smallest is unlikely to extend across the whole range of preterm birth.

PA1.07.08
Association of sleep quality in pregnancy with obesity and cardiometabolic traits in childhood
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Background: Sleep disorders in pregnancy may be associated with increased weight gain and complications such as hypertension, pre-eclampsia and gestational diabetes mellitus, as well as adverse perinatal outcomes including intrauterine growth restriction and low birth weight. In adults and children, sleep deprivation has been linked to obesity and adiposity, however to our knowledge there are no studies assessing associations of sleep disorders in pregnancy with adiposity and cardiometabolic risk factors in childhood. The precise molecular mechanisms linking sleep disorders with these outcomes are complex and proposed mechanisms involve intermittent hypoxia-induced oxidative stress and inflammation (also affecting the placenta), activation of the sympathetic nervous system with up-regulation of counter-regulatory hormones, and high circulating concentrations of leptin. Our aim was to evaluate the impact of sleep quality during pregnancy in offspring obesity and cardiometabolic traits at 4 and 7 years in 649 mother-child pairs from the RHEA pregnancy cohort in Crete, Greece.

Methods: Information on sleeping habits (sleep duration; snoring; daytime sleepiness) was collected through a computer-assisted interview at the third trimester of pregnancy. Furthermore, we created a sleep quality score based on the sum of 3 sleep-related responses: a) sleep duration (>8 hrs = 0, 6-7 hrs = 1, ≤5 hrs = 2), b) snoring (non-snorers (never/rarely) = 0, occasional snorers (sometimes/often) = 1, severe snorers (frequently/always) = 2), and c) excessive daytime sleepiness (Epworth Sleepiness Scale score: ≤ 10 = 0, 11-14 = 1 and ≥15 = 2). This score ranges from 0-6 with higher values indicating worse sleep quality. We measured child weight, height, body mass index (BMI), waist circumference, skinfold thicknesses, percent body fat (%BF), serum leptin, and serum lipids and blood pressure levels at age 4 and 7 years. Adjusted associations were obtained via multivariable regression analyses.

Results: Short sleep duration (≤5 hours per day) was associated with higher cholesterol, LDL and triglyceride levels at age 7 (% change (95%CI): 9% (3, 15); 13% (4, 24) and 30% (10, 55) respectively). Severe snoring and daytime sleepiness in late pregnancy were associated with reduced sum of skinfolds and %BF [-25% (-39, -8) and -21% (-34, -4) respectively] at age 4. A per unit increase in the sleep quality score was associated with lower child weight [β = -0.30 kg (-0.57, -0.03)] and BMI [-0.21 kg/m² (-0.38, -0.03)] but higher LDL and triglyceride levels [2.95% (0.15, 5.83) and 5.41% (-0.14, 11.27) respectively] at age 7. Conclusions: These findings suggest that sleep disorders in late pregnancy may influence child weight, adiposity and serum lipids in childhood. Further prospective studies are needed to examine these associations and explore the underlying mechanisms.

PAI.08 – Environmental stressors

PAI.08.01

DOHaD and the early life exposome

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Major environmental hazards may lead to serious, chronic pathologies, especially when exposure occurs during critical early-life periods of development, but work has almost uniquely focused on single exposure-health effect relationships. The “exposome” concept was proposed to encompass the totality of exposures from conception onwards, complementing the genome. New analytical frameworks are required to interpret multi-dimensional exposome data. HELIX, the Human Early Life Exposome, is a collaborative research project commissioned in the EU exposome programme. HELIX uses six existing, prospective birth cohort studies to measure a range of chemical and physical environmental hazards in food, consumer products, water, air, noise, and the built environment, in pre and postnatal periods, and link these with molecular omics profiles and child health outcomes. We will present first results of the HELIX project, including a description of the correlation structure of multiple exposure data, as a first step in developing analytical tools appropriate to exposome data. The exposome concept provides an important new framework to improve knowledge on the environmental component of disease aetiology, with early life as a crucial developmental period. Challenges in the measurement, analysis, and interpretation of complex longitudinal exposome-health associations require efficient collaboration between the environmental health and life-course epidemiology fields.

PAI.08.03

Effects of prenatal exposure to particulate matter air pollution on lateral ventricles, corpus callosum and behavioral problems in children

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Background: Exposure to particulate air pollution matter have been proposed as environmental risk factors for autism in children. The effects of these pollutants on brain structures potentially involved in the pathophysiology of autism are unknown. The aim of this study was to investigate the effects of prenatal exposure to particulate air pollution on cerebral grey matter, white matter, amygdala, lateral ventricles and corpus callosum volumes and behavioral problems in primary school age children.

Methods: We conducted an imaging study in 187 children aged 8-12 years from the general population in the city of Barcelona, Spain. Exposure at home to fine particulate matter whose median aerodynamic diameter is less than 2.5 mm (PM2.5) during the prenatal period was estimated at the geocoded postal address of each participant’s mother at the time of pregnancy using land use regression models. Brain volumes were derived from structural MRI scans using automated tissue
segmentation. Children’s behavior was assessed using the Strengths and Difficulties Questionnaire (SDQ) completed by the parents and using the Attention Deficit Hyperactivity Disorders (ADHD)/symptoms Scales. (American Psychiatric Association 2002) completed by teachers.

**Results:** Prenatal exposure to PM$_{2.5}$ was associated with corpus callosum and lateral ventricles volumes (i.e., an inter-quartile range increase in PM$_{2.5}$ level during the prenatal period (5.4 μg/m$^3$) was significantly linked to a decrease in the corpus callosum body volume (mm$^3$) and an increase in the lateral ventricles volume (mm$^3$) (β = -33.0, 95% CI [-63.7, -2.2], p = 0.036, and β = 880.0, 95% CI [311.1, 1449], p = 0.003 respectively) independently of intracranial volume, age, sex, maternal education and socioeconomic vulnerability index at home). Furthermore, a 1000mm$^3$ increase in the lateral ventricles volume was significantly associated with higher SDQ and hyperactivity scores. Finally, SDQ and hyperactivity scores increased in children with higher prenatal exposure to PM$_{2.5}$, but these associations were not statistically significant.

**Conclusions:** Prenatal exposure to PM$_{2.5}$ is associated with changes on the lateral ventricles and corpus callosum volumes in children. The consequences of these induced brain changes might be an increase in behavioral problems. This neuroimaging study, by providing biological plausibility in the relationship between particulate matter air pollution exposure and higher risk of behavioral problems in children observed in many epidemiological studies, highlights the urgent necessity to reduce anthropogenic emissions of air pollutants.

**PAI.08.04**

**Maternal circulating cotinine concentration in pregnancy and persistent short stature in children from a multi-ethnic Asian cohort**


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**Introduction:** Several studies have reported an association between maternal smoking during pregnancy and persistent short stature in the offspring. However, most of these studies used self-reported parental smoking instead of an objective quantification of a specific biomarker such as cotinine. This study aims to examine the relationship between maternal cotinine levels in pregnancy and child length/height trajectory from birth to 60 months of age.

**Methods:** 968 mother-child pairs were identified from the GUSTO birth cohort, comprising Chinese, Malay and Indian subjects. Cotinine levels in maternal plasma collected at 26-28 weeks of gestation were measured by LC/MS/MS with a detection limit (LOD) of 0.17 ng/mL. Offspring length was measured at birth and at age 3, 6, 9, 12, 15, 18, 24, 36, 48, 54 and 60 months. All subjects were categorized into 4 groups by cotinine levels and history of environmental tobacco smoke exposure (ETS); Group 1: cotinine below LOD and no ETS (n = 510); Group 2: cotinine below LOD but self-reported ETS (n = 283); Group 3: cotinine concentration between 0.17-13.99 ng/mL (n = 139); Group 4: cotinine concentration ≥14 ng/mL (n = 36), consistent with active smoking. Age- and sex-specific z-scores for offspring length/height were calculated using the WHO 2006 reference. Associations of maternal circulating cotinine with offspring stature at each time point were estimated using general linear models, while length/height trajectory was analyzed using linear mixed-effect models.

**Results:** Compared with Group 1, maternal circulating cotinine ≥14ng/mL (Group 4) was associated with a reduction of 0.77 cm in birth length (β = -0.77 (95% CI -1.44, -0.11)) and a z-score β of -0.43 (95% CI -0.79, -0.07), after adjusting for infant sex, gestational age at birth, ethnicity, maternal age, education level, parity, maternal BMI in the 1st trimester, and maternal height. Offspring in Group 4 continued to be shorter than those in Group 1 from 3 to 60 months, with statistically significant z-score differences at 3 months [β = -0.58 (95%CI -0.95, -0.20)], 36 months [β = -0.54 (95% CI -0.92, -0.15)], 48 months [β = -0.43 (95% CI -0.81, -0.04)], and 60 months [β = -0.57 (95% CI -0.96, -0.17)]. The association was stronger in boys [β = -0.52 (95% CI -0.92, -0.12)] than in girls [β = -0.16 (95% CI -0.58, 0.25)] for the overall trajectory. No significant differences in offspring stature were observed in Groups 2 and 3 compared with Group 1.

**Conclusions:** To our knowledge, this is the first longitudinal study reporting the association between maternal smoking during pregnancy and persistent short stature from birth and into early childhood in an Asian population. Further research is needed to define the possible mechanisms.
Trisodium citrate (TSC) is a white, crystalline, water-soluble salt that is commonly used in various applications due to its pH buffering properties. However, the role of TSC in the coagulation process is not well understood. In this study, we investigated the effects of TSC on the coagulation cascade.

**Methods:** A series of in vitro experiments were conducted to evaluate the impact of TSC on the coagulation process. Whole blood samples were incubated with different concentrations of TSC, and clotting times were measured using a thromboelastography (TEG) system.

**Results:** The results showed a significant increase in clotting times with increasing concentrations of TSC. The maximum effect was observed at 5 mmol/L, with a 50% increase in clotting time compared to the control group.

**Conclusion:** These findings suggest that TSC has a significant effect on the coagulation process, acting as a potent anticoagulant. Further studies are needed to elucidate the mechanisms underlying this effect and to determine the clinical implications of these findings.
Consequences of maternal overweight and obesity in pregnancy on offspring diabetes risk: a record linkage study in Aberdeen, Scotland

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Background: Maternal obesity in pregnancy is associated with cardiovascular disease and mortality in the offspring. With the rising prevalence of obesity in pregnancy it is vital to understand the underlying mechanisms in order to design appropriate interventions to prevent adverse offspring outcomes. We aimed to determine whether maternal obesity is also associated with increased risk of offspring type 2 and type 1 diabetes as a candidate mechanistic pathway.

Methods: Birth records of 118,201 children from 1950-2011 from the Aberdeen Maternity and Neonatal Databank were linked to Scottish Care Information-Diabetes, the national register for diagnosed diabetes in Scotland, to identify incident and prevalent type 1 and type 2 diabetes up to 01/01/2012. Maternal body mass index (BMI) was calculated from height and weight measured at the first antenatal visit. The effect of maternal obesity on offspring outcomes was tested using time-to-event analysis using Cox-proportional hazard regression to compare outcomes in offspring of mothers in underweight, overweight or obese categories of BMI, compared to offspring of women with normal BMI.

Results: Offspring of obese (BMI > 30 kg/m²) and overweight (BMI > 25-29.9 kg/m²) mothers had increased risk of type 2 diabetes compared to normal BMI mothers after adjustment for gestation when weight was measured, maternal history of diabetes before pregnancy, age at delivery, parity, socio-economic status, and offspring sex (Hazard ratio (95% confidence interval) 3.48 (2.39, 5.06) and 1.39 (1.06, 1.83), respectively. There were no significant associations of maternal BMI with offspring Type 1 diabetes.

Conclusions: Maternal obesity is associated with increased risk of type 2 diabetes in the offspring. Evidence-based strategies to reduce obesity among women of reproductive age are urgently required.
Most cancer research in human populations has focused on a range of exposures in the middle to later years of the lifespan. While this narrow age range yields the highest number of cancer cases, it is a phase of life in which cancer prevention efforts are more difficult and perhaps less effective. The emerging evidence that early life exposures affect cancer development later in life calls for a refocusing of efforts targeting the early life spectrum. This paradigm shift in cancer research has the potential to translate into substantial gains in cancer prevention and control. Emerging epidemiological evidence and research efforts focused on early life factors and cancer development will be presented. Advancement of cancer research efforts focused on early life factors and the links to cancer have been slow due to methodological issues related to human study designs and research resources.

PA1.09.03
Environment, DNA methylation and risk of childhood acute lymphoblastic leukaemia: a novel Mendelian randomization study
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Previous literature has identified multiple environmental exposures to be associated with an increased risk of acute lymphoblastic leukaemia (ALL). DNA methylation is modifiable by the environment and is therefore a plausible mediating mechanism of environmental exposures on ALL risk. An altered methylation has also been found in ALL patients. Therefore two sample Mendelian randomization (MR) will be used to strengthen evidence about the causal pathway for childhood ALL, and determine whether DNA methylation acts as a mediator between early life environmental exposures and ALL development. MR is a relatively new approach to causal inference. It addresses limitations of observational epidemiology study designs (i.e. bias, confounding and reverse causation) in assessing the causal role of modifiable exposures/risk factors, and can be used to examine causality when randomized controlled trials (RCTs) are not feasible. The approach uses genetic variation (such as single nucleotide polymorphisms (SNP)) as an instrumental variable (proxy) for an exposure of interest; the underlying principle of the approach is that, if a genetic variant alters or emulates the biological effect to the outcome. The genetic variant should also be related to disease risk. An epigenome-wide association study (EWAS) previously carried out identified altered methylation at individual CpG sites associated with an ALL-risk exposure (e.g. maternal smoking, alcohol consumption, and folic acid supplementation). It has been shown that cis-SNPs are associated with methylation status of nearby CpG sites. Therefore the methylation quantitative loci database (mQTLdb; http://www.mqtldb.org/) will be used to select specific cis-SNPs to represent the identified CpG sites of interest; these will act as genetic proxies for the methylation sites of interest (i.e. they will be the instrumental variables). To validate each cis-SNP, the instrumental variable assumptions (see Figure) will be tested. Further statistical tests to check these assumptions will be undertaken once the MR analysis has been run (see Supplementary and sensitivity analyses). To estimate the causal effect genome-wide association study (GWAS) data for 2487 childhood ALL cases and 1014 cancer-free control children will be used to investigate whether the cis-SNPs representing each CpG site are associated with childhood ALL. Analysis will be carried out in R using packages designed at the University of Bristol (MRInstruments and TwoSampleMR). These enable: extraction of user-specified SNP effects; linkage disequilibrium pruning of exposure SNPs; and harmonisation of direction of effects between exposure and outcome association. Supplementary and sensitivity analyses will be carried out to further enhance the causal inference from the initial MR analysis, and to establish the robustness of the findings. These include exclusion of nonspecific SNPs; pleiotropy analyses; and weighted median estimator, gene-environment interaction, multiple independent instrument, multi-SNP instrument, and MR-Egger regression analyses.

PA1.09.04
DNA methylation as a potential mediator of early life exposures on risk of childhood acute lymphoblastic leukaemia
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Childhood acute lymphoblastic leukaemia (ALL) arises from genetic abnormalities that can occur in utero. Reported
frequencies of certain genetic ALL-related abnormalities at birth are significantly higher than the number of associated ALL cases arising, suggesting secondary hits are required for disease development. Childhood ALL incidence is currently increasing in westernised populations and evidence suggests several environmental exposures influence childhood ALL risk. With peak incidence of diagnosis between 2-5 years of age, early life exposures are likely to be key. DNA methylation, a mechanism of gene regulation, is modifiable by environment and altered in childhood ALL. Therefore DNA methylation may be involved in the causal pathway towards disease by acting as a mediator between in utero and early life environmental factors and childhood ALL development. A meet in the middle approach was used to investigate the potential role of DNA methylation in ALL disease development. The Avon Longitudinal Study of Parents and Children cohort (ALSPAC) hold environmental data on mothers throughout pregnancy. Genome-wide DNA methylation data previously generated using the Illumina Infinium HumanMethylation450k platform, at birth using cord blood (n = 861) and age seven using blood (n = 927) from a subset of children from the ALSPAC cohort were assessed in relation to environmental factors associated with childhood ALL. The effect of environmental exposures associated with childhood ALL risk on DNA methylation at individual CpG sites were analysed using linear regression. DNA methylation was modelled as a continuous variable, in a multivariate regression model accounting for potential confounders (sex, parity, gestation, and batch). The resultant data were integrated with a compiled list of gene loci with methylation changes associated with overt ALL disease (identified using published literature). DNA methylation changes were found at birth in association with maternal exposure to smoking, alcohol, radiation exposure, folic acid, sugary caffeinated drinks, iron, caffeine, and household paints. At age seven, DNA methylation changes were observed with day care attendance. Hypergeometric tests suggested that the overlap between the number of genes found to have altered methylation in ALL and in response to the majority of ALL-risk exposures was not due to chance. This supports the hypothesis that DNA methylation may mediate the effect of environmental risks factors associated with disease development. If alterations in DNA methylation underlie disease susceptibility, then the altered DNA methylation should be present in both diseased and normal cells and thus should be at least partially retained in ALL patients in remission. Therefore, DNA methylation was measured using pyrosequencing for several identified environmentally responsive gene loci (AHRR, CYP1A1, BHMT, and LCK) in ALL patient remission samples (as proxy for pre-disease methylation measurement) and healthy controls. In agreement with our hypothesis, significant differences were found between the ALL remission samples and controls for all environmentally responsive genes. Further studies to understand the importance of these methylation changes in inducing or contributing to disease development will be important, as such findings may provide predictive disease biomarkers and offer insights into how preventative strategies may be introduced.

**PA1.09.05**

**Epigenetic precursors of childhood cancer and associated early-life exposure**

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**Background:** Childhood cancer remains the first cause of disease-related death in children, with increasing incidence worldwide. Its risk factors are largely unidentified and underlying biological mechanisms remain poorly understood. During embryogenesis, a global reprogramming of the epigenome (including DNA methylation) occurs to enable tissue differentiation, and it has been proposed that this profound epigenome reconfiguration constitutes susceptibility windows. Hence, we hypothesize that DNA methylation during in utero development may act as a sensor of environmental exposures and mediate risk to childhood cancer later in life.

**Methods:** We profiled the genome-wide methylation levels in cord blood samples from the International Childhood Cancer Cohort Consortium (I4C), the largest prospective investigation into childhood cancer based on mother-child birth cohorts. Starting with a major I4C cohort (MoBa, Norway), DNA methylation levels of more than 450,000 cytosines (CpGs) were compared (using HM450-BeadChip) between nested cases (n = 80, representing similar proportions of leukemias, central nervous system tumors and other tumors) and controls (n = 160, matched to cases by birth year). Findings were then replicated in two independent cohorts from different continents using both epigenome-wide and targeted DNA methylation approaches.

**Results:** We identified two differentially methylated 200-bp regions (DMRs) in leukemias relative to controls (FDR < 0.05). A mean difference of 5-10% methylation was consistently found across several CpG sites in each DMR and was validated using bisulfite sequencing. The observed associations were not influenced by covariates such as blood cell subtype distribution and age. These epigenetic signatures of childhood leukemia were replicated in two independent cohorts and are currently being analyzed in relevance to early-life exposure factors in these and in additional I4C cohorts. Preliminary findings suggest a role for early-life infection and maternal smoking during pregnancy.

**Conclusions:** These findings may place DNA methylation in the causal pathways linking early-life exposures and childhood
leukemia and may contribute to a leap forward in deciphering mechanistic precursors of childhood cancer.

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PA1.09.06
Associations between early-life body size factors and pubertal onset by breast cancer family history in the LEGACY Girls Study
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Background: Earlier onset of breast development, which has been observed globally, is a known risk factor for breast cancer. Growing evidence suggests that age at onset of breast development as well as other markers of puberty may be influenced by maternal pre-pregnancy body mass index (BMI), maternal gestational weight gain (GWG) and infant body size. To date, all of the epidemiologic evidence, however, has come from cohorts of girls not enriched with a breast cancer family history (BCFH). As maternal BMI and GWG may be modifiable, we investigated whether maternal BMI, GWG and size at birth were associated with earlier pubertal onset, and whether these associations varied by BCFH, using a prospective cohort of girls in which approximately half have a history of breast cancer in a first or second degree relative.

Methods: Using longitudinal Weibull models and data from girls ages 5-7 years at baseline (n = 240), we assessed whether maternal pre-pregnancy BMI, GWG, and daughter’s weight and length at birth were not associated with earlier pubertal onset, and whether these associations varied by BCFH, using a prospective cohort of girls in which approximately half have a history of breast cancer in a first or second degree relative.

Results: The median ages of thelarche and pubarche were 10.1 (95% confidence interval (CI) = 9.9, 10.4) and 10.9 (95% CI = 10.5, 11.3) years, respectively. Higher maternal pre-pregnancy BMI was associated with earlier thelarche in their daughters (Hazard ratio (HR) adjusted for age and race/ethnicity = 1.05, 95% CI = 1.01, 1.08 per kg/m²). However, the association between maternal BMI and onset of thelarche was modified by GWG. Compared to daughters whose mothers had a pre-pregnancy BMI of <25 kg/m² and gained <30 pounds, girls whose mothers had a pre-pregnancy BMI <25 kg/m² and gained ≥30 pounds (HR = 1.96, 95% CI 1.13, 3.39) and girls whose mothers had a pre-pregnancy BMI of ≥25 kg/m² had an approximately twofold increased risk of earlier thelarche regardless of the mother’s GWG (HR = 2.11, 95% CI 1.17, 3.80 for GWG <30 lbs and HR = 2.19, 95% CI 1.07, 4.47 for GWG ≥30 lbs). Associations were similar after adjustment for childhood BMI at baseline. Associations between maternal pre-pregnancy BMI and GWG were stronger for girls without a BCFH, although the interactions were not statistically significant. There were no consistent patterns between maternal pre-pregnancy BMI or GWG and pubarche. Daughter’s weight and length at birth were not associated with the timing of thelarche or pubarche.

Conclusion: In a prospective cohort enriched for breast cancer family history, we found that earlier onset of breast development in girls was associated with two potentially modifiable risk factors – maternal pre-pregnancy BMI and gestational weight gain – and that the effect of these risk factors on timing of breast development were independent of childhood body size.

PA1.09.07
Exposure to chemotherapy induces epigenetic damage in normal cells in childhood cancer patients
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Survival rates for childhood cancers have improved dramatically in recent years, leading to an increase childhood cancer survivors. Long term follow up has shown that survivors of childhood cancer are at very significantly increased risk of developing many common chronic diseases and early death compared to the general population. Recently the British Childhood Cancer Survivor Study found a ~ nine-fold increased death rate in cancer survivors, with secondary malignancies, circulatory conditions and respiratory conditions accounting for the majority of excess deaths not related to disease re-occurrence. Recent reductions in therapy, particularly reduction in the use of radiotherapy and anthracyclines, may have had some effect in reducing premature deaths in cancer survivors, but rates remain highly elevated (Fidler et al, 2016). The mechanisms underlying the high rates of chronic illness and premature deaths in survivors of childhood cancer are not fully understood. One potential mechanism could involve epigenetic damage induced by anti-cancer therapies. Epigenetic changes, such as altered DNA methylation, are an attractive potential mechanism as these changes, once induced, can be stable over many years and thus could underlie later health problems. To begin to explore this, we assessed the impact of chemotherapy on DNA methylation at six candidate genes in normal cells from ALL patients in early and late remission.
Five of the six candidates exhibited no increase in methylation between early and late remission samples. However HOXA4 was found to exhibit dramatically increased methylation in late remission compared with early remission. Furthermore the extent of the increase in methylation was associated with the duration of the treatment, implying that increased exposure to chemotherapy was associated with an increased level of aberrant DNA methylation.

Based on this initial evidence, we expanded these studies to assess genome wide DNA methylation changes in response to therapy. We performed genome wide methylation analysis using Illumina MethylationEpic arrays, which cover > 850,000 CpG sites across the genome in 32 sets of paired DNA samples (derived from peripheral blood) taken from initial remission (or diagnosis in solid tumours) and late remission (up to 2 years) in childhood cancer patients. This analysis confirmed that the highly significant increase in methylation at the HOXA4 locus. In addition a further 153 differentially methylated regions (DMRs) were found to exhibit altered DNA methylation in normal, non-cancer cells, in later remission compared with early remission after correction for FDR. This demonstrates that exposure to chemotherapy induces large and wide spread changes in DNA methylation across the genome in healthy cells from childhood cancer patients. Furthermore, the induced methylation changes were highly similar in solid tumour patients (primarily neuroblastoma patients) and in leukaemia patients, suggesting that altered DNA methylation occurs largely independently of the specific chemotherapeutic regimes used. Further studies will be required to determine if the altered DNA methylation induced in childhood cancer patients is sustained into later life and if it plays a mediating and/or predictive role in the development of long term health effects associated with the treatment of childhood cancer.


Methods: Secondary analysis of a multicenter randomized controlled trial, in which pregnant women with BMI ≥ 25kg/m² received either Lifestyle Advice or Standard Care. Paternal anthropometric measures included height, weight; BMI; waist, hip, calf and mid-upper arm circumferences; biceps and calf skinfold thickness measurements (SFTM); and percentage body fat. Newborn anthropometric outcomes included length; weight; head, arm, abdominal, and chest circumferences; biceps, triceps, subscapular, suprailiac, thigh, and lateral abdominal wall SFTM; and percentage body fat.

Results: Increasing paternal BMI was associated with a significant increase in infant suprailiac (p = 0.05) and thigh SFTM (p = 0.04), particularly in men with BMI ≥35.0kg/m². The effect of an antenatal maternal dietary and lifestyle intervention among women who were overweight or obese on neonatal anthropometric measures, was significantly modified in infants whose fathers’ BMI ≥35.0kg/m², with a significant reduction in infant triceps, suprailiac, and thigh SFTM, and percent fat mass, to below that observed in offspring of lean fathers.

Conclusion: Further research is required to determine whether our observed associations are causal, and, if so, whether paternal weight loss prior to conception would affect infant adiposity, as a potential strategy to reduce the adverse intergenerational effects of obesity.

PA1.10.02
Effect of maternal cafeteria diet and taurine supplementation on body and organ weights of the offspring
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Background: Maternal over-nutrition may disrupt the developmental process of the fetus during gestation and lactation. Several studies demonstrate that taurine amino acid exerts antioxidant, anti-inflammatory, antitumorigenic and hepatorenal protective effects. The possible protective influence of maternal taurine supplementation in the setting of maternal over-nutrition is not well documented. This study aimed to examine the effect of maternal cafeteria diet and/or taurine supplementation on body and organ weights of the offspring.

Methods: Female Wistar rats were fed a control (CON) diet, CON supplemented with 1.5% taurine in drinking water (CONT), cafeteria diet (CAF) or CAF supplemented with taurine (CAFT) from weaning. After 8 weeks all animals were mated and maintained on the same diets during pregnancy and lactation. Birth weights were recorded and bodyweights of offspring were measured during lactation. At the end of lactation, two offspring from every dam were weaned onto a control diet and the rest were culled. Blood and tissue samples were taken. Major organ weights (liver, brain, kidneys and heart) were recorded. The effect of gestational diet on maternal and
fetal outcomes was assessed using a general linear model analysis of variance (ANOVA) (fixed factors, maternal diet and sex). Where longitudinal data were available (for example, weekly body weights or energy intake), the week of study was used in a repeated-measures analysis.

**Results:** Birth weights of pups did not differ between groups (p = 0.532), but male offspring's birth weights were higher than female offspring (CON male: 5.87±0.13 g, female: 5.40±0.10 g; CONT male: 5.70±0.11 g, female: 5.36±0.11 g; CAF male: 5.64±0.11 g, female: 5.30±0.12 g and CAFT male: 5.64±0.12 g, female: 5.37±0.11 g (p < 0.001). Maternal cafeteria diet and taurine supplementation affected body weight during lactation and both CAF and CAFT pups were leaner than CON and CONT pups (CON: 19.02±0.25 g, CONT: 20.30±0.26 g, CAF: 16.93±0.24 g and CAFT: 16.45±0.23 g) (p < 0.001). An effect of maternal diet was observed on offspring's liver weights (relative to body weights) which indicated a significant reduction in CAF and CAFT compared to CON and CONT (CON: 4.28±0.07, CONT: 3.93±0.07, CAF: 3.45±0.07 and CAFT: 3.47±0.06) (p < 0.001). The relative weight of brain was significantly heavier in CAFT than CON and CONT (CON: 3.58±0.08, CONT: 3.54±0.08, CAF: 3.75±0.08 and CAFT: 3.97±0.07) (p < 0.001). The heart was heavier in CAFT offspring compared to CON, CONT and CAFT offspring (CON: 0.51±0.01, CONT: 0.52±0.01, CAF: 0.56±0.01 and CAFT: 0.52±0.01) (p = 0.002).

**Conclusions:** Maternal cafeteria diet and/or taurine supplementation induced alterations in body and organ weights of offspring. Despite these differences, cafeteria diet supplemented with taurine did not exert a profound protective effect on body and organ weights. Future studies will continue to examine the influence of maternal cafeteria diet and taurine supplementation on physiological and metabolic changes in the offspring.

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**PA1.10.03**

**DNA-methylation and body composition in pre-school children of the CHOP study- Are methylation variants associated with further body composition development?**


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**Background:** In a recent cross-sectional epigenome-wide-association-study (EWAS) conducted by our group in 374 pre-school children of four European countries (BE, DE, IT, ES) 13 DNA-methylation (DNAm)-variants were found significantly associated with body size (BMI(kg/m²), ZBMI (WHO-z-score)) and body composition measures (fat-mass (FM (kg)), fat-free-mass (FFM (kg)) and its height related indices (FMI (kg/m²), FFMI (kg/m²)) at age 5.5 years. These DNAm-variants were located in genes related to lipid and glucose metabolism, obesity or diabetes. This study aims to investigate whether these epigenetic marks are associated with further growth until age 11 years.

**Methods:** The European Childhood Obesity Project (CHOP) study is an ongoing prospective study with multiple anthropometric measurements from birth and body composition measures derived from bio-impedance analysis collected at age 5.5, 6, 7, 8 and 11 years. Genome wide DNAm data were determined in whole blood for these children using the Illumina-HumanMethylation450K BeadChip array at the age of 5.5 years. Latent growth curve modelling (LGCM) was applied to construct BMI, ZBMI, FM, FMI, FFM and FFMI trajectories. We analyzed whether any of the 13 DNAm-variants previously identified were associated with body composition at age 5.5 years or with respective trajectories. Analyses were adjusted for all covariates as in the detection EWAS (6-WBC-celotypes, 30 control probe principal components, sex, age at blood draw, country, education). Further adjustments were child’s birth weight, gestational age, maternal age at delivery, pre-pregnancy BMI and smoking during pregnancy. In the LGCM a cubic shaped trajectory with random intercept and slope and fixed quadratic and cubic terms was specified. The intercept and latent linear slope of each of the 6 body-size and composition trajectories were regressed on each of the 13 DNAm-variants previously identified adjusted for the covariates listed above.

**Results:** Except for CpG 2, 6 and 10 all DNAm-variants were significantly associated with at least one linear slope (=velocity of development) of some body composition trajectory. BMI development (linear slope) was associated with CpG: 8, 9, 12 (P-values: 1.10E-04, 8.66E-07, 4.67E-02, respectively). ZBMI slope was associated with CpG: 1, 3, 4, 5, 7, 11, 13 (P-values: 5.63E-07, 1.07E-04, 1.15E-02, 1.66E-03, 4.04E-02, 3.55E-03, 3.02E-02, 3.45E-02). FM slope was associated with CpG: 1, 3, 5, 8, 9, 12 (P-values: 3.12E-02, 2.74E-02, 3.93E-02, 3.44E-07, 3.36E-10, 6.67E-03). FMI slope was associated with CpG: 8, 9, 12 (P-values: 5.71E-07, 4.19E-10, 4.73E-02). FFMI slope was associated with CpG: 8, 9, 12 (P-values: 2.24E-02, 4.52E-03, 1.83E-02). FMFMI slope was associated with CpG: 1, 9 (P-values: 3.49E-02, 1.79E-02).
Conclusions: Most of the previous identified DNAm-variants associated with body composition at age 5.5 y in our study have long-term effects on body composition. Provided replication they may be considered as early markers for further development of body composition. The finding that some DNAm-variants affect development of BMI, FM and FFM whereas others are specific for FM may be of future interest. Assessment of epigenetic stability of these identified DNAm-variants is also required.

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PA1.10.04

Maternal diabetes impairs fetal brown adipose tissue development

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Background: Intrauterine growth restriction is a common clinical complication in babies born to women with pregestational type 1 diabetes. Epidemiological studies show that these babies are more prone to develop obesity and related metabolic disorders later in life, but the mechanism remains unclear. There are emerging evidences that brown adipose tissue (BAT) is important not only for thermoregulation in the neonatal period, but also plays a key role in controlling body weight and preventing obesity in adulthood via dissipating stored chemical energy in the form of heat. This study aims to use a mouse model to determine whether BAT development is impaired in fetuses exposed to intrauterine type 1 diabetes, which increases their propensity to develop obesity and metabolic disorders in postnatal life.

Methods: Pregnancies were obtained by mating non-diabetic male ICR mice with streptozotocin-induced diabetic or non-diabetic female ICR mice. The interscapular BAT (iBAT) weight and body weight of near-term fetuses at gestational day 18 (GD18), and neonates on the day of birth (postnatal day 1: PD1) were measured. Differentiation of fetal iBAT was assessed by oil Red O staining of lipids and measurement of triglycerides content. As a critical component for BAT functions, mitochondrial number and mass were determined by transmission electron microscopy, MitoTracker Red staining, and mRNA expressions of mitochondrial DNA-encoded genes cytochrome c oxidase I (Cox1) and NADH dehydrogenase 5 (ND5). The mRNA and protein levels of the BAT-specific gene uncoupling protein 1 (Ucp1), which sets the thermogenic process, were measured by real-time qRT-PCR and Western blot. Thermogenic capacity of PD1 neonates was assessed. Offspring of diabetic dams were fostered by non-diabetic dams. After weaning, they were challenged with a high-fat diet. The body weight of offspring was monitored at regular intervals. Insulin tolerance test and glucose tolerance test were conducted at 4 months of age.

Results: The birthweight of PD1 neonates of diabetic dams was 30% lower than that of non-diabetic dams. At GD18, concomitant with a lower iBAT-to-body weight ratio, there were prominently less lipid droplets and lower concentrations of triglycerides in the iBAT of fetuses of diabetic mice. Moreover, mitochondrial number and mass were markedly reduced. The upregulation of mRNA and protein levels of Ucp1 prior to birth was dramatically suppressed by over 90%. In line with these findings, the PD1 neonates had significantly lower body temperature at the interscapular region and showed reduced capacity to maintain their body temperature. Despite having a lower birthweight, offspring of diabetic dams that were fostered by non-diabetic dams showed rapid catch-up growth. When challenged with a high-fat diet, they gained more weight, and were more insulin resistant and glucose intolerant than offspring of non-diabetic dams.

Conclusions: Our results show that in growth-restricted fetuses of mice with streptozotocin-induced diabetes, development of BAT is impaired. Further studies are required to determine whether there is a link between defective BAT development during gestation and predisposition to adiposity and metabolic disorders in postnatal life in offspring exposed to type 1 diabetes in utero.

PA1.10.05

Effect of dietary lipid structure in early life improves metabolic function of adult adipose tissue in mice

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Background: The incidence of childhood obesity is increasing worldwide and is associated with adult obesity and metabolic disease. Environmental factors in early life, including nutrition, have shown to impact lifelong health. For instance, breastfeeding is associated with a reduced risk of childhood obesity and adult metabolic disease. We developed an infant milk formula with a complex lipid matrix (Nuturis®) more closely resembling the lipid structure of human milk. Early life exposure to Nuturis® has consistently resulted in a beneficial effect on adult fat mass accumulation in mice. In this study we investigated the potential underlying mechanism in adipose tissue in more detail.

Methods: A diet containing either Nuturis® or a standard infant milk formula (CTRL) was provided to mice from postnatal day (PN) 15 to 42, a time period corresponding to infancy and childhood. Subsequently, mice were challenged with a moderate Western style diet (WSD; 40 En%) or fed a standard rodent chow during adolescence and adulthood until dissection at PN112. Body composition (BC) was monitored by EchoMRI bi-weekly from PN42 to PN98. Adipocyte cell
size and macrophage content were determined by epididymal white adipose tissue (epiWAT) staining and epiWAT gene expression analysis by means of microarrays at PN112.

**Results:** BC analysis confirmed reduced adiposity in the Nuturis® mice after a WSD challenge, whereas no differences were found between Nuturis® and CTRL mice after the standard chow. Adipocyte cell size was smaller in Nuturis® compared to CTRL mice independent of the adult diet. Nuturis® mice showed a trend towards reduced crown-like structures and individual macrophages infiltration in WAT after the WSD challenge, suggesting a reduced inflammation risk. In addition, expression of genes related to metabolic function and energy metabolism were beneficially affected in Nuturis® mice.

**Conclusion:** Our study showed that the reduced fat accumulation in mice after a WSD in adult life was associated with selective changes in adipocyte size, inflammatory markers and markers related to metabolic function and energy metabolism. These changes indicate that early modulation of epiWAT function may contribute to the protective effects of Nuturis® on later life health.

**PA1.10.06**

**Adult glucose dysregulation after severe prenatal food restriction in the Dutch Hunger Winter: only partial mediation by current body size.**

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**Background:** Previous studies show that fetal exposure to the Dutch famine of 1944-45 is associated with increased body size and impaired glucose dysregulation in later life. The interrelation of these outcomes has not yet been examined taking time order into account.

**Methods:** We recruited 342 men and women in three birth clinics in the western Netherlands whose mothers were exposed to famine during or immediately preceding pregnancy (births between January 1945 and March 1946); 291 men and women born in 1943 or 1947 in the same clinics as time-controls; and 302 prenatally unexposed same-sex siblings of individuals above as family controls. Study participants were administered a 75-g oral glucose tolerance test after overnight fasting. We examined baseline glucose and insulin, HOMA-IR as a measure of insulin resistance and 2-hr post-challenge glucose. Type 2 diabetes mellitus (DM) was defined by a positive medical history prior to examination or a fasting glucose concentration ≥7.0 mmol/L or 2-hr glucose concentration ≥11.1 mmol/L. We asked participants to recall their weight at age 20. Current body size was defined by weight, body mass index (BMI), waist circumference (WC), or sagittal abdominal diameter (SAD) at the age of examination (~59 years). Weight gain was defined as current minus recalled weight at age 20. We used multi-level linear and logistic regression models to estimate the degree of glucose dysregulation associated with famine exposure relative to controls. We used methods proposed by Baron and Kenny to examine the relation between weight gain, current body size and glucose dysregulation after prenatal famine exposure.

**Results:** Prenatal famine exposure was not related to recalled weight at age 20. In agreement with previous studies, famine exposed subjects had higher levels of fasting glucose (0.19 mmol/L; 95% CI: 0.05 to 0.33), 2-hr glucose (0.37 mmol/L; 95% CI: 0.03 to 0.71), and insulin resistance (log HOMA-IR units) (0.09; 95% CI: 0.00 to 0.18); they also had an increased odds for DM (OR = 2.20; 95% CI: 1.34 to 3.60). After adjustment for BMI (or WC or SAD) these estimates reduced to 0.13 mmol/L (95% CI: -0.01 to 0.27), 0.27 mmol/L (95% CI: -0.06 to 0.61), and 0.01 log HOMA-IR units (95% CI: -0.07 to 0.09) respectively. The odds for DM remained elevated (OR = 1.86; 95% CI: 1.13 to 3.06) after adjustment for BMI. DM prevalence among the exposed was 18.7%. Adjustment for recalled weight had no impact on glucose outcomes.

By contrast, adult weight gain and current body size mediated a significant proportion of the famine effects on fasting and 2hr glucose (20-50%), HOMA-IR (60-90%), and DM (15-25%) (Figure). We confirmed our results in sibling pairs.

**Interpretation:** The increase in body size after age 20 as expressed by weight gain or current body size is an important mediator of glucose dysregulation after prenatal famine but provides only a partial explanation of long-term health effects. Further studies should therefore also include glucose handling and pancreas functions in famine-exposed individuals that are independent of body size.

**PA1.10.07**

**Prenatal exposure to phthalates in relation to epigenetic and metabolomic markers in a birth cohort with high risk of obesity**

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**Background:** The prospective nature of birth cohort studies and wealth of epidemiological data and biological samples provide unique opportunities to address effects of early life exposures on health outcomes later in life in light of the DOHaD paradigm. Several lines of evidence highlight phthalates as potential key obesogens. Epigenetic mechanisms attract increasing attention as a potential link between the genetic and environmental determinants of health. We aimed to study the relationship of prenatal exposure to phthalates with epigenetic modifications and obesity in children from birth through adolescence.

**Methods:** Urinary phthalate metabolites were measured during pregnancy in 400 women from the CHAMACOS study, an ongoing longitudinal birth cohort of low-income Mexican-Americans from California. We characterized DNA methylation using 450K Infinium BeadChips, pyrosequencing of imprinted genes as well as LINE-1 and Alu repeats in blood collected from children at several time-points. Expression of human miRNAs was measured by Next Generation Sequencing using the novel HTG platform. Health outcomes included length of gestation, birth weight, and obesity and metabolic health parameters through age 14 years.

**Results:** Maternal phthalate concentrations in CHAMACOS women were similar to other US and European cohorts, and were correlated with several markers identified by targeted metabolomics. More than 55% of CHAMACOS children aged 9-14 years were overweight or obese. Phthalate metabolites were associated with child BMI Z-score, waist circumference, isoprostane and adipokine levels. miRNA expression and DNA methylation differed by sex and were also associated with phthalate exposure and prenatal factors after adjusting for blood cell composition.

**Conclusions:** Our findings provide evidence that in utero exposure to phthalates may contribute to obesity development in children. Furthermore, the relationship of prenatal phthalate exposure with altered DNA methylation and miRNA profiles suggest epigenetics as a potential molecular pathway through which prenatal exposure can affect obesity in children at older ages. Unlike genetics, epigenetic mechanisms could be reversible and understanding their role may lead to better protection of pregnant women and children, and improved public health.

**PL1.02 – Mechanistic studies in DOHaD**

**PL1.02.01**

**Exploring mechanisms and examples of paternal epigenetic inheritance**

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Multiple reports, some more convincing than others, describe how paternal and even grandparental exposures can impact the phenotypes of un-exposed offspring. This intergenerational or transgenerational inheritance occurs through non-DNA based mechanisms and has been termed epigenetic inheritance. Despite the now numerous studies demonstrating the phenomena of transgenerational inheritance, following dietary, toxicant and even stress exposures, there remain significant questions about the nature of the mechanism(s) responsible for the transmission of these environment-induced defects between generations. We do know that for such transmission to occur, it must involve mechanisms that operate in the germline. To date, histones, DNA methylation and non-coding RNA have been implicated in transgenerational inheritance. The sperm epigenome is highly unique in comparison to the oocyte; the majority of histones are replaced with sperm-specific nucleoproteins, the protamines. In mice and men about 1% and 10% of histones are retained respectively primarily at CpG rich regions. Sperm is also highly enriched in noncoding RNA and has a unique DNA methylome where in general regions that are enriched for histones tend to be hypomethylated. We will discuss how alterations in the epigenome (epimutations) might resist extensive epigenetic reprogramming that takes place during the normal development of the germ line between generations. In the workshop we will explore examples of epigenetic inheritance, the mechanisms involved, the technological limitations and how we can best study epigenetic inheritance in the future.

**PL1.02.02**

**Programming by maternal over-nutrition: a developing obesity crisis**

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Obesity prevalence is increasing in both the developed and developing world in all age groups within the population.
including women of childbearing age. In many countries, such as the UK, over half of women are now overweight or obese during pregnancy. This is of concern as growing evidence suggests that developing in utero in an obesogenic environment not only has short term detrimental effects for both mother and baby but also has long-term effects on the metabolic and cardiovascular health of the child later in life. This evidence has been gained from studies in both humans and in a range of animal models. The strongest evidence from humans to suggest that development in utero in an obesogenic environment "programmes" increased risk of obesity and cardio-metabolic disease has come from the study of siblings born before and after maternal bariatric surgery. These revealed that the sibling born post-surgery when the mother was leaner had reduced adiposity, lower blood pressure and increased insulin sensitivity compared to their sibling born prior to maternal weight-reducing surgery. Studies in animal models have been key in showing that these relationships are causal and in defining underlying mechanisms. We have used a mouse model of maternal diet-induced obesity to define the mechanisms by which obesity during pregnancy impacts on the long-term cardio-metabolic health of the offspring. These studies have demonstrated that the offspring of obese dams develop insulin resistance, cardiac dysfunction, hypertension and fatty liver when weaned onto a healthy low fat diet and have a normal body weight. Offspring of obese dams are also more susceptible to diet-induced obesity which can exaggerate the programmed phenotype. Studies in animal models have also helped in the identification of key factors associated with obesity during pregnancy that mediate programmed effects in the offspring. Our studies have identified maternal insulin as a key "programming" factor and highlight it as an important target of intervention studies such as those involving increased maternal physical activity. These studies therefore provide important insight in strategies for prevention of transmission of obesity from mother to child and thus reduce the burden of some of the most common non-communicable diseases of the 21st century.

PL1.02.03
Genetics of birth weight and later life diseases
R.M. Freathy
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Individuals with birth weights approaching the lower and upper ends of the population distribution are more at risk of adverse neonatal and later-life health outcomes than those of average weight. The factors influencing birth weight are complex and involve both maternal and fetal genetic contributions in addition to the environment. Genome-wide association studies have identified more than 60 regions of the genome in which common genetic variants are robustly associated with birth weight. This presentation will describe the most recent genome-wide association studies of birth weight. These include analyses of both fetal and maternal genetics, which have provided biological insights into important intrauterine factors and relevant pathways, in addition to estimates of the genetic contribution to the inverse observational associations between birth weight and later life diseases. The findings, their limitations, and future directions will be discussed.

PAI.11 – Experimental fetal and neonatal methods
PAI.11.01
Consequences of fetal hypoxia: Does it all come down to timing, duration and severity?
J. Morrison¹

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The complex developmental trajectory of fetal growth and development requires adequate oxygen delivery throughout gestation. Interruption of that oxygen supply may be brief, repetitive or sustained, and may occur at any time, thus producing a spectrum of pathophysiological responses that have implications for the fetus’ immediate and long-term wellbeing. Detailed animal studies allow dissection of how timing, duration and severity of a hypoxic insult modifies fetal and postnatal health. This insight may lead to different interventional approaches in babies or children that were exposed to different types of hypoxemia. This talk will include examples of cardiopulmonary adaptation to fetal hypoxemia and suggest potential therapeutic strategies.

PAI.11.03
Consequences of fetal and neonatal adaptation to a hypoxic environment
I.K.M. Reiss
ErasmusMC-Sophia, ROTTERDAM, The Netherlands

Reduced oxygenation of the placenta is linked to severe complications including intra-uterine growth retardation and pre-eclampsia. Despite reductions in systemic oxygen supply, the fetus is able to cope with physiologic hypoxic conditions. A similar reduction in systemic oxygen supply occurs at high altitude, making high altitude a good model for hypoxia research. While many studies have addressed the hypoxic placenta’s vascular remodeling and metabolic changes, data on the mature fetal adaptation to a hypoxic environment are scarce. We will present data on microvascular density in healthy term neonates born to mothers living at high altitude during pregnancy. We were able to demonstrate that microvascular density was 14% higher than in neonates born at sea level, pointing towards a possible adaptive fetal strategy to cope with reduced oxygenation. In preterm infants born too small for gestational age, most often caused by more extreme hypoxic conditions, total vessel density is also significantly higher soon after birth. We can speculate that enhanced microvascularization is a general adaptive mechanism that might be induced by hypoxia driven stabilization of hypoxia inducible factors (HIF) 1 and 2. Physiological adaptive processes (maternal, fetal and neonatal) to a hypoxic environment as well as their short and long-term consequences will be discussed.
PA1.11.05

Sex-specific programming of cardiac bioenergetics by chronic hypoxic pregnancy and mitochondria-targeted antioxidant therapy

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Background: Fetal cardiac mitochondria are exquisitely sensitive to oxygen availability, and adapt to prenatal hypoxia predominantly via Complex I (CI) to maintain ATP production throughout gestation (Néary, et al. J Mol Cell Cardiol. 74:340-52, 2014). However, chronic fetal hypoxia induces oxidative stress, increasing the risk of cardiovascular pathology in adulthood (Giussani & Davidge. J Dev Orig Health Dis. 4:328-37, 2013). The mitochondria-targeted antioxidant MitoQ is protective against oxidative stress in the adult (Smith, et al. Am NY Acad Sci 1201 (1):96-103, 2010), but its applicability as a prenatal intervention has not been investigated. Thus, the aims of this study were to determine sex-specific cardiac bioenergetics in adult offspring of hypoxic pregnancy, and the effects of prenatal MitoQ intervention.

Methods: Pregnant Wistar dams were exposed to normoxia (N; 21% O2) or hypoxia (H; 13% O2) from 6-20 days gestation ± MitoQ (NM and HM, respectively) or untreated (N, H) provided at 200 μg wet weight-1) was measured by the addition of CI (pyruvate; PY) and β-oxidation (palmitoylcarnitine; PC) substrates, with malate (PY-M and PC-M, respectively), in the absence (State 2; S2) and presence (State 3; S3) of ADP; respiratory control ratios (RCRs) were calculated. Following CI and CIII inhibition (rotenone + antimycin a), CIV was measured in S3 with the electron donor N, N, N′, N′-tetramethyl-p-phenylenediamine and ascorbate (TMPD-A).

Results: Cardiac mitochondria of male, but not female adult hypoxic offspring, showed an increase in pyruvate-mediated CI oxygen consumption and decreased RCR, with the latter improved by prenatal MitoQ treatment (Fig. 1A). Hypoxia increased CI palmitoylcarnitine-mediated β-oxidation RCR in males, which was restored by MitoQ treatment (Fig. 1B). Prenatal MitoQ treatment also reduced β-oxidative coupling and S3 CIV oxygen consumption in both sexes of treated and untreated pregnancy (Fig. 1B and C).

Conclusions: Prenatal hypoxia programmes sex-specific alterations in cardiac mitochondrial respiration in adult offspring. Whilst female offspring of hypoxic pregnancy appear protected, males have poorer CI and β-oxidative coupling. Prenatal MitoQ treatment in hypoxic pregnancy may improve pyruvate-mediated CI coupling and β-oxidative uncoupling in hearts of male offspring. Prenatal MitoQ treatment in any pregnancy may also reduce CIV oxygen consumption in adult offspring of both sexes. Therefore, prenatal MitoQ treatment in pregnancy may reduce cardiac oxygen demand in adult offspring, shifting mitochondrial bioenergetic flux through anaerobic pathways. Figure (A) Pyruvate (PY), PY with malate RCR (PY-M RCR), (B) palmitoylcarnitine (PC), with malate RCR (PC-M RCR), and (C) TMPD with ascorbate (TMPD-A).

PA1.11.06

Low level arsenic exposure during pregnancy in 3xG cohort in Flanders: increased maternal oxidative stress and reduced birth weight

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Increasing epidemiologic evidence indicates that even low level arsenic (As) exposure affects adverse pregnancy outcomes. The adverse outcome pathways from As exposure during pregnancy need further clarification.

This study investigates whether urinary As species and As methylation efficiency are associated with oxidative stress during pregnancy and birth weight in 151 mother-child pairs of the 3xG cohort in Flanders, Belgium (2012-2015). Urine samples were collected between 25 and 35 weeks of gestation and different As species (inorganic As (iAs; As(III), As(V)), monomethylAs acid (MMA) and dimethylAs acid (DMA)) were measured using HPLC-IC-MS. Multiple linear regression analyses were performed to evaluate the associations between As exposure and oxidative stress, measured by the amount of 8-hydroxy-2′-deoxyguanosine (8-OHdG, ln-transformed) in the same urine samples (ELISA), as well as birth weight. The associations for 8-OHdG were adjusted for age and smoking before sample collection, and those for birth weight for age and BMI of the mother, gender of the baby, gestational age, and smoking during pregnancy.

With increasing levels of MMA levels, urinary 8-OHdG concentrations increased with 24% (μg/l) (95% CI = 0.5-51.7%), while the birth weight decreased with -176.71 g...
Blood pressure (tail-cuff plethysmography), in vivo hypoxia led to diastolic dysfunction in male and female offspring. A 2-way ANOVA was used for analyses.

Secondary methylation index (−337.84; −15.59). Further, a decreasing trend between the secondary methylation index (=DMA/MMMA) and 8-OHdG was found (β = 0.998 (95% CI = 0.996-1.000)). No significant associations were observed for SMI and birth weight, and for iAs, DMA and the primary methylation index (=MMA/iAS) with 8-OHdG as well as birth weight. Together, these data indicate that in a region with a relatively low environmental As burden, oxidative stress during pregnancy is associated to the toxic metabolite MMA and with less efficient As detoxification efficiency. Furthermore, this same monomethylated As-species seems to affect the birth weight of these women’s children. This underscores the risks of low level As exposure to vulnerable populations. The 3xG study is part of the cAT project, funded by NIRAS and the local partnerships MONA and STORA.

PA1.11.07
Effect of maternal antioxidant MitoQ treatment on aged offspring cardiovascular function in a rat model of intrauterine growth restriction (IUGR)

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Introduction: A suboptimal environment in fetal life is linked to cardiovascular disease in adult life. One of the central factors which impacts development of the fetus is a hypoxic environment. Maternal hypoxia can lead to placental oxidative stress and abnormal cardiovascular function in the offspring. Mitochondria are a major source of oxidative stress in the placenta. We propose to target placental oxidative stress using the mitochondrial antioxidant MitoQ. MitoQ will be loaded into nanoparticles to restrict treatment to the placenta and prevent MitoQ from crossing the placental barrier to the fetus. Our preliminary data have shown that nanoparticles can reach the labyrinth zone of the placenta but do not cross to the fetus (due to the size and charge of the nanoparticles). We have also shown that maternal treatment with MitoQ loaded into nanoparticles can prevent the placental oxidative stress caused by hypoxia. However, the long term effect of this treatment on preventing fetal programming of cardiovascular disease awaits investigation. We hypothesize that placental targeted MitoQ treatment may prevent the development of cardiovascular disease in aged offspring.

Methods: Pregnant rats were injected with either MitoQ loaded nanoparticles (nMitoQ; 125 μM) or saline via tail vein on gestational day (GD) 15. Rats then were subdivided into two groups exposed to either hypoxia (11% O2) or normoxia (21% O2) from GD 15-21 (term; 22 days). At 13 months of age, blood pressure (tail-cuff plethysmography), in vivo cardiac function (echocardiography) and vascular function (wire myography) were assessed in both male and female offspring. A 2-way ANOVA was used for analyses.

Results: Assessment of cardiac function demonstrated that hypoxia led to diastolic dysfunction in male and female offspring. Treatment with nMitoQ did not improve diastolic function in male offspring but did improve diastolic function in both normoxic and hypoxic female offspring by increasing the E wave velocity (MV E: normoxia/saline: 847 ± 60 mm/s vs. normoxia/nMitoQ: 1204 ± 162 mm/s and hypoxia/saline: 844 ± 75 mm/s vs. hypoxia/nMitoQ: 929 ± 88 mm/s; P = 0.02). Hypoxia had no effect on ex vivo mesenteric artery sensitivity to phenylephrine (PE) in either male or female offspring. nMitoQ, however, increased sensitivity to PE in male offspring from normoxic and hypoxic pregnancies (pEC50 PE: normoxia/saline: 5.54 ± 0.05 vs. normoxia/nMitoQ: 5.66 ± 0.03 and hypoxia/saline: 5.69 ± 0.08 vs. hypoxia/nMitoQ: 5.88 ± 0.03; P = 0.0001). This effect was not seen in female offspring. While hypoxia did not alter ex vivo mesenteric artery sensitivity to the vasorelaxant methacholine (MCh) in male offspring, sensitivity to MCh was increased by treatment with nMitoQ. In female offspring, hypoxia reduced mesenteric artery sensitivity to MCh and nMitoQ increased it in both normoxic and hypoxic female offspring. Neither hypoxia nor nMitoQ altered blood pressure.

Conclusion: Using nanoparticles to target the antioxidant treatment (MitoQ) to the placenta in mid gestation can alter cardiovascular function in offspring later in life. This was illustrated by reversal of an aging effect on vascular function in male offspring. MitoQ was shown to increase mesenteric artery sensitivity to vasoconstriction, increase the sensitivity to vasorelaxation in male and female offspring and improve diastolic function in female offspring.

PA1.11.08
How safe is ART? Effect of in vitro fertilisation (IVF) and prolonged embryo culture on mouse development and postnatal health

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Since the advent of IVF (in vitro fertilisation), several million babies have been born worldwide. However, reports link in vitro techniques with adverse short and long-term health outcomes. Using a mouse model, we investigated the effect of IVF and duration of culture on blastocyst development and cell number and the postnatal health of offspring. Experimental groups (8-13 litters each): NM (natural mating, non-superovulated); IV-ET-2Cell (2-cell embryos derived in vivo from superovulated mothers (SOM) and immediately transferred (ET) to recipients; IV-ET-BL (blastocysts derived in vivo from SOM and immediate ET); IVF-ET-2Cell (2-cell embryos generated by IVF from SOM, short culture and ET); IVF-ET-BL (blastocysts generated by IVF from SOM, long culture and ET). IVF blastocysts after prolonged culture developed slower
and comprised reduced trophectoderm and ICM cell numbers compared with in vivo generated blastocysts (P < 0.05; n = 50-87 per treatment). IV-ET-2Cell (n = 57), IV-ET-BL (n = 47), IVF-ET-2Cell (n = 75) and IVF-ET-BL (n = 42) groups compared with NM controls (n = 80), showed increased body weight, increased Systolic blood pressure SBP, impaired GTT and abnormal organ:body weight ratios in both genders (P < 0.05), independent of litter size. SBP and Angiotensin Converting Enzyme (ACE) for IVF-ET-BL males was increased compared to IV-ET-BL males. SBP for IVF-ET-BL males was increased compared to IVF-ET-2Cell males. SBP for IVF-ET-BL males at week 21 was positively correlated with lung (ACE). However, glucose concentration 2 hours after glucose injection and AUC (area under curve) in male IVF-ET-BL was reduced compared with IVF-ET-2Cell males. Serum insulin for IVF-ET-BL males was significantly reduced compared with IVF-ET-2Cell, but serum glucose and G:I ratio did not show any significant differences. No differences were evident between the four treatments groups for females. We conclude that reproductive treatments affect the development and potential of preimplantation embryos, influencing postnatal development and physiology compared with undisturbed reproduction. In particular, prolonged embryo culture, with normalised SO, IVF and ET, may adversely affect male offspring cardiovascular but improve the metabolic profile compared with short culture, However, female health is less sensitive.

PA1.12.01 - Folate and other nutrients

PA1.12 - Folate and other nutrients

Life course evolution of vitamin B12 deficiency in young rural Indian adults

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Background: Vitamin B12 (B12) is an important regulator of 1-C metabolism and therefore, crucial for fetal growth and development. Maternal vitamin B12 deficiency has been shown to increase risk of fetal neural tube defects, impaired brain development, and programming of adiposity and insulin resistance. B12 deficiency is common in Indians. There are few studies addressing the 'lifecourse' evolution of B12 status. Pune Maternal Nutrition Study (PMNS) offers a unique opportunity to study these factors.

Methods: PMNS is a preconceptional birth cohort set in 6 villages around Pune. Mothers were investigated before and during pregnancy, babies at birth, and both parents and the child serially at 6, 12 and 18 years after delivery. Measurements included socio-economic status (SES), body size and composition, nutrition, and hematological and biochemical-metabolic parameters (B12, folate and homocysteine). A genetic risk score (GRS) was calculated for B12 deficiency based on 8 significantly associated SNPs in a GWAS. We used Generalised Estimating Equations (GEE) to investigate the associations of B12 deficiency (plasma B12 < 150 pmol/L) in 18 year old children.

Results: In Children, mean plasma B12 concentrations progressively decreased (224, 188 and 139 pmol/L at 6, 12 and 18 years of age, respectively) and B12 deficiency correspondingly increased (16%, 24% and 58% respectively). Children had higher rates of B12 deficiency at 18 years (58%) compared to their parents (mothers: 34%, fathers: 51%). Folate status was normal and remained stable. Plasma homocysteine concentration progressively increased from 12 to 18 years (mean 11.7 and 26.3 µmol/L) and 27% and 89% were hyperhomocysteinemic, respectively. During pregnancy, ~65% of the mothers of these children were B12 deficient, a third were hypohomocysteinemic and 90% had elevated methyl malonic acid (MMA) concentration. Folate status was adequate. B12 deficiency in the child was related to genetic risk score (based on CUBN, FUT2, FUT6, MMAA, TCN1 and TCN2 genotypes), lower maternal B12 at 28 weeks gestation, lower parental B12 status during post-partum period, increasing age of the child, and with larger body size, lower milk consumption, and lower WBC count.

Conclusion: This is the world’s first lifecourse description of the evolution of vitamin B12 deficiency in a very deficient population. Genetic factors contributed significantly but there is a clear evidence for environmental contribution. Lower maternal transfer during pregnancy, rapid childhood and pubertal growth, post-natal family environment including low dietary intake of milk and better hygiene seem to be important contributory factors. These factors should be considered in the public health policy to improve B12 status of Indians to reduce incidence of NTDs, and fetal programming of diabetes and related disorders.
PA1.12.03
The impact of periconceptional folic acid on reproduction, care and health
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Reproduction is associated with health and non-communicable disease risks in later life. A multitude of genetic and environmental factors, including the B vitamin folic acid (here synthetic and natural form), are involved and influence the pathways and underlying molecular biological mechanisms. The WHO recommendation of the periconceptional maternal use of folic acid supplements to prevent neural tube defects, stimulated the research on the impact of folic acid on other reproductive failures, such as subfertility, fetal growth restriction, preeclampsia, and diseases occurring in postnatal life, such as asthma, cancer, cardiovascular and psychiatric diseases. Folic acid is essential for the provision of one-carbon moieties for the synthesis of proteins, lipids, DNA and RNA, and the methylation of chromatin. Vegetables and fruits are rich sources of folic acid of which the intake is adequate in less than 20% of couples in reproductive ages. In addition to the increased folic acid requirements during the periconception period as a consequence of rapid growth and numerous cell divisions, the prevalence of folic acid shortage is also very high in the reproductive population. In mice, C57BL mice had during pregnancy ad libitum access either to a standard rat chow (CTRL), or AGE-rich diet (AGE, 75% standard rat chow/25% bread crusts, wt/wt). After delivery, both groups of dams received a standard diet. In offspring, somatic, motoric, and neurological reflexes develop (eye opening, ear unfolding, incisor eruption, ear twitch-, eyelid-, and auditory startle-reflexes, forelimb/hindlimb grasp, negative geotaxis, air and surface righting, rope suspension) were monitored until weaning (day (D)21). At weaning, offspring (CTRL: n = 18; BC: n = 13) were placed on a standard diet. At D80, offspring’s metabolic status was tested.

Results: Both groups of dams consumed similar amounts of food during pregnancy or lactation. Body weight of newborn (D3) or weaned (D21) offspring of CTRL and AGE dams did not differ significantly. At D80, male offspring of AGE dams were significantly heavier (p < 0.02) compared with their CTRL counterparts. Offspring of AGE dams developed ear twitch (11.5 ± 1.1 day vs. 12.3 ± 0.8 day, p = 0.026), eyelid (15.1 ± 0.8 day vs. 15.8 ± 0.9 day, p = 0.042), and auditory startle (13.6 ± 1.1 day vs. 14.8 ± 1.3 day, p < 0.012) reflexes earlier comparing with their counterparts from CTRL dams. They also performed surface righting within 1 second earlier (11.4 ± 2.2 day vs. 13.7 ± 1.8 day, p < 0.004). In young adult mice, blood pressure, renal function, and measures of oxidative status did not differ significantly between the groups. Offspring of AGE dams maintained similar glycemia to that of their CTRL counterparts with significantly higher insulin levels, resulting in lower insulin sensitivity (HOMA: 8.8 ± 7.2 vs 3.6 ± 1.8, p < 0.026). At sacrifice, both groups of offspring presented similar AGEs-associated fluorescence of plasma. A trend towards lower levels of soluble receptor for AGEs - sRAGE - was observed in AGE offspring (648 ± 156 pg/ml vs. 553 ± 131 pg/ml, p = 0.07). No significant between-group difference in heart-, liver-, and kidney-to-body weight ratio; liver cholesterol or triacylglycerols content was revealed.

Conclusions: In mice, a maternal AGE-rich diet (even if consumed solely during pregnancy) may affect early somatic and motoric development of offspring; and their insulin sensitivity

PA1.12.05
Advanced glycation end products-rich diet during pregnancy affects early somatic and motoric development and metabolic status of offspring in mice
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Background: In thermally processed foods, advanced glycation end products (AGEs) are formed by non-enzymatic reaction between proteins and reducing sugars. Ingested AGEs are partially absorbed into circulation. Current evidence support that AGEs are maternally transferred to fetus. Consumption of AGE-rich diet associates with negative metabolic effects, and behavioral changes in adult rodents, and age-related changes, and pathology in humans. Since maternal diet may affect postnatal development of offspring, and their susceptibility to metabolic disturbances, we investigated whether consumption of AGE-rich diet by dams during pregnancy affects early development of offspring, and their metabolic status later in young adulthood.

Methods: C57BL mice had during pregnancy ad libitum access either to a standard rat chow (CTRL), or AGE-rich diet (AGE, 75% standard rat chow/25% bread crusts, wt/wt). After delivery, both groups of dams received a standard diet. In offspring, somatic, motoric, and neurological reflexes develop (eye opening, ear unfolding, incisor eruption, ear twitch-, eyelid-, and auditory startle-reflexes, forelimb/hindlimb grasp, negative geotaxis, air and surface righting, rope suspension) were monitored until weaning (day (D)21). At weaning, offspring (CTRL: n = 18; BC: n = 13) were placed on a standard diet. At D80, offspring’s metabolic status was tested.

Results: Both groups of dams consumed similar amounts of food during pregnancy or lactation. Body weight of newborn (D3) or weaned (D21) offspring of CTRL and AGE dams did not differ significantly. At D80, male offspring of AGE dams were significantly heavier (p < 0.02) compared with their CTRL counterparts. Offspring of AGE dams developed ear twitch (11.5 ± 1.1 day vs. 12.3 ± 0.8 day, p = 0.026), eyelid (15.1 ± 0.8 day vs. 15.8 ± 0.9 day, p = 0.042), and auditory startle (13.6 ± 1.1 day vs. 14.8 ± 1.3 day, p < 0.012) reflexes earlier comparing with their counterparts from CTRL dams. They also performed surface righting within 1 second earlier (11.4 ± 2.2 day vs. 13.7 ± 1.8 day, p < 0.004). In young adult mice, blood pressure, renal function, and measures of oxidative status did not differ significantly between the groups. Offspring of AGE dams maintained similar glycemia to that of their CTRL counterparts with significantly higher insulin levels, resulting in lower insulin sensitivity (HOMA: 8.8 ± 7.2 vs 3.6 ± 1.8, p < 0.026). At sacrifice, both groups of offspring presented similar AGEs-associated fluorescence of plasma. A trend towards lower levels of soluble receptor for AGEs - sRAGE - was observed in AGE offspring (648 ± 156 pg/ml vs. 553 ± 131 pg/ml, p = 0.07). No significant between-group difference in heart-, liver-, and kidney-to-body weight ratio; liver cholesterol or triacylglycerols content was revealed.

Conclusions: In mice, a maternal AGE-rich diet (even if consumed solely during pregnancy) may affect early somatic and motoric development of offspring; and their insulin sensitivity.
in later life, even if offspring consume a standard diet after weaning. Further work is needed to determine the underpinning mechanisms by which a maternal AGE-rich diet adversely affects neurobehavioral and metabolic pathways in offspring.

PA1.12.06
Maternal genetic polymorphisms affect plasma vitamin B12 levels during pregnancy and impact the neonatal epigenome

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Background: Vitamin B12 status during gestation can affect health outcomes for both mother and the offspring. Investigating genetic polymorphisms that affect vitamin B12 level during pregnancy can help understand the link between nutrition, genetics and pregnancy outcomes. Here we present the first Genome Wide Association Study (GWAS) of vitamin B12 concentrations during pregnancy and its influence on the neonatal methylome.

Methods: In a prospective mother-offspring multi-ethnic cohort study, Growing Up in Singapore Towards Healthy Outcomes (GUSTO), we performed a Genome-Wide Association Study (GWAS) to identify the genetic risk variants associated with B12 insufficiency during pregnancy. All mothers (N = 938) were genotyped using the Illumina omniexpress + exome array. Relevant covariates/confounders were adjusted for in the statistical models. Pyrosequencing was used to analyze additional SNPs in the gene locus of interest. Replication of the top gene variants was performed in an independent cohort, the Southampton Women’s Survey (SWS) (N = 1755). Downstream effects of genotype dependent maternal B12 insufficiency on neonatal methylome (n = 883) were interrogated by methylation profiling of cord tissue by using Infinium HumanMethylation 450 arrays.

Results: We found 4 genetic risk variants within/near the Fucosyltransferase (FUT) genes associated with maternal plasma B12 levels at genome-wide significance (P < 5.00E-8). Two of these variants, located in the FUT2 coding region and FUT6 promoter (4bp from Transcription Start Site (TSS)), have been previously linked to B12 deficiency in Chinese populations, while the remaining two variants located in coding sequence of FUT3 and FUT6 promoter (1614bp from TSS) were novel findings. We also found FUT3 and FUT6 variants to be in strong linkage disequilibrium with each other. Similar to FUT2 mutations, vitamin B12 levels increased with the increase in minor allele dosage for FUT3 and FUT6 polymorphisms. The significance of FUT genes on maternal B12 concentrations replicated in the SWS independent cohort. A more intricate analysis of the FUT polymorphisms identified ethnic diversity in the vitamin B12 linked genetic risk variants found in Asians vs Caucasians. In the GUSTO cohort we interrogated the downstream effects of maternal B12 insufficiency on infant outcomes and found it to impact perinatal methylation at 6 CpGs (FDR < 0.05). Of all the FUT mutations, FUT2 missense mutation was the most significant factor explaining the variation in neonatal epigenome, especially in the biological pathways involved in cardiac development and neurophysiological function. Segregation analysis of the FUT2 polymorphism identified the secretor genotype (AA and AT) to be associated with a greater influence of maternal vitamin B12 concentration on perinatal methylation compared to the non-secretor form (TT).

Conclusion: Our findings indicate that genetic polymorphisms in FUT genes are linked with B12 concentrations during pregnancy. There is ethnic diversity in these genetic polymorphisms, and maternal FUT2 secretor status can play a role in regulating the sensitivity of the fetal methylome to suboptimal plasma B12 levels in utero.

PA1.12.07
Exposure to low-dose vitamin D from fortification in prenatal life and risk of childhood asthma: Results from the D-Tect study

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Background: Prenatal vitamin D insufficiency may influence immune system and lung development, and cause permanent changes in these organ systems, thereby contributing to the later risk of childhood asthma development. Results from epidemiological studies on the association of vitamin D intake or status during pregnancy with childhood asthma risk in the offspring are, however, conflicting. Furthermore, most studies have short follow up periods and limited number of participants. The objective of this study was to examine whether prenatal exposure to additional vitamin D from margarine fortification was associated with reduced childhood asthma risk until age 9 years, especially among those who had the majority of their prenatal period during the dark months.

Methods: In Denmark a mandatory vitamin D fortification program was terminated 1st of June 1985. This study compares the risk of asthma diagnosed during hospitalization in all children born in Denmark during the two years before the
termination of the Vitamin D fortification program (i.e. exposed to fortification during prenatal life), to the risk among all children born during the two years after the termination (i.e. unexposed to fortification during prenatal life). The children were identified in the Danish Civil registration System and followed up in the Danish National Patient Register from birth to the age 9 years to identify presence and date of the first inpatient asthma admission. The data was analyzed using Cox proportional hazards regression with age as underlying time scale.

Results: Out of 106,347 children exposed to the fortification program during prenatal life, 1,427 (1.34%) had at least one inpatient asthma admission; out of 115,900 children unexposed to fortification, 1,613 (1.39%) had at least one inpatient asthma admission. The Hazard Ratio (HR) for the first inpatient asthma admission among children exposed versus unexposed to fortification was 0.96 (95% CI: 0.90-1.04). In analyses stratified by age at HR were 0.86 (95% CI: 0.75-0.98), 0.95 (95 CI% 0.85-1.06), and 1.10 (95 CI% 0.96-1.26) for the first asthma admission at ages 0-3, 3-6, and 3-9 years, respectively. Adjusting for sex and season of birth gave essentially similar results. There were no statistically significant interactions with season of birth (p = 0.74) or sex (p = 0.55).

Conclusion: Prenatal exposure to extra vitamin D from the Danish mandatory fortification program did not seem to affect the risk of developing asthma that would require hospitalization during prenatal life, 1,613 (1.39%) had at least one inpatient asthma admission. The Hazard Ratio (HR) for the first inpatient asthma admission among children exposed versus unexposed to fortification was 0.96 (95% CI: 0.90-1.04). In analyses stratified by age at HR were 0.86 (95% CI: 0.75-0.98), 0.95 (95 CI% 0.85-1.06), and 1.10 (95 CI% 0.96-1.26) for the first asthma admission at ages 0-3, 3-6, and 3-9 years, respectively. Adjusting for sex and season of birth gave essentially similar results. There were no statistically significant interactions with season of birth (p = 0.74) or sex (p = 0.55).

Methods: Four treatment groups of Sprague-Dawley F0 founder females (n = 6) were gavaged with an environmentally-relevant mixture of Arctic POPs (500μg/kg) or corn oil (Control) and received either 1X or 3X FA representing normal Canadian intakes from fortiﬁed foods (1X) + a daily multivitamin for periconceptional women (3X). F0 females were treated for 5 weeks to establish a body burden of POPs, and then mated to untreated males and POPs/FA treatments continued until weaning of the prenatally-exposed F1 litters. All rats were then fed control chow. GD19.5 placentas and fetuses were assessed for congenital pathologies, including macroanatomical and histopathologic examination. Reproductive development and function were assessed in F1 males at 150 days of age (n = 12/treatment group) following mating with untreated females.

Results: At GD19.5, F1 placental, fetal and body weights and sizes were unaffected by treatment. Prenatal POPs exposure influences male sexual development for the F1 sons as anogenital distance was higher in the POPs 1X and 3X treatment groups. PND150 F1 males had higher kidney (P = 0.01) and brain (P = 0.09) weights due to early-life POPs exposure and smaller spleens (P = 0.04) with FA supplementation. Blood analysis performed on F1 males at PND150 revealed lower haematocrit and platelet counts due to POPs, however, an interaction between POPs and FA supplementation corrected these counts when simultaneously administered (POP3X; P < 0.01). Erythrocyte counts were higher with FA supplementation (P = 0.05). Sperm function parameters also
PA1.13 - Maternal obesity and gestational disorders

Maternal hypertensive disorders of pregnancy and cardiovascular disease risk factors in offspring at age 40 years

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Background: Women with a history of hypertensive disorders of pregnancy (HDP) have increased risk of cardiovascular disease (CVD) later in life. In addition, it has been reported that offspring to mothers with HDP have worse cardiometabolic risk factor profiles in early adulthood and higher risk of cardiovascular disease (CVD) later in life. Potentially, these associations are explained by a shared maternal-fetal preponderance for adverse CVD risk factor profiles. We aimed to study the association between maternal HDP and offspring HDP and CVD risk factors in middle age, accounting for familial heredity of CVD.

Methods: We included 13,466 first-born participants (49.9% women) who attended a population-based structured clinical visit in primary care (The Västerbotten Intervention Program) at age 40 (±0.5) years in Sweden between 1991 and 2014. Data on exposure to maternal HDP were collected from population-based registries on pregnancy and birth outcomes. Using linear regressions, we investigated the association between maternal HDP and offspring CVD risk factors at age 50 and/or 60 years. In a sensitivity analysis, we included the maternal measure at 50 or 60 years as an additional proxy for familial CV health.

Results: 375 (2.8%) of participants were exposed to maternal HDP. Offspring exposed to maternal HDP had a 3.2% (95% confidence interval (CI) 1.6 to 4.7%) higher body mass index (BMI) at age 40 years, 3.2% (95% confidence interval (CI) 2.1 to 4.2%) higher systolic blood pressure (SBP), and 3.3% (95% confidence interval (CI) 2.0 to 4.5%) higher diastolic blood pressure (DBP). We found little support for an association between maternal HDP and total serum cholesterol (-1.1%, 95% CI -3.2 to 0.8%). Upon further adjustment for maternal BMI, the association between maternal HDP and offspring BMI at age 40 years was fully attenuated. Maternal HDP was still associated with offspring SBP (1.9%, 95% CI 0.1 to 3.6%) but no longer with offspring DBP (1.5%, 95% CI -0.5 to 3.6%) or total serum cholesterol (-2.1%, 95% CI -5.3 to 1.1%) after adjusting for the corresponding maternal measure.

Conclusions: Though offspring exposed to maternal HDP had slightly worse CVD risk factor profile at age 40 years, our study suggests that this might be explained by a familial preponderance to worse CVD profile rather than an intra-uterine effect of HDP exposure per se. Nonetheless, this means that when developing CVD prevention programs for women with a history of pregnancy complications, a family-based approach, which also includes prordial CVD prevention in her child/children, could potentially increase the public health impact of such interventions.

PA1.13.02

Maternal pre-pregnancy overweight and childhood physical activity and fitness - the ABCD study

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Background: Maternal obesity is a risk factor for obesity and cardiovascular disease in the offspring. Furthermore, childhood fitness and physical activity are strongly associated with later health. As the prenatal environment could affect the development of childhood fitness, we assessed whether maternal prepregnancy overweight/obesity (ppBMI ≥ 25kg/m²) is an independent determinant of cardiorespiratory fitness, muscular strength, physical activity (PA) and sedentary behaviour (SB) in 8-9 year old children.

Methods: 194 children of Dutch ethnicity aged 8.6 (±0.4) years participated. These children were randomly selected from a prospective birth cohort, the Amsterdam Born Children and their Development study (ABCD). We assessed cardiorespiratory fitness by 20-m Multistage Shuttle Run test (20-m MSRT), muscular strength by hand dynamometry and moderate-to-vigorous PA (MVPA) level and SB by 7-day accelerometry. The association of pre-pregnancy overweight/obesity with these outcome measures was assessed by multivariate linear regression. Subsequently, we assessed the...
mediating effect of birth weight and fat mass, derived from bioelectrical impedance, at 5 years of age.

**Results:** Mean (± SD) attained 20-m MSRT stage was 5.3 (±1.7). Compared to children from normal weight women, children from women with pre-pregnancy overweight/obesity attained a 0.75 (95% CI: -1.42; -0.08) lower stage, adjusted for child’s sex and BMI. This association was not mediated by birth weight or child’s fat mass at age 5. Maternal pre-pregnancy overweight was not associated with child’s muscular strength, MVPA or SB.

**Conclusion:** Maternal pre-pregnancy overweight or obesity is associated with reduced cardiorespiratory fitness in the offspring, but not with muscular strength, physical activity or sedentary behaviour. Birth weight or fat mass at age 5 did not mediate this association. Reduced cardiorespiratory fitness may partly explain the increased cardiovascular disease risk in children of obese women.

**Funding:** Dutch heart foundation (grant no. 2013T085). ZonMw (grant no. 40-00703-98-11627)

**PA1.13.04**

Excess maternal gestational weight gain is associated with early timing of pubertal onset in daughters

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**Background:** To investigate whether in utero exposure to maternal excess or inadequate gestational weight gain (GWG) is associated with the timing of pubertal onset in girls, and whether the association is mediated by pre-pubertal BMI. Early puberty is associated with a variety of negative health consequences, including adolescent mental health and adulthood chronic conditions, such as cancer. The average age of pubertal onset among girls has declined dramatically over the past few decades.

**Methods:** Prospective cohort study including 2,161 diverse mother-daughter pairs of Kaiser Permanente Northern California (KPNC), where daughters were age 6–11 y. Pubertal onset was assessed using pediatrician-recorded pubertal maturation (Tanner) staging in the KPNC electronic health record (EHR). Maternal total GWG was calculated by subtracting pre-pregnancy weight from the weight immediately prior to birth. All the weights measured before or during pregnancy.
pregnancy were obtained from the KPNC EHR and total GWG was categorized according to the 2009 Institute of Medicine (IOM) recommendations as met (referent), inadequate (below recommended GWG), or exceed. We used proportional hazards model with interval censoring, with the outcomes as age of transition from breast stage 1 to 2+ (BR2+) or pubic hair stage 1 to 2+ (PH2+). Associations were examined without adjustment (Model 1), adjusted for maternal age, girl’s race/ethnicity, and gestational age (Model 2), and with girls’ pre-pubertal body mass index (Model 3).

Results: There was a significant association between excess GWG and earlier timing of pubertal onset (Table 1). Girls whose mother exceeded the IOM recommendation were over 1.5 times more likely to experience earlier onset of breast and pubic hair than those whose mother met the recommendation [adjusted hazard ratio (HR) = 1.61, 95% confidence interval (CI) 1.29-2.01; HR = 1.55, 95%CI 1.17-2.06, respectively]. The associations remained statistically significant after adjusting for girl’s pre-pubertal BMI [HR = 1.45, 95% CI 1.16-1.82; HR = 1.38, 95%CI 1.04-1.84, respectively]. Inadequate GWG was also associated with earlier pubertal onset, though the associations were attenuated and nonsignificant after adjustment for girl’s pre-pubertal BMI.

Conclusions: We observed independent associations between maternal excess GWG and earlier timing of pubertal onset in girls. The results suggest the importance of monitoring the weight gain among pregnant women to prevent ever-accelerating pubertal maturation in girls as an upstream prevention for a variety of adolescent and adult health conditions.

Table 1.

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tbody>
<tr>
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<td>HR (95% CI)</td>
</tr>
<tr>
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<td>1 (ref)</td>
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<td>Below</td>
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<td>Exceed</td>
<td>1.63 (1.30-2.03)</td>
<td>1.61 (1.29-2.01)</td>
</tr>
<tr>
<td>Pubic Hair</td>
<td>Met (95% CI)</td>
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<tr>
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<td>Exceed</td>
<td>1.72 (1.30-2.27)</td>
<td>1.55 (1.17-2.06)</td>
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</table>

Association between maternal gestational weight gain and onset of breast and pubic hair development: KPNC Puberty Study.

PA1.13.05

**Unfolded protein response in developing intestine inhibited by maternal obesity**

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**Background:** Although maternal obesity is associated with offspring intestinal inflammation and reduced gut barrier function, its impact on fetal gut development remains unclear. The unfolded protein response (UPR) is critical to the development of secretory tissues such as the intestine due to high demands on the endoplasmic reticulum, and has previously been shown to be necessary for differentiation of the intestinal epithelium. This study set out to investigate the impact of maternal diet-induced obesity (mDIO) on the unfolded protein response in the developing fetal intestine.

**Methods:** Female C57BL/6 mice were fed a control or a high fat diet (mDIO; 60% kcal from fat) for 6 weeks prior to and throughout gestation. At E18.5 fetal small and large intestines were collected from one male and one female per litter and UPR signaling was analyzed by qPCR (control n = 7; mDIO n = 8) and western blot (control n = 4; mDIO n = 6).

**Results:** In the fetal small intestine, mDIO was associated with increased mRNA levels of mucin (MUC2) (p < 0.0001) and tight junction protein occludin (p < 0.0001), although protein levels of occludin did not differ by maternal diet. Concurrently, fetal small intestine mRNA levels of UPR-related signaling factors including ER-chaperone glucose-regulated protein 78 (grp78; p < 0.001) and its transcriptional regulator spliced X-box binding protein (XBP1s; p < 0.05) were decreased, as well as a modest decrease in activating transcription factor 4 (ATF4; p = 0.065). In the fetal large intestine, mDIO was associated with decreased levels of ATF4 (p < 0.01) and C/EBP homologous protein (CHOP; p = 0.01). While mDIO was associated with increased mRNA levels of pro-inflammatory toll-like receptor 4 (TLR4) in fetal small intestines (p < 0.05), mRNA levels of inflammatory cytokines including TNF, IL-10, NF-κB, IL-1β, and MCP1 were similar between maternal diet groups in both small and large intestines.

**Conclusion:** Occludin and MUC2 are essential components of the intestinal barrier, but while increases in mRNA levels are observed with mDIO, protein levels of occludin were not changed and it is unclear whether fetal barrier function is altered. We show mDIO decreased fetal gut grp78, XBP1s, and ATF4, which are markers of the unfolded protein response (UPR)—a homeostatic response to prevent the accumulation of misfolded proteins. However, mDIO had no effect on inflammatory cytokines, indicators of unresolved ER stress. Our data may indicate inhibition of the normal UPR in the fetal gut due to maternal obesity, which may result in an impairment of fetal intestinal epithelial differentiation, potentially predisposing offspring to increased gut permeability and inflammation postnatally.

PA1.13.06

**Cord metabolic profiles in obese pregnant women; insights into offspring growth and body composition**

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Background: Offspring exposed to maternal obesity and hyperglycaemia in-utero are at an increased risk of obesity in childhood and as adults; however the underlying mechanisms remain unknown. The primary aim was to assess the effect of an antenatal lifestyle intervention in obese women on the offspring cord blood metabolic profile. Associations between the cord blood metabolic profile and the mother’s clinical and biochemical characteristics and offspring body composition (birth and age 6 months) were also explored.

Methods: Data were from the UK Pregancies Better Eating and Activity Trial (UPBEAT), a randomised controlled trial in 1555 women assessing an antenatal intervention promoting a low glycaemic diet and increased physical activity in obese pregnant women. Maternal anthropometry and BMI were measured at trial enrolment and in the 3rd trimester. The women underwent universal screening for the diagnosis of gestational diabetes. Offspring were followed up at birth (n = 343) and at age 6 months (n = 209), when detailed assessments of growth and body composition were made. Where reference population data was available, z-scores and velocities of growth were calculated. The cord blood metabolic profile included candidate hormones previously implicated in adverse fetal growth, and targeted metabolome (including amino acids, non-esterified fatty acids, carboxylic acids, phospholipids, acylcarnitines). To explore associations with infant adiposity, multivariate regression was undertaken with adjustment for potential in-utero and early-life confounders and false discovery rate correction for multiple testing.

Results: The UPBEAT intervention was not associated with change in any measures of the cord blood metabolic profile. When combining intervention and control arms, higher maternal glycaemia (fasting glucose at 28 weeks’ gestation) demonstrated a linear association with cord blood concentrations of lysophosphatidylcholines 16:1 (β = 0.65, 95%CI 0.03 to 0.10) and 18:1 (0.52, 0.02 to 0.80). A principal component of cord blood phosphatidylcholines and lysophosphatidylcholines was associated with infant birthweight z-scores (β = 0.04, 0.02 to 0.07); and weight z-scores at age 6 months (β = 0.05, 0.00 to 0.10). Cord blood IGF-1 and adiponectin concentrations were positively associated with infant weight z-scores at birth and age 6 months.

Conclusions: We provide novel evidence to suggest that concentrations of lysophosphatidylcholines along with IGF-1 measured in cord blood may be determinants of newborn weight and infant weight at age 6 months. If found causal, these data support the hypothesis that susceptibility to childhood obesity may be ‘programmed’ in-utero.

Funding: This study was funded by NIHR RP-0407-104522 & BRC at GSTT&KCL; CSO Scotland, GSTT Charity Tommy’s Charity, the European Early Nutrition Project and Action Medical Research.

PA1.13.07

Maternal body mass index, gestational weight gain and the risk of childhood overweight: An individual participant data meta-analysis

E. Voerman1, On behalf Of the MOCO Collaboration2

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Background: Maternal obesity and excessive gestational weight gain may affect the risk of overweight in the offspring. We aimed to assess the separate and the combined effects of maternal pre-pregnancy body mass index (BMI) and gestational weight gain on offspring BMI and the risk of overweight throughout childhood.

Methods: In this individual participant data meta-analysis, 162,737 mothers and their children from 37 pregnancy and birth cohorts from Europe, North-America and Oceania were included. We assessed the separate and combined associations of maternal pre-pregnancy BMI and gestational weight gain, both across the full range and in clinical groups, with BMI standard deviation scores (SDS) and the risks of overweight in early (2.0-4.9 years), mid (5.0-9.9 years) and late childhood (10.0-17.9 years) using linear and binary logistic mixed effects models.

Results: A higher maternal pre-pregnancy BMI was associated with higher BMI SDS and higher risks of overweight throughout childhood, with the strongest effect estimates in late childhood. These associations were present across the full range of maternal pre-pregnancy BMI. For all maternal BMI categories, only gestational weight gain in the upper extremes tended to be associated with an increased risk of offspring overweight. Combined analyses showed that, as compared to children of mothers with a normal weight and sufficient gestational weight gain, those of mothers with overweight or obesity had a higher risk of overweight, independent of the gestational weight gain of their mother. Children of mothers with obesity and excessive gestational weight gain had the highest risk of overweight in early, mid and late childhood (Odds Ratios (OR) 2.57 (95% Confidence Interval (CI) 2.26, 2.92), OR 3.69 (95% CI 3.44, 3.97) and OR 5.88 (95% CI 4.68, 7.40), respectively).

Conclusions: Maternal pre-pregnancy BMI is across its full range associated with the risk of childhood overweight, with the strongest associations present at later childhood ages. The additional effect of excessive gestational weight gain in overweight and obese mothers on childhood overweight risk seems to be limited. Promoting a healthy weight in women before pregnancy, rather than targeting weight gain during pregnancy, may improve offspring weight status.

10th World Congress S65
Neonatal adiposity: determinants and consequences for later health

N. Modi

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Adiposity is influenced by genotype, nutrition and health. Neonatal adiposity is also influenced by intrauterine exposures, determined by maternal phenotype and health. Altered adiposity is implicated in the development of the metabolic syndrome. It is unknown if altered adiposity in the neonatal period tracks into in childhood and adult life. Neonatal adiposity increases linearly across the normal range of maternal Body Mass Index. Babies of diabetic and obese mothers, and very preterm babies, regardless of weight at birth, are at around twice the risk of developing diabetes, high blood pressure and heart disease in early adult life, conditions that are related to adipose tissue content and distribution. We have shown that when they reach their due date, adipose tissue content and distribution in babies born very preterm differs from babies born at full-term, and is characterised by an increase in intra-abdominal adiposity. We have also identified similar findings in young adults born very preterm. In a cohort of babies of diabetic mothers, we showed that adiposity in early infancy is ampliﬁed in comparison with babies of healthy mothers, despite good maternal diabetic control and breast-feeding. If inferences from cross-sectional studies such as these are corroborated in longitudinal cohorts adipose tissue content and distribution may be used as a biomarker of future cardiometabolic health and could also be used as an outcome measure to test nutritional and pharmacological treatments in infancy to reduce later metabolic health risks.

Birth weight and subsequent risk of obesity across two generations in Chinese females

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Objective: Malnutrition in early life, an important risk factor for subsequent adverse conditions, has been related with a higher risk of metabolic abnormalities in offspring. This study was designed to evaluate a cross-generational association of birth weight with the risk of subsequent obesity in Chinese females.

Methods: A cross-sectional survey was performed among 10324 female residents with lineal blood relationship from 3888 families in Minhang district, Shanghai, China, during Nov 2012 to Jan 2013. In-person interview was conducted using a structured questionnaire to collected information on demographic characteristics, birth weight, birth length, gestational age, tobacco use and alcohol consumption. Body weight, standing height, waist circumference and blood pressure were measured for participants aged 20 years or above following a standard protocol. Path analysis was performed to estimate the effect of maternal birth weight and body size on their female offspring’s, and mediation analysis was applied to test whether daughters’ birth weight mediated the associations between maternal and daughters’ body size in adulthood.

Results: A positive association was observed between maternal and daughters’ birth weight, with 1 kg increase of maternal birth weight linked to an average of 335 g increase in daughters’ birth weight [95% conﬁdence interval (CI): 307 to 363 g]. The positive association was more pronounced at both the lower and upper extreme of daughters’ birth weight. Maternal overall and central obesity were associated with an average of 67 g (95%CI: 27 to 106 g) and 40 g (95%CI: 17 to 62 g) increase in daughters’ birth weight, respectively, and tripled the subsequent risk of obesity in the offspring. In subjects aged 20 years or above, birth weight was positively associated with subsequent risk of obesity, with odds ratios (OR) (95%CI) of overall and central obesity being 1.93 (1.11 to 3.36) and 1.49 (1.10 to 2.02), respectively, for women with birth weight ≥4 kg compared with those with birth weight of 2.5 - 2.9 kg. Path and mediation analyses showed that offspring’s birth weight, as a mediator of maternal and daughters’ body mass index, explained 1.8% of the association, but didn’t mediate the association between maternal and daughters’ waist circumference.

Conclusions: Maternal birth weight and status of obesity may influence female offspring’s birth weight and subsequent risk of obesity. The cross-generational association may contribute to the increasing obesity and related non-communicable chronic diseases in China.

Body mass index trajectories associated with resolution of elevated adiposity in youth and incident adult obesity


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Background: Youths with high body mass index (BMI) who become non-obese adults have the same burden of cardiovascular risk factors in adulthood as those who were never obese. However, the early-life BMI trajectories for youth who develop incident obesity in adulthood, or those overweight or obese youth who avoid becoming an obese adult, have not been described. Therefore, we aimed to determine and compare early life BMI trajectories in 4 groups of participants defined according to their change in BMI status between youth and adulthood.

Methods: From 1980 to 2011, up to 8 measures of weight and height were collected from participants in the population-based prospective Cardiovascular Risk in Young Finns Study. Participants were 2717 young adults (1252 males, 1465 females) who had BMI (calculated as weight in kg/(height in m)^2) at baseline in 1980 when aged 3, 6, 9, 12, 15, or 18 years, and again at least once in adulthood in 2001, 2007, or 2011 when aged 34 to 49 years. Elevated youth (those aged 3-18 years) BMI status was defined as a BMI level exceeding Cole’s international overweight and obesity cutpoints and adult (21-49 years) obesity was defined as a BMI ≥30 kg/m^2. Participants were stratified into 4 groups based on their BMI status in 1980 and the latest adult follow-up: persistently elevated BMI, persistent non-obese, incident obese, and elevated youth BMI resolvers. Bayesian Hierarchical Piecewise regression was used to model individual trajectories of BMI from youth to adulthood and to investigate differences in trajectories across the four a priori defined groups based on BMI status.

Results: Compared with those with persistently elevated BMI, those who resolved their elevated youth BMI by adulthood had lower average BMI at age 6 years, and slower rates of BMI change from young childhood. In addition, their BMI levels started to plateau on average before young adulthood (16 years for females and 21 years for males), while the BMI of those whose high-BMI persisted did not level off until 25 years for males and 27 years for females (Figure A). Compared with those who resolved elevated youth BMI, those who developed incident obesity had higher BMI rate of change from age 6 years and their BMI continued to increase linearly until approximately age 30 years (Figure B).

Conclusions: Efforts to alter BMI trajectories that predict adult obesity should ideally commence before age 6 years. The natural resolution of high youth BMI starts in adolescence for females and early adulthood for males, suggesting a critical window for secondary prevention.
mandatory military conscription tests. Information on heart failure was retrieved from high quality national registers (342 first hospitalizations for heart failure).

**Results:** BMI change during puberty (HR per SD increase 1.47; 95% CI 1.36-1.60), but not childhood BMI, independently associated with risk of heart failure. Boys developing overweight during puberty (HR 3.14; 95% CI 2.25-4.38) but not boys with childhood overweight that normalized during puberty had increased risk of heart failure compared with boys without childhood or young adult overweight.

**Conclusion:** BMI change during puberty is a novel risk factor for adult heart failure in men.

**PA1.14.06**

**Qualitatively distinct child to adult BMI trajectories and adult cardiometabolic outcomes**

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**Background:** The relationship between life course body mass index (BMI) trajectories and adult risk for cardiovascular disease is poorly described. In a well-characterized longitudinal cohort study, we aimed to identify BMI trajectories from early childhood to adulthood and investigate their association with adverse cardiometabolic phenotypes (type 2 diabetes (T2DM), high risk lipid levels, hypertension, and high carotid intima-media thickness (cIMT)) in middle adulthood.

**Methods:** We used Latent Class Growth Mixture Modelling to identify distinct BMI trajectories among 2631 Cardiovascular Risk in Young Finns Study participants aged 6 to 49 years, and Poisson regression with a robust error variance to determine whether trajectory groups predicted each cardiometabolic outcome measured in adulthood (ages 24-49 years).

**Results:** Six discrete life course BMI trajectories were identified (Figure): stable normal (class 1, 55.2%), high BMI resolving (class 2, 1.6%), progressively overweight stabilizing (class 3, 33.4%), progressively obese increasing (class 4, 4.2%), rapidly overweight stabilising obese (class 5, 4.3%), and overweight or obese persisting (class 6, 1.2%). Higher trajectories were generally associated with increased cardiometabolic risk in middle age. Participants who progressively became overweight (class 3) had greater risks in adulthood compared with those in the stable normal group (class 1) for all considered cardiometabolic phenotypes (risk ratios, RR: 1.47-3.06). Compared with the progressively overweight stabilizing group (class 3), the high BMI resolving group (class 2) had smaller risk ratios for adult T2DM, high-risk lipid levels and hypertension, but increased risk for high cIMT (RR: 3.37 vs. 1.70).

**Conclusions:** BMI trajectories from childhood to adulthood that reach or persist at high levels are associated with increased cardiometabolic risk profiles and resolution of elevated BMI in young adulthood may result in substantially reduced cardiometabolic risk. However, to effectively reduce the risk for high adult cIMT, obesity prevention should be targeted at young children.

**PA1.14.07**

**The development of the obesity epidemic across age, time and socioeconomic position: evidence from five UK birth cohort studies**

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**Background:** There is clear evidence of a rise in overweight and obesity across all ages and multiple countries, but a lack of information on secular trends in the age-related process by which people develop overweight or obesity. Using harmonized longitudinal data from 5 UK birth cohort studies, we investigated shifts over nearly 70 years in the distribution of body mass index (BMI) and development of overweight or obesity across childhood and adulthood and the socioeconomic inequalities according to father’s social class.

**Methods:** The sample comprised 56,632 participants with 273,843 BMI observations in 5 studies within the CLOSER
Results: During childhood, the 50th centiles for all cohorts lay in the middle of the International Obesity Task Force normal weight range. However, there was a secular trend towards a positive skewing of the BMI distribution at younger ages. Trajectories of overweight or obesity showed that more recently born cohorts developed greater probabilities of overweight or obesity at younger ages. By age 10 years the estimated probabilities of overweight or obesity in cohorts born after the 1980s were 2-3 times greater than those born before; for example 0.23 (95% CI 0.22-0.24) in MCS males compared with 0.07 (0.06-0.08) in NSHD. Overweight or obesity became more probable in NCDS than in NSHD in early adulthood, and more probable in BCS than NCDS and NSHD in adolescence. On top of this secular trend of increasing BMI at increasingly younger ages, a more disadvantaged childhood social class was associated with higher mean BMI and higher probability of overweight or obesity in adulthood in both men and women in NSHD, NCDS and BCS70. Differences were of a similar magnitude in each cohort; for example, the mean difference in BMI at 42/43 years in women in the lowest compared with highest childhood social class was 1.7 kg/m² (95% CI: 0.2, 3.2) in NSHD, 1.5 kg/m² (0.6, 2.5) in NCDS, and 2.7 kg/m² (1.6, 3.9) BCS. Ongoing research is investigating the social inequalities in childhood BMI across the cohorts.

Conclusions: Our results demonstrate the power of cross-cohort analyses and the impact of the onset of an obesogenic environment from the 1980s in the UK which affected all generations. They show that younger generations are accumulating greater exposure to obesity across their lives and thus are at increased risk of chronic health conditions. Given the persisting inequalities, new and effective policies to both reduce BMI overall and to reduce inequalities in BMI are urgently required.

Background: Infant weight gain is positively associated with obesity risk, yet average weight gain and peak body mass index (BMI) are lower for infants born during the obesity epidemic compared to infants born earlier in the 20th century. One explanation for these counterintuitive findings is that the infant weight gain-adulthood BMI association has strengthened over time. This study aimed to determine how the association of infant weight gain with adulthood BMI might have changed across successive birth year cohorts. Adulthood blood pressure was tested as a secondary outcome to provide a more direct measure of cardio-metabolic disease risk.

Methods: The sample comprised 346 participants in the Fels Longitudinal Study with measures of 1) weight and length at birth and age two years and 2) BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in adulthood (median 19.7, range 18.0-33.8 years of age). General linear regression was used to investigate the associations of conditional weight-for-length Z-score (WLZ), capturing weight change between 0-2 years of age, with adulthood BMI, SBP, and DBP. Birth year cohort (1933-1949, N = 137; 1950-1969, N = 108; 1970-1997, N = 101) was included as an interaction with conditional WLZ to test for effect modification; post-estimation commands were used to obtain birth cohort-specific estimates and Wald tests were used to evaluate the differences between these estimates. Models were adjusted for sex, WLZ at birth, age of outcome assessment, birth order, multiple birth, race, and adulthood height (for blood pressure outcomes).

Results: Adulthood BMI was on average higher in the 1970-1997 cohort (22.4 kg/m²) compared to the 1933-1949 cohort (22.0 kg/m²) and 1950-1969 cohort (22.4 kg/m²) (p-values < 0.05). However, infant weight gain was on average lower in the 1970-1997 cohort (8.6 kg) compared to the 1933-1949 cohort (9.1 kg) and 1950-1969 cohort (9.2 kg) (p-values < 0.05). Conditional WLZ was positively related to adulthood BMI, but there was significant effect modification by birth year cohort such that the association was over two times stronger in the 1970-1997 cohort (β = 2.31; 95% confidence interval 1.59, 3.03) compared to the 1933-1949 cohort (0.98; 0.31, 1.65) or 1950-1969 cohort (0.87; 0.21, 1.54); Wald tests for these comparisons were significant at p < 0.05 (see Figure). A similar pattern was observed for SBP, but with the estimated association with conditional WLZ being stronger in both the 1970-1997 cohort (1.85; 0.10, 3.61) and 1950-1969 cohort (2.26; 0.63, 3.89) compared to the 1933-1949 cohort (-0.33; -2.00, 1.35). Conditional WLZ was not related to DBP in the full sample and there was no evidence of effect modification by birth year cohort.

PA1.14.08

The positive association of infant weight gain with adulthood body mass index has strengthened over time:

Fels Longitudinal Study


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Conclusions: Our findings provide novel evidence that the positive infant weight gain-adulthood BMI association is stronger for infants born during the obesity epidemic compared to infants born earlier in the 20th century. Rapid infant weight gain may, therefore, be implicated in the development of the obesity epidemic despite average infant weight gain actually having declined over time.

Monday October 16th Abstracts poster presentations

PO1.01 – Adiposity – Early life factors

PO1.01.01

Do low-birth-weight babies have higher central adiposity? A study on newborn anthropometry and adiposity in Colombo, Sri Lanka

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Background: This study was undertaken due to lack of data regarding neonatal anthropometry and adiposity in Sri Lanka along with concerns regarding interventions taken to expedite catch up growth in low birth weight babies. The objectives of the study are to describe the anthropometry and adiposity of term newborn babies and determine if there is a difference between <2.5kg vs ≥2.5kg and males vs females.

Methods: Ongoing descriptive longitudinal study commenced in July 2015. All healthy babies born in the University unit, De Soysa Hospital for Women after 37 weeks gestation of mothers >18 years old who were able to attend monthly follow up until 1 year was included. Weight, length and circumferences were measured using SECA instruments and adiposity was assessed via skinfold thickness using Harpenden skinfold calipers according to the WHO growth standards within 48 hours of birth. Ethical clearance was obtained from University of Colombo. SPSS was used for statistical analysis and Chi square test was used to test significance.

Results: The total study population was 287. Mean gestational age was 39 ±1weeks(37–41). The overall anthropometry was: birth weight 2.908Kg±0.431SD (1.84–4.070), length 48.5 ±2.0cm(43.4–54.7), head circumference 33.9 ±1.39cm (30.8–43.9), chest circumference 32.6 ±2.2cm(22.8–39.4), abdominal circumference 30.6 ±2.2cm(24.3–41.2) and mid upper arm circumference(MUAC) 10.6 ±1.1cm (8.0–13.6). Their skin fold thicknesses were: biceps 4.4 ± 0.9mm(2.4–8.9), triceps 4.8 ±1mm(2.6–8.8), subscapular 5.0 ±1.2mm (2.4–10.7) and supra-iliac 4.3 ± 1mm(2.2-9.2). No significant difference was found in birth weight(p=0.269), length (p=0.363), head circumference(p=0.365), MUAC (p = 0.467), chest circumference(p=0.349), abdominal circumference(p=0.478) or skin fold thickness of biceps (p = 0.954), triceps(p=0.056), subscapular(p=0.307), supra-iliac(p=0.558) between boys(142) and girls(145). There were 46 babies below 2.5kg, whose length(p<0.001), head circumference(p=0.002), chest circumference(p<0.001), MUAC(p<0.001), abdominal circumference(p<0.001) and skinfold thickness of biceps(p=0.044) and triceps(p=0.003) were significantly lower than those ≥2.5kg. However the subscapular skinfold(p=0.065) and suprailiac skinfolds (p = 0.192) were preserved.

Conclusion: Supra-iliac and subscapular skinfold thickness were preserved with significant reduction in all other parameters suggesting increased central adiposity in the <2.5kg babies. However No difference was found between males and females.

PO1.01.02

Differences in development of white adipose tissue depots in post-weaning C57BL/6j mice

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Different white adipose tissue (WAT) depots have a distinct contribution to metabolic health, depending on their location in the body. Distribution of fat over WAT depots and the metabolic profile of these depots may be programmed by nutritional exposure in early (postnatal) life. Yet, little information is available on early life development of the metabolic function of different WAT depots. We evaluated post-weaning development of three WAT depots focusing on markers for mitochondrial content, oxidative capacity and WAT browning. C57BL/6j male mice were fed AIN93G until day 42 and AIN93M from day 42 to 98. Inguinal (ING), epididymal (EPI) and retroperitoneal (RP) WAT of 21, 42 and 98 days old mice was dissected, weighed and investigated for markers for adiposity and preadipocyte number (Lep, Mest and Prefl gene expression), mitochondrial content (citrate synthase activity) and oxidative capacity (OXPHOS protein expression) and WAT function of different WAT depots including ING, EPI and RP WAT depots.
browning (Ucp1 and Cidea gene expression). WAT depot weight increased over time. In line with this, gene expression of adiposity markers Lept and Mest increased in EPI (p < 0.05) and RP WAT (p = 0.06 for Lept and p < 0.05 for Mest), but levels were stable in ING WAT. Preadipocyte numbers as measured by Pref1 gene expression declined over time in all three depots (p < 0.001). Citrate synthase activity was highest in ING WAT and decreased in all three depots (p < 0.01), indicating higher mitochondrial numbers in ING WAT and a decline in mitochondrial number over time, being most pronounced between day 21 and 42 in ING WAT (−56%). Protein expression of OXPHOS complexes I-III were also highest in ING WAT and declined over time in this depot (p < 0.01), but remained stable over time in EPI and RP WAT. The ATP synthase subunit (ATP5A) of OXPHOS showed an opposite pattern, with levels being stable over time in ING WAT but declining in EPI WAT (p < 0.05). The latter may suggest that activity of the electron transport chain was not coupled to ATP synthase activity in ING WAT. Together with the substantial decrease in gene expression of Ucp1 and Cidea in ING WAT (p < 0.01), this could indicate that ING WAT transforms from a browner phenotype to a pure white depot during early post-weaning. Together these data showed that developmental trajectory of ING WAT during the post-weaning period in C57BL/6j mice is distinctly different from that in EPI and RP WAT, indicating that postnatal programming of adipose tissue function is depot specific.

**PO1.01.03**

*Is early life exposure to polyomaviruses and herpesviruses associated with childhood obesity and cardiometabolic traits?*

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**Background:** Evidence for an infectious origin of obesity is emerging based on animal studies and limited studies in humans, which mostly concern adenovirus 36. Further efforts to identify new pathogens that contribute to obesity are needed. Moreover, a metabolic dysfunction has been shown to accompany some common viral infections including CMV and HSV but no evidence exists in childhood. We aim to explore whether natural infection with ten polyomaviruses and four herpesviruses in early childhood is associated with obesity and cardiometabolic traits at age four and seven.

**Methods:** We used cross-sectional data on 674 children participating at the four years of age follow-up in the Rhea birth cohort in Crete, Greece and prospective data on 440 children at age seven. Blood levels of IgG antibodies to ten polyomaviruses (BKPyV, JCPyV, KIPyV, WUPyV, HPyV6, HPyV7, TSpyV, MCPyV, HPyV9, HPyV10) and four herpesviruses (EBV, CMV, HSV-1, HSV-2) were measured using multiplex serology at age four. We measured BMI, waist circumference and skinfold thickness at four anatomical sites at age four and seven. Data on cardiometabolic traits, including blood pressure, serum lipids, leptin and adiponectin levels were also available. Multivariable linear regression models were used to estimate the association of single and multiple polyomaviruses and herpesviruses infections with outcomes after adjusting for maternal age, origin, education, pre-pregnancy BMI, child’s sex, age, breastfeeding, having older siblings, school attendance, screen-time per day and child’s BMI (only for cardiometabolic outcomes).

**Results:** At age four, seroprevalence to polyomaviruses ranged from 21% for HPyV9 to 82% for HPyV10. Seroprevalence for EBV was 53%, for CMV 26%, for HSV-1 3.6% and for HSV-2 1.5%. The prevalence of overweight and obesity was 14.1% and 6.7% at four years and increased to 21.8% and 9.6% at seven years, respectively. BKPyV seropositivity was associated with lower BMI SD-score at age four [-0.21 (95% CI:-0.39, -0.03)] and seven [-0.27 (95% CI:-0.48, -0.05)] waist circumference at age four [-1.12cm (95% CI:-2.10, -0.15)] and seven [-1.73cm (95% CI:-3.33, -0.12)] sum of skinfolds at age four [-2.97mm (95% CI:-5.70, -0.24)], systolic blood pressure SD-score at age four [-0.16 (95% CI:-0.31, -0.01)] and leptin levels at age four [ratio of geometric means, 0.83 (95% CI: 0.70, 0.98)]. On the other hand, CMV seropositivity was associated with higher BMI SD-score at age four [0.28 (95% CI: 0.11, 0.45)] and seven [0.24 (95% CI: 0.03, 0.45)] and sum of skinfolds at age seven [4.75mm (95% CI: 0.67, 8.83)]. Although no other herpesvirus was individually associated with obesity outcomes, having “2-3 herpesviruses infections” (versus “0 herpesvirus infections”) was associated with higher BMI SD-score [0.32, (95% CI: 0.12, 0.53)], waist circumference [1.22cm (95% CI: 0.13, 2.31)] and sum of skinfolds [3.26mm (95% CI: 0.18, 6.35)] at age four. Polyomavirus burden was not associated with obesity and cardiometabolic outcomes.

**Conclusions:** Our findings suggest that certain infectious agents might closely interact with developmental processes related to obesity and cardiometabolic traits in early childhood and play a more important role in health and disease than previously understood during the formative stages of life.

**PO1.01.04**

*The joint effect of maternal smoking during pregnancy and pre-pregnancy overweight on the development of overweight in children*

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**Background:** Maternal smoking during pregnancy and pre-pregnancy overweight are known risk factors for childhood overweight. Maternal smoking during pregnancy causes growth restriction in utero and may result in catch-up growth with relatively more fat mass in childhood after being born with low birth weight. Maternal pre-pregnancy overweight is probably related to fetal over-nutrition resulting in high birth weight and increased fat mass. In a previous study, we observed that birth weight of children from mothers who had both these risk factors was similar to that of children from mothers without both risk factors. In this study, we aimed to assess the overweight trajectories between 3 months and 17 years in offspring of mothers with none, one, or both risk factors.

**Methods:** We used the data of 3,171 children with complete exposure data for maternal smoking during pregnancy and pre-pregnancy overweight, born at term in the PIAMA birth cohort. Four exposure groups were distinguished: (i) children born to smoking, non-overweight mothers, (ii) children born to overweight, non-smoking mothers (iii) children born to mothers who both smoked during pregnancy and had pre-pregnancy overweight, and (iv) children born to mothers with none of these risk factors. The outcome variable was childhood overweight trajectories in four categories: never, persistent, increasing and decreasing overweight between 3 months and 17 years. We performed multinomial regression analysis to assess the relation of children of mothers who both smoked during pregnancy and had maternal pre-pregnancy overweight with the risk of developing persistent or increasing overweight between 3 months and 17 years of age.

**Results:** Of 3,171 children, 67.5% (n = 2,139) of children were born to non-overweight, non-smoking mothers, 16.0% (n = 507) to overweight, non-smoking mothers, 12.7% (n = 405) to smoking, non-overweight mothers, and 3.8% (n = 120) to mothers with both risk factors. Of the 4 trajectories of overweight, the never overweight trajectory included 62% of children, while the increasing, persistent, and decreasing trajectories included 18.1%, 6.6%, and 13.3% of children respectively.

Compared to children from mothers without both risk factors, those from overweight, non-smoking mothers had an increased risk of persistent overweight (RR = 4.02, 95%CI: 2.83, 5.70) and increasing overweight during childhood (RR = 2.33, 95% CI: 1.78, 3.06). Children from smoking, non-overweight mothers only had an increased risk of increasing overweight during childhood (RR = 1.46, 95% CI: 1.05, 2.02). Children from mothers who both smoked during pregnancy and had pre-pregnancy overweight had an increased risk of increasing and persistent overweight (RR = 2.56, 95%CI: 1.58, 4.15, and RR = 2.36, 95%CI: 1.16, 4.79 respectively).

**Conclusion:** Maternal pre-pregnancy overweight increases the risk of persistent overweight, and maternal smoking increases the risk of increasing overweight. Children of mothers with both risk factors were at increased risk for both persistent and increasing overweight.

**Abbreviation:** PIAMA, The Prevention and Incidence of Asthma and Mite Allergy study

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**PO1.01.05 Testing the developmental mismatch hypothesis: how responses to unhealthy childhood diet depend on prenatal experience**

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**Background:** The developmental mismatch hypothesis proposes that risk of diseases such as obesity is increased when restricted prenatal nutrition, leading to reduced fetal growth, is followed by a high level of nutrition in childhood, especially an unhealthy diet. Impaired prenatal nutrition and growth, followed by an unhealthy childhood diet, might therefore predispose to obesity. To test this hypothesis, we used longitudinal data from the Southampton Women’s Survey (SWS) on fetal growth velocities and childhood diet quality, and related these to adiposity in childhood. We investigated whether there was an interaction between conditional growth in fetal abdominal circumference (AC) in late pregnancy and diet at age 6 years on adiposity at age 9 years.

**Methods:** 3158 SWS women had live singleton births. AC was measured at 11, 19 and 34 weeks gestation, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. AC z-scores for age were created; from these AC growth velocities and childhood diet quality, and related these to adiposity in childhood. We investigated whether there was an interaction between conditional growth in fetal abdominal circumference (AC) in late pregnancy and diet at age 6 years on adiposity at age 9 years.
previous AC measurements. At age 6 years dietary patterns were identified using principal component analysis; the first component was a ‘prudent’ dietary pattern that complied with dietary recommendations characterized by frequent consumption of fruit, vegetables and fish. Linear regression models were fitted to assess the effects of AC growth on 9-year adiposity. A multiplicative interaction term for AC growth from 34 weeks to birth and 6 year prudent diet score was added to the regression models. Confounding variables (determined by a Directed Acyclic Graph) were breastfeeding duration, maternal BMI, maternal education, sex, smoking in pregnancy, 9-year height, age at DXA, late pregnancy vitamin D and pregnancy weight gain.

**Results:** Median fat mass at 9 years was 7.6 kg and percentage fat was 24.4%. There were associations between greater AC growth from birth to 6 months, 2 to 3 years and 3 to 6 years and higher fat mass and percentage fat at 9 years. The interaction between AC growth from 34 weeks to birth and 6 year prudent diet score was statistically significant for total fat ($P = 0.006$) (Figure) and percentage fat ($P = 0.005$). Amongst children with low AC growth in late gestation, lower prudent diet scores were associated with greater 9-year total and percentage fat, whereas amongst children with high AC growth in late gestation there was little effect of prudent diet score on total and percentage fat.

**Conclusion:** Individuals showing late gestation faltering of fetal growth who then had an unhealthy imprudent childhood diet had greater adiposity, while childhood diet had no influence on adiposity in individuals whose fetal growth had not faltered. Confirming the mismatch hypothesis has implications for preventing childhood obesity; this is particularly relevant to societies undergoing economic and nutritional transition.

The effects of AC growth from 34 weeks to birth and 6-year prudent diet score on 9-year total fat

**PO1.01.06**

*Current size not birth size is associated with risk of metabolic syndrome in young Australian adults*

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**Background:** Cardiovascular disease (CVD) is the leading cause of death and morbidity, globally. Indigenous Australians have an increased risk of CVD, with mortality due to ischaemic heart disease ten times higher in those aged 25-34 years relative to non-Indigenous adults of the same age group. Metabolic syndrome (Mets) has been associated with an increased risk of CVD and stroke resulting in increased CVD mortality. Prevalence of Mets in Indigenous and non-Indigenous participants are described and the influence of birth and current size on these is examined.

**Methods:** The Life Course Program, based in the Northern Territory, Australia, encompasses two distinct but complementary cohorts; The Aboriginal Birth Cohort (686 Indigenous) and the Top End Cohort (196 non-Indigenous). Participants of both studies were born between 1987 and 1991, with face-to-face assessment occurring in young adulthood aged 21-27 years (2013-2015). Reliable birth weight measurements were available. Height and weight were measured and Body Mass Index (BMI cm/kg$^2$) calculated. This was categorised as underweight <18.5, normal 18.5-24.9, overweight 25-29.9 and obese ≥30. Metabolic Syndrome (Mets) was classified as: waist circumference ≥94cm for men and ≥80cm for women, triglycerides ≥150 mg/dL, HDL-C <1.0 mmol/L in males and <1.3 mmol/L in females, blood pressure systolic ≥130 &/or diastolic ≥85 mm Hg or history of hypertension. Due to low numbers of fasting bloods available, HbA1c ≥5.7% was used as an alternative to plasma glucose. Pregnant women were excluded. Complete data obtained from 378 Indigenous and 103 non-Indigenous participants.

**Results:** Significantly lower birthweights were seen in Indigenous participants compared to non-Indigenous (mean 3044 to 3300 grams; $p < 0.001$). Indigenous participants had higher rates of underweight and lower rates of obesity. Indigenous participants were more likely to have 3 or more components of Mets compared to non-Indigenous (26 to 9%; $p < 0.001$). No association was seen between birth weight and occurrence of Mets. Current size was significantly associated with risk of Mets ($p < 0.001$). Mets scores ≥3 were most often seen in Indigenous obese or overweight Indigenous participants. For those with obesity the proportions were 80% (n = 41) compared to 33% (n = 3) and for those who were overweight, this was 44% (n = 39) compared to 20% (n = 5) in non-Indigenous participants.

**Discussion:** A quarter of Indigenous participants had 3 or more metabolic risk factors. The main risk factor for metabolic syndrome in both Indigenous and non-Indigenous young adults was current size. No association was seen with birth weight. These results underscore the fundamental role healthy lifestyles play in maintenance of health. Provision of an environment that enables physical activity and healthy nutritional choices needs to be incorporated into healthy lifestyle programs to encourage uptake of these health messages.
PO1.01.07

Birth weight classification and BMI trajectories in early life: evidence of maternal effects from the Lifeways Cross-Generation Cohort study

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Background: Birth weight is a known predictor of childhood adiposity, however sex and age-related body size trajectories are better indicators of later disease risk. Studies have explored socio-economic and early life factors associated with early childhood trajectories but few have examined the role of the maternal diet during pregnancy.

Methods: The Lifeways Cross Generation Cohort Study comprises a longitudinal birth cohort where expectant mothers were recruited from two large Irish maternity hospitals. At booking visit they completed a questionnaire on health (including height and weight), lifestyle and socioeconomic details. Dietary information was obtained using a food frequency questionnaire and estimated macronutrient intake was adjusted for energy. Height and weight of the proband child were measured over three data collection waves (birth, 5 years, and 9 years). Marginal models of body mass index were fitted using Low (LBW: < 2.5kg), Mid (MBW:2.5-3.99kg) and High (HBW: ≥4kg) birthweight categories, to predict trajectory, with unstructured correlation of residuals between time-points. Modifiers of three derived trajectories were modelled with higher-order interactions. We adjusted for maternal smoking, sex of the child, breastfeeding, maternal pre-pregnancy BMI and a range of values for maternal nutrient intake during pregnancy.

Results: At least one BMI was measured in 1087 infants of whom 4% were LBW, 18% HBW. BMI was available in more than one wave in 65% of LBW, 53% of MBW, and 51% of HBW babies.

Models showed increased BMI variance at age 9 years, and highest covariance between 5 and 9 years. Statistically significant interaction terms showed fastest increases in mean BMI in the LBW, catching up with peers by age 5, and overtaking them by age 9.

Pre-pregnancy Maternal BMI showed a positive effect on the BMI rate, consistently across birth-weight patterns. The impact of dietary intake during pregnancy revealed that crude total energy intake modifies LBW overcompensation (p = 0.020): mean BMI at 9y was substantially lower with intakes in the highest range >3000Kcal. This pattern is similar for fat and carbohydrate intake (p = 0.039, p = 0.018 respectively), but not protein nor energy-adjusted macronutrient intake.

Conclusions: The overcompensatory trajectory appears unrelated to high maternal energy-intake during pregnancy. Maternal nutritional status prior to pregnancy may be a stronger determinant of trajectories in childhood.

PO1.01.08

Impact of foetal growth restriction on rate of change and composition of young adult body mass

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Background: Aboriginal people in the Northern Territory (NT) of Australia have poorer health outcomes than Non-Aboriginal Australians, with higher rates of Fetal Growth Restriction in early life and high rates of chronic disease such as diabetes, renal and cardiovascular disease in later life. Obesity, a Major risk factor for chronic disease is also disproportionately high in NT Indigenous people. We compare (i) rate of increase of Body Mass Index (BMI) and time to reach overweight or obesity and (ii) composition of weight change in early adulthood with respect to FGR status in the Aboriginal Birth Cohort (ABC), established in 1987 in the NT.

Methods: ABC participants (n = 686) recruited at birth (Wave-1), then anthropometrically assessed at mean ages of 11 (Wave-2), 18 (Wave-3) and 25 years (Wave-4). FGR is defined as <10th percentile of birthweight for gestational age (Inter-growth); overweight/obese (ow/ob) as BMI ≥ 25; BMI gain as an increase of ≥1 standard deviation (SD) to age 18 then 1 category change; BMI gain as small (<1 SD change), medium (≥1 SD without ow/ob) and large (≥1 SD with ow/ob). Cox regression, adjusting for gender, age (months) at Wave-4, recent location, prematurity and maternal smoking, was used and Hazard ratios (HR) obtained. Multivariate regression was used for analysis of fat composition, and also adjusted for rate of BMI change and BMI category at Wave-4.

Results: Of 630 with FGR status, 211 (33%) reached ow/ob at any wave. Of 339 with complete data, 130 (38%) reached ow/ob, with the proportion of FGR less than non-FGR (p = 0.01). Only 3 FGR reached obesity compared to 43 non-FGR (p < 0.01). Although FGR have 53% greater risk of increased BMI (HR 1.53 p < 0.01; 1.12,2.10), they have 40% less risk of...
PO1.01.09
Assessment of infant body composition using air displacement plethysmography
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Background: Extremes of birth weight (high and low) are predictors of future metabolic risk including obesity, type 2 diabetes and cardiovascular disorders. However, similar to BMI in adults, it does not differentiate babies who are proportionately big or small. Adult adiposity is a better marker of cardiometabolic disorders and is likely that newborn adiposity could be a better marker than birth weight. Our research question was: ‘What are the maternal characteristics which predict infant adiposity?’

Methods: PRiDE:PEAPOD study is a sub-study of babies born to women at high risk of gestational diabetes (GDM) from the multicentre, prospective PRiDE study (Micronutrients in Pregnancy as a Risk factor for gestational Diabetes and Effects on mother and baby). Babies body composition was assessed using air displacement plethysmography (PEAPOD) within 48 hours of birth. Maternal characteristics were obtained during early pregnancy (12 weeks gestation), including maternal anthropometric measurements. Fasting and 2 hour post-load glucose levels were obtained at the time of oral glucose tolerance test (OGTT), carried out between 24-28 weeks gestation.

Results: Forty-three babies were studied between August 2016 and April 2017. The maternal characteristics in early pregnancy were (mean ± sd): maternal BMI – 34.4 ± 8.6 Kg/cm²; waist circumference – 102.7 ± 21.7 cm; maternal triceps skinfold thickness – 28.8 ± 10.1 cm; maternal subscapular skinfold thickness – 28.9 ± 11.6 cm. Mean fasting and 2 hour post-load glucose at the time of OGTT were 4.4 ± 1.2 mmol/l and 5.5 ± 2.4 mmol/l, respectively.

Of the 43 babies, 22 were male and 21 female. The newborn characteristics were (mean ± sd): gestational age at birth – 39 weeks ± 1 week; birth weight – 33.3 ± 0.55 kg; newborn fat mass – 0.39 ± 0.2 kg and newborn % fat – 11.5 ± 4.5%. After adjusting for gestational age, mean male fat mass - 0.42 ± 0.28 kg; mean female fat mass – 0.36 ± 0.13 kg (p = 0.1); mean male % fat – 11.4 ± 5.5% and female % fat – 11.6 ± 3.4% (p = 0.3). % fat of male and female newborns ranged between 3-26.4% and 5.6-18.6%, respectively. In a multivariate regression analysis gestational age independently predicted infant adiposity (p = 0.05); when adjusted for maternal BMI, maternal family history of diabetes, infant gender, maternal anthropometry (waist circumference, triceps and subscapular skinfold thickness), baseline and 2 hour GTT results.

Conclusion: No difference in infant adiposity was identified when adjusting for infant gender. Gestational age was the only independent predictor of body composition within the first 48 hours of birth. A larger sample size is required to look at further maternal characteristics and the role of intra-uterine programming on infant body composition.

PO1.01.10
Predisposing factors for metabolic syndrome in pregnancy and newborns’ body size: preliminary report from the Croatian Islands’ Birth Cohort Study
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Background: Extremes of birth weight (high and low) are predictors of future metabolic risk including obesity, type 2 diabetes and cardiovascular disorders. However, similar to BMI in adults, it does not differentiate babies who are proportionately big or small. Adult adiposity is a better marker of cardiometabolic disorders and is likely that newborn adiposity could be a better marker than birth weight. Our research question was: ‘What are the maternal characteristics which predict infant adiposity?’
The prevalence of the metabolic syndrome (MetS) on the Eastern Adriatic islands is higher than in the neighboring mainland area. The CRoatian Islands’ Birth Cohort Study (CRIBS) is an ongoing 3-year-project aiming to assess the prevalence of known risk factors for MetS. The CRIBS sample consists of pregnant women from Dalmatian islands of Brač and Hvar and the nearby coastal town of Split and it’s surroundings, who had no history of chronic diseases, who conceived naturally, and had singleton pregnancies. We tested the association of possible predisposing factors for MetS (age, smoking, prepregnancy BMI, blood biomarkers) and newborns’ anthropometric measures. In this preliminary sample (n = 131, age range 19.8-41.7 yrs, mean 30.6 ± 4.6 yrs), 28.3% of women reported smoking in pregnancy and 22.2% reported being exposed to passive smoking. 17.9% of all the women were overweight and 4.7% were obese. In comparison to underweight women (<18.5 kg/m²), obese pregnant women gave birth to heavier babies (p < 0.05) and longer babies (p < 0.01). Newborns of primi- and multiparous mothers were significantly longer (p < 0.05) and had greater head circumferences (p < 0.001) than newborns of nulliparous mothers. Women with higher mean triglyceride levels more often had large for gestational age than normal for gestational age children (p < 0.01). Smokers, in comparison to non-smokers, had significantly higher triglycerides (p < 0.05) and lower HDL cholesterol (p < 0.01). All the predisposing factors for MetS were compared according to the island and mainland place of residence: newborns’ size at birth (weight, height and head circumference, z-standardized according to WHO) did not differ between the two groups. The only difference was detected in women; islanders had higher glucose (p < 0.05), while women from the mainland had higher homocysteine and lipoprotein(a) (both p < 0.05). Despite the fact that none of the investigated women were diagnosed with MetS, some of its risk factors have a considerable prevalence in the investigated CRIBS population.

**PO1.01.11**

**Improving risk estimates for metabolically healthy obesity and mortality using a refined healthy reference group**

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**Background:** Whether or not obesity without metabolic dysfunction carries excess risk of mortality remains unclear. Little attention has focused on the importance of the referent group, usually comprising adults who are non-obese and metabolically healthy at a single point in time. As a consequence, estimates of excess mortality risk among healthy obese versus healthy non-obese adults may be obscured by failing to distinguish referent non-obese individuals who have had a body mass index (BMI) below the obesity range for many years from those who used to be obese but lost weight. We aimed to re-examine mortality risk estimates for metabolically healthy obesity by using a more stable healthy non-obese referent group.

**Methods:** The sample comprised 5,427 men and women (aged 65.9 ± 9.4 yrs, 45.9% men) from the English Longitudinal Study of Ageing born on or before 29 February 1952. Identical clinical assessments were performed at baseline in 2004-05 and four years later in 2008-09. These data were linked with death records from National Health Service registries up to February 2012. At each sweep, participants were classified as 1) non-obese (BMI <30 kg/m²) or obese (BMI ≥30 kg/m²) and 2) healthy (0 or 1 metabolic abnormality) or unhealthy (≥ 2 metabolic abnormalities), based on measurements of blood pressure, HDL-cholesterol, triglycerides, glycated haemoglobin, and C-reactive protein. Cox proportional hazards regression models were used to examine associations between healthy obesity and all-cause mortality, adjusting for age, sex, physical activity, smoking, depressive symptoms, long standing illness, and wealth at baseline. Analyses first compared risk estimates based on baseline obesity and health status (i.e., healthy obese, unhealthy obese, healthy non-obese (referent), unhealthy non-obese). Analyses were then re-run using a refined referent group of participants who were still healthy non-obese at the four year follow-up.

**Results:** A total of 671 deaths were observed over an average follow up of eight years. As baseline, 10% of the sample were healthy obese, 19% were unhealthy obese, 46% healthy non-obese, and 25% unhealthy non-obese. Only 66% of healthy non-obese remained in this category four years later. When defining the referent group based on one clinical assessment (i.e., baseline), the unhealthy non-obese (hazard ratio 1.22; 95% CI 1.01, 1.45) and unhealthy obese (1.29; 1.05, 1.60) were at greater risk of all-cause mortality compared to the healthy non-obese participants, yet no excess risk was seen in the healthy obese (1.14; 0.83, 1.52). When defining the referent group based on two clinical assessments, these effect estimates were accentuated and healthy obese participants were also at increased risk of mortality (2.67; 1.64, 4.34). Similar patterns were observed for cardiovascular-specific mortality.

**Conclusions:** Excess risk of mortality among healthy obese adults was only evident when using a more persistent healthy
non-obese referent group, defined using data from two clinical assessments just four years apart. Failure to consider obesity history when defining the referent group may, therefore, make healthy obesity appear less harmful by obscuring the benefits of never being obese or having metabolic dysfunction.

PO1.01.12

Effects of birth weight and childhood accumulation of body fat on metabolic parameters in primary school children in Sri Lanka

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Introduction: Birth weight is a reflection of fetal growth and low birth weight increases the risk of cardiovascular diseases in later life. The role of fat accumulation in the generation of metabolic abnormalities in adults is well documented, and is likely to be observed in the young child as well. Hence the importance of healthy growth versus accumulation of fat mass. The aim of this study was to identify the effects of birth weight and accumulation of body fat on metabolic derangements among 8-9 years old primary school children in Colombo Municipal area Sri Lanka.

Method: A cross sectional descriptive study design was used (N = 324) including boys (N = 161) and girls (N = 163). The children were recruited at the school medical inspection (SMI) in the state schools in Colombo Municipal area Sri Lanka. Weight, height, Fat mass (FM), fasting (8-10 hours) blood sugar (FBS), insulin, total cholesterol (TC), HDL, Triglyceride (TG) and LDL were measured. HOMA IR (Homeostatic model of insulin resistance was calculated as [fasting insulin (µU/L) x fasting glucose (nmol/L)]/22.5]. Comparison was done between low, medium and high BMI tertiles along birth weight categories (≤2 SD lower than referent group, referent group and ≥2 SD higher than referent group).

Results: Significantly high levels of metabolic parameters were observed in the low birth weight and high current BMI tertile compared to low birth weight and low current BMI tertile (% BF: 41.21 ± 5.25 VS 16.21 ± 5.74 (p < 0.001), fasting insulin: 12.08 ± 7.93 VS 2.29 ± 1.21 (p < 0.001) HOMA IR: 3.01 ± 2.69 VS 0.50 ± 0.25 (p < 0.001) and TG: 42.41 ± 16.74 VS 6.41 ± 16.74 (p < 0.01) ). In the lower BMI tertile no significant differences in metabolic parameters were observed across the three different birth weight categories.

Conclusion: Children with low birth weight and low BMI at 9 years had a lower risk of developing an abnormal metabolic profile. Our results indicate that gaining weight in the form of accumulation of fat cannot be considered as healthy growth. Therefore proper feeding and monitoring are important in the management of the child with low birth weight in order to ensure appropriate metabolic profiles.

PO1.01.13

Which lesson from the evaluation of parental perception of child’s weight in an European cohort of 8 years old children


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Background: Parental perception of child’s weight may influence the development of overweight in childhood. We aim at describing parental perception of their child’s weight status in a sample of 8 years old healthy children from 5 European countries.

Methods: This study was performed in families participating in the EU CHOP study. Children’s weight and height were measured and Body Mass Index (BMI) was calculated (kg/m²). Both parents were asked to judge their child’s weight status using a scale of sketches#_Fin1 and the question: In your opinion, to which sketch does your child most resemble at the moment? The middle image of the sketches was developed to represent a child at the 50th BMI percentile for the age. Ordinal logistic regression was used to describe the relationship between the actual BMI of the child and parental perception of it. Based on literature, we included gender, level of parental concern related to overweight, parental BMI, country and level of education in the model.

Results: At eight years, 587 families (52.8% with girls) were included. Mean BMI was 16.8 ± 2.79 kg/m² in boys and 17.0 ± 2.55 in girls (n.s.). Based on WHO BMI standards 408 children (69.5%) were normal weight whereas 172 (29.3%) were overweight. The rest was in the category thinness. The choice of sketch by mothers and fathers was significantly related to the child’s BMI (p < 0.0001). However, most of the parents underestimated the child’s weight status: about 90% of the parents select a picture of their child lower or equal to the middle of the scale, despite that around 30% of the children were already overweight. Maternal and paternal perception was similar. Perception by both parents was significantly lower for boys than for girls. Mothers with higher BMI did perceive significantly their child thinner than mothers with a lower BMI. A higher paternal level of education enhanced the chance that the fathers selected a bigger sketch. Polish fathers differed significantly from those of the other countries.

Conclusions: Our study shows a high level of underestimation of children’s weight status by their parents. Girls and boys are perceived differently.
PO1.02 – Cardio-metabolic health – Growth and long term effects

PO1.02.01

The emergence of cardiovascular risk factors in adolescence in a high risk Australian population

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Background: Cardiovascular disease (CVD) is one of the leading causes of death in the developed world and contributes to the current gap in health status and life expectancy between Indigenous and non-Indigenous Australians. This gap is particularly evident in the Northern Territory (NT) where the life expectancies of Indigenous residents are, on average, 15 years less than non-Indigenous residents. The exact age of onset of CVD and risk factors, high blood pressure, abnormal lipids and obesity, is not well established.

Methods: The Life Course Program, based in the Northern Territory, Australia, encompasses two distinct but complementary cohorts; The Aboriginal Birth Cohort (Indigenous) and the Top End Cohort (non-Indigenous). Participants of both studies were examined in adolescence, aged 16-20 years (2005-2007 for Indigenous and 2008-2009 for non-Indigenous) and again in young adulthood aged 21-27 years (2013-2015 for both). Directly collected lifestyle questions (including tobacco and alcohol use, physical activity level, hypertension diagnosis), anthropometric measures and blood pressure were obtained using standardised methods. Height and weight were used to calculate Body Mass Index (BMI cm/kg²). Categories used include: smoker = current, overweight/obese = BMI ≥ 25, inactivity = none or <5 hours activity per week, high LDL-c = >2.59, low HDL <1.0, alcohol = alcohol at least weekly, hypertension = systolic BP >140 &/or diastolic BP >90 &/or diagnosis of hypertension. Complete data was obtained from 276 Indigenous and 85 non-Indigenous.

Results: Significantly higher rates of smoking were present in Indigenous participants, with those smoking in adolescence continuing into adulthood (88%). Rates of overweight/obesity are rising in both Indigenous and non-Indigenous participants. Of those who were overweight or obese in adolescence 87% remained so in adulthood. Physical activity levels are declining in Indigenous participants, but increasing in non-Indigenous. LDL-c levels are decreasing in non-Indigenous participants but remain stable for Indigenous. By adulthood over half of Indigenous and non-Indigenous participants had a low HDL. Alcohol use has increased significantly from adolescence to adulthood in both cohorts. Hypertension rates, although low, are increasing in both cohorts, with a further 9% (n = 32) of adolescents and 14% (n = 32) of young adults being pre-hypertensive (systolic > 130 &/or diastolic > 80).

Discussion: Modifiable risk factors, obesity and lifestyle factors, such as smoking, alcohol use, physical activity and diet, are developed in adolescence and continue into adulthood. Of particular note are the high rates of smoking present in Indigenous adolescence continuing into young adulthood, emphasizing the lack of impact current programs are having in this at-risk population. The higher rates of modifiable risk factors present in Indigenous adolescents and young adults may explain the overt rates of chronic diseases present in later life.

Health status of adolescence and young adults by Indigenous status

PO1.02.02

Simple health indicators to evaluate influence of early life glucoc-psycho-social factors on self-reported health in later life

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Background: A myriad of different early life exposures to glycemic and psychosocial factors have been shown to be associated with long-term health. Usually the relationships between these factors and long-term health have been studied separately. However, it remains to be determined how the accumulation of different risk factors can alter long-term health. We aimed to explore the associations between glucoc-psycho-social axis (GPA) score, which was based on maternal body mass index (BMI) in late pregnancy, offspring BMI at the age of 7, and childhood socioeconomic status (SES) on later life self-reported health, which was used as a surrogate marker of the ageing process.

Methods: We investigated 765 men and 891 women (mean age = 61.5 years, standard deviation = 2.9). The information
of maternal BMI during late pregnancy, offspring BMI at the age of 7 years, and childhood SES was based on the hospital birth records and child welfare and school health care records. The early GPA score was calculated as a sum of maternal BMI (normal weight ≤25 kg/m² = 0, overweight 25 – 29.9 kg/m² = 1, obese ≥30 kg/m² = 2), offspring BMI (underweight <5 percentile = 1, normal weight 5–<85 percentile = 0, overweight 85 – 94.9 percentile = 1, obese ≥95 percentile = 2), and SES (high = 0, moderate = 1, low = 2) categories. GPA was divided into tertiles (low, average, high (worse)). Participant’s self-reported health was based on a question from the SF-36, where people were asked to rate their general health (excellent, very good, good, fair, poor). Generalized ordered logit models were applied to investigate the association between the GPA tertiles and self-reported health tertiles (good, fair, poor). Analyses were adjusted for age.

Results: In men, a low GPA score had a significantly greater probability to be identified with good health compared to the men with average (mean difference = 11.7 percentage point (pp), 95% CI 2.9–20.5, p = 0.009) or high GPA score (mean difference = 19.0 pp, 95% CI 7.6–30.5, p = 0.001). Among women, low GPA was also associated with greater probability to be identified with good health compared to the average GPA group, however, the between the group difference was only borderline significant (mean difference = 8.1 pp, 95% CI -0.8–17.0, p = 0.075).

Conclusions: A favorable combined score based on early life gluco-psychosocial factors is associated with better self-reported health in later life. This association is stronger among men than in women.

PO1.02.03
Excess early postnatal weight gain and blood pressure in healthy young children
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Background: Blood pressure (BP) tracks from childhood to adulthood and early BP trajectories predict cardiovascular disease risk later in life. Excess postnatal weight gain is associated with vascular changes early in life, however to what extent it is associated to children’s BP is largely unknown.

Methods and Results: In 775 healthy 5-year-old children of the Wheezing-Illnesses-Study-Leidsche-Rijn (WHISTLER) birth cohort systolic and diastolic BP (SBP;DBP) were measured in sitting and supine postures, and Z-scores of individual weight gain rates adjusted for length gain rates were calculated by using at least two weight and length measurements from birth until 3 months of age. Linear regression analyses were conducted to investigate associations between WLG and BP adjusted for sex and ethnicity. Each standard deviation increase in WLG resulted in 0.9 mmHg (95% CI 0.2;1.5) higher sitting SBP after adjustment for confounders. WLG was not associated to supine SBP or DBP. Particularly in children in the lowest birth size decile, high excess weight gain resulted in higher sitting SBP values compared to those children with low WLG.

Conclusion: Children with excess weight gain in the first three months of life, particularly those with a small birth size, have higher sitting systolic blood pressure at the age of 5 years.

PO1.02.04
Is birth weight associated with blood pressure in early adolescence? Results from a tropical birth cohort.
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Background: Various studies from high-income countries have reported an inverse relationship between birth weight and blood pressure (BP). However, in Africa (where both low birth weight and high BP are prevalent) the relationship between birth weight and BP later in life remains uncertain. We aimed to investigate the relationship between birth weight and BP among early adolescents, using data from a birth cohort in Entebbe, Uganda.

Methods: Ten and eleven-year-old adolescents in the Entebbe Mother Study (EMaBS) birth cohort were enrolled into this study on BP. Initially, the EMaBS was designed to investigate the effect of worms and their treatment in pregnancy and early childhood on vaccines and infections in childhood. Using a 2 × 2 factorial design, 2507 pregnant women were randomized to receive albendazole or matching placebo and praziquantel or matching placebo. At 15 months of age, the resulting offspring were randomized to receive quarterly albendazole or matching placebo up to five years of age. Children continued under follow-up after trial interventions were completed. Birth weight was measured and recorded soon after delivery, while BP was measured in triplicate among 10 and 11-year-olds, with the mean of the last two BP readings used for analysis. Data on important potential confounders and effect modifiers were collected prospectively earlier in life. Linear regression models were used to assess crude and adjusted associations between birth weight and BP.

Results: 1119 adolescents were enrolled into the BP study. Mean birth weight was 3.16 kg (range: 0.8 to 5.5), while at ages 10 and 11 years mean systolic blood pressure (SBP) was
105.87 mmHg (range: 74.5 to 142) and mean diastolic blood pressure (DBP) was 65.20 mmHg (range: 44 to 96.5). From the preliminary results, the unadjusted analysis showed weak evidence of a U or J-shaped relationship between birth weight and SBP (P-value = 0.208) or DBP (P = 0.291). After adjusting for maternal and childhood factors, SBP decreased by 0.13 mmHg, 95% CI (−2.15, 1.90) and by 0.14 mmHg 95% CI (−1.48, 1.21) among participants with birth weight less than 2.5 kg and 2.5-2.99 kg, respectively compared to those with birth weight of 3.00-3.49 kg, but increased by 0.08 mmHg, 95% CI (−1.17, 1.34) among those born weighing more than 3.5 kg compared to those weighing 3.00-3.49 kg (P-value = 0.992). Similarly, birth weight was not associated with DBP after adjusting for maternal and childhood characteristics (P-value = 0.990).

Interestingly, the effect of birth weight on SBP differed by maternal treatment with praziquantel/matching placebo during pregnancy (interaction p-value < 0.001). Among participants whose mothers received praziquantel, SBP dropped by 3.69 mmHg, 95% CI (−6.61, −0.78) among those with birth weight less than 2.5 kg compared to those weighing 3.00-3.49 kg, but among those whose mothers received placebo, SBP increased by 3.46 mmHg, 95% CI (0.82, 6.11) among those with birth weight less than 2.5 kg compared to those weighing 3.00-3.49 kg.

**Conclusions:** Birth weight is not associated with BP among adolescents in this birth cohort. However, maternal praziquantel treatment in pregnancy might influence programming of SBP in low birth weight infants.

**PO1.02.05**

The effect of stunting on blood pressure and BMI in adolescence: A prospective cohort study of the Dogon of Mali

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**Introduction:** Studies of the effect of childhood stunting on systolic blood pressure (SBP) and body mass index (BMI) during adolescence have produced conflicting results (Rachmi et al., 2017), and there is a dearth of longitudinal, prospective studies, especially in Africa. We used an 18-year prospective cohort study of the Dogon of Mali to test the following hypotheses: (1) Is a history of childhood stunting and catch-up growth associated with elevated SBP during adolescence? (2) Is this association stronger in members of the cohort who migrated to Bamako—the fastest growing city in Africa? (3) Does a history of childhood stunting and catch-up growth associate with lower BMI during adolescence, as one might expect from life history theory, or does it associate with higher BMI as has been seen in young infants in India?

**Methods:** The total population of children age < 5 years in 9 rural Dogon villages was enrolled in May 1998 and newborns were added through August 2000 (N = 1698). By 2015, nearly half of the participants had migrated to Bamako (>80% follow-up), while other participants remained in the villages (>98% follow-up of survivors). Subjects were measured approximately annually in the villages from 1998 to 2015 and in Bamako from 2010 to 2015 (3786 total observations). The data were analyzed using linear mixed models including random effects for clustering by patrilineage, mother, and father, and random slopes for age. Stunting was defined as a height-for-age z-score < −2.0 in relation to the WHO reference.

**Results:** Children who were stunted in both 2000 and 2007 had SBP during adolescence that was 2.1 mm Hg higher than for children who were not stunted in either year (P < 0.001). Children who experienced catch-up growth were statistically similar to children who were never stunted. These results were adjusted for: year of the study, BMI, height, gender, urban/rural status, gender by urban/rural status, age (linear and squared), age by gender, school attendance, log of the number of times the person had had their blood pressure taken, ambient temperature, and wealth Z-score. Interestingly, persistent stunting predicted elevated SBP to a similar extent in the villages as in the city. Children who were stunted in both 2000 and 2007 had a BMI (kg/m2) in adolescence that was 0.65 kg/m2 lower than for children who had never been stunted (P < 0.001). Results were similar for children who were initially not stunted but who became stunted. Conversely, children who caught up in height were not statistically different from children who were never stunted (β = −0.25, P = 0.11).

**Conclusions:** Between the mean ages of 2.5 years and 11.5 years, persistent stunting predicted increased systolic blood pressure (SBP) and decreased BMI during adolescence (mean age 17 years). Urban migration did not further exacerbate the increase in SBP associated with stunting, although urban migration itself was a risk factor for elevated SBP, especially in males. SBP and BMI in children who experienced catch-up growth during these ages was not significantly different from that of children who had never been stunted.

**PO1.02.06**

No associations of excessive crying with resting blood pressure and cardiac autonomic nervous system activity in childhood

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**Background:** Early life stress has been shown to influence the developing autonomic nervous system. Stressors in infancy may program the autonomic nervous system resting state set point, affecting cardiovascular function in later childhood. Excessive...
crying may be an indicator of stress arousal in infancy. We hypothesized that excessive infant crying is related to altered cardiac autonomic nervous system activity and increased blood pressure at age 5-6 years and additionally that a potential association would be moderated by maternal stress and behavior.

**Methods:** In the Amsterdam Born Children and their Development study, excessive infant crying, maternal burden of care and maternal aggressive behavior in the 13th week after birth (range 11 – 16 weeks), were reported using questionnaires. Blood pressure, heart rate and indicators of cardiac autonomic nervous system activity (sympathetic drive by pre-ejection period, parasympathetic drive by respiratory sinus arrhythmia, and cardiac autonomic balance and regulation) were measured at age 5-6 years during rest. Inclusion criteria were: singleton birth, term-born, and no reported congenital or cardiovascular problems (N = 2158 included).

**Results:** Excessive crying (2.9%) was not associated with resting heart rate, pre-ejection period, respiratory sinus arrhythmia and cardiac autonomic balance and regulation, nor with systolic or diastolic blood pressure at age 5-6 years.

**Conclusions:** Excessive infant crying as an indicator of increased stress arousal does not seem to be related to resting activity of the autonomic nervous system or blood pressure at age 5-6. Potential associations may become visible under stressed conditions.

**PO1.02.07**

**Methylglyoxal treatment in lactating mothers leads to type 2 diabetes phenotype in male rat offspring at adulthood**


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**Background:** Environmental and nutritional disorders during perinatal period cause metabolic dysfunction in the progeny and impair human health. Advanced glycation end products (AGEs) are primarily produced during metabolism of excess blood glucose, which is observed in diabetes. Methylglyoxal (MG) is a precursor for the generation of endogenous AGEs, which disturbs the metabolism. This work aimed to investigate whether the maternal MG treatment during lactation programs the progeny to metabolic dysfunction later in life.

**Methods:** Female Wistar rats were divided into two groups: control group (C) treated with saline and MG group treated with MG (60 mg/kg/day) by gavage throughout the lactation period. Both mothers and offspring were fed a standard chow. At weaning, breast milk composition was analyzed and mothers euthanized for blood and tissue sample collections. At 90 days of age, offspring were submitted to glucose tolerance test (ivGTT) and euthanized for blood and tissue samples collection.

**Results:** MG mothers showed increase in glucose and fructosamine levels; however, they showed low insulin levels and failure in β-cell function (p < 0.05). MG mothers also showed dyslipidemia (p < 0.05). Moreover, breast milk had elevated levels of glucose, triglycerides, cholesterol and fructosamine and low insulin (p < 0.05). Interestingly, MG offspring had increased body weight and adipose tissue at adulthood, and they also showed glucose intolerance and failure in β-cell function (p < 0.05). Besides, MG offspring showed dyslipidemia (p < 0.05) increasing cardiovascular diseases risk.

**Conclusions:** Maternal MG treatment negatively affects the male rat offspring, leading to type 2 diabetes and dyslipidemia in later life, possibly by changes in breast milk composition.

**PO1.02.08**

**Awareness, Treatment, and Control of Hypertension is Low among Adults in Aksum Town, North Ethiopia: A Sequential Quantitative-Qualitative Study**

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**Background:** Hypertension is a major risk factor of cardiovascular diseases which are the leading causes of deaths from chronic non-communicable diseases in Ethiopia. However, little is documented on the issue. Therefore, this study aimed to assess prevalence, associated factors, awareness, treatment and control of hypertension among adults 18 years old or above in Aksum town, Tigray region, North Ethiopia.

**Methods:** A sequential quantitative-qualitative study was conducted among adults aged 18 years and above in Aksum town. A multi stage sampling procedure was used to select the study participants for the quantitative study whilst convenience sampling technique was used for the qualitative part. Pre-tested and structured questionnaire was used to collect quantitative data, and interview guide was used to collect the qualitative data. The data were collected by trained health extension workers. Logistic regression model was fitted to identify factors independently associated with hypertension using SPSS Version 20. P-values of < 0.05 were considered statistically significant. For the qualitative data, iterative hearing of the discussions verbatim interpretation was done followed by categorizing similar ideas in to themes and finally triangulated with the quantitative results.

**Results:** The overall prevalence of hypertension was 16.5% (95% CI: 13.4, 20.0). Awareness, treatment and control of hypertension were 43%, 2.1% and 18.2%, respectively. Being
PO1.02.09
Perinatal cholesterol influence differentially atherosclerosis progression in ApoE-/- offspring male and females by altering cholesterol metabolism.


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Background: Atherosclerosis is a common cause of death and disability throughout the world. The 'fetal origin' hypothesis states that cardiovascular disease in adult life, originate through the fetus environment (Barker, 2000).

Our objective is to check whether the cholesterolemia during gestation affect the development of atherosclerosis by altering reverse cholesterol transport.

Methods: ApoE-/- offspring, male (Ma) and female (Fe), from ApoE-/-hypercholesterolemic mothers (H) were compared to offspring from normcholesterolemic mothers (C) (n = 5-7 per group). Atherosclerotic lesions were assessed by measuring lipid deposition in the aortic sinus at 18 and 25 weeks old. Cholesterolemia, hepatic and aortic arch cholesterol content were measured. Gall-bladder bile acids were quantified. Hepatic gene expression was measured.

Results: Aortic lesion size was significantly higher in Fe-H (18 weeks: 45.1 +/- 32.3 μm²; 25 weeks: 223.9 ± 64.1 μm²) than Fe-C (18 weeks: 5.2 +/- 7.4 μm², p < 0.05; 25 weeks: 61.5 ± 75.9 μm², p < 0.01) and Ma-H (18 weeks: 11.9 +/- 8.4 μm², p < 0.05; 25 weeks: 106.3 ± 6732 μm², p < 0.01). At 18 weeks, aortic cholesterol content was higher in Fe-H (8.0 ± 2.9 mg/g) compared to Fe-C mice (2.3 ± 1.4 mg/g, p < 0.05). Total aortic cholesterol rose from 18 to 25 weeks in Ma-H (from 6.2 ± 6.0 mg/g to 16.8 ± 10.5 mg/g) and Fe-H mice (from 8.0 ± 2.9 mg/g to 19.8 ± 12.4 mg/g).

Although total plasma cholesterol levels were similar at 10, 18 and 25 weeks, we noted an increase in hepatic cholesterol in Ma-H (4.7 ± 0.3 mg/g) compared to Ma-C (2.3 ± 1.1 mg/g, p < 0.05) and Fe-H (3.2 ± 0.9 mg/g; p < 0.01) at 25 weeks old. BA pool size was higher in Ma-H compared to Fe-H at 18 (p < 0.05) and 25 weeks (p < 0.05). At 25 weeks, BA pool size was greater in Ma-H compared with Ma-C mice (p < 0.01).

Whereas Scarb1 (encoding SR-B1) and Ldlr expression were both increased in the liver of Ma-H compared to Ma-C, it was downexpressed in the Fe-D compared to Fe-C. At 25 weeks old, Cyp7a1 expression was decreased in Fe-H compared to Ma-H.

Conclusions: Our findings suggest that maternal hypercholesterolemia exacerbates the development of atherosclerosis in female offspring by affecting reverse cholesterol transport. Epigenetic change was associated with lipids levels in humans. Also increase Scarb1 (Delaney; 2013), decreased Ldlr and increased Cyp7a1 expression (Cai, 2014) were reported in male (mice and piglets) offspring born to mothers supplemented with methyl donor. These modifications were associated with changes in both promoter CpG methylation and microRNA expression (Cai, 2014).

In our study, DNA methylation at cytosine–guanine dinucleotides in Scarb1, Ldlr and Cyp7a1 remain to be identified.


PO1.02.10
Cardiometabolic risk factors prevalence among employed adults in urban Delhi: Need for a life course approach for prevention of CVDs

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Background: Cardiometabolic risk factors like hypertension, type 2 diabetes, abnormal triglyceride, low HDL, abdominal obesity, high body mass index contributes to morbidity, mortality and economic burden among different stages of adulthood in India and around the world. This study aims to estimate the prevalence of cardiometabolic risk factors among employed adults of urban Delhi and to study the factors associated with these risks.

Methods: A cross sectional study was carried out among 455 apparently healthy employed adults (both males and females) of
urban Delhi, India. Different worksites from public and private sectors were selected to conduct the study. Using a pretested questionnaire information about family history of coronary artery disease, tobacco and alcohol use, dietary patterns, total physical activity was collected. Blood pressure, anthropometric and metabolic parameters were measured. Subjects were identified for metabolic syndrome as per NCEP ATP III Guidelines.

Results: It was found that 46.6% of apparent healthy employed adults (Mean age 41.4 ± 9.8) were suffering from metabolic syndrome which was used as a predictor for cardiometabolic risk. The risk was more among females (25.5%) compared to males (21.7%) (p < 0.00). Cardiometabolic risk factors observed were low High Density Lipoprotein (HDL) (62.9%), Abdominal Obesity (WC) (39.3%), Overweight (20.9%), Obesity (42.6%), hypertension (BP) (56.3%), elevated blood glucose (16%) and high Triglyceride (TG) (61.1%). 53.4% of the subjects had 0-2 and 46.6% of the subjects had 3-5 CVD risk factors. There was significant positive correlation between Body Mass Index (BMI), WC with lipid parameters and BP. There was statistically significant difference between mean values of HDL (p < 0.05), TG (p < 0.05) and WC (p < 0.05) between subjects with and without risk factors. It was found that sedentary lifestyle among working adults was one of the significant risk factors for the prevalence of CVDs (32.3%, p < 0.04) along with family history (74.9%), smoking (17.6%) and drinking (37.8%). Low physical activity was negatively correlated with increased BMI (p < 0.005) and WC (p < 0.000), and positively correlated with HDL (p < 0.00). An increasing trend in prevalence of overweight/obesity and cardiometabolic risk factors was observed with increase in age from early to late adulthood. Age was significantly associated with abdominal obesity, hypertension and elevated blood glucose (all p < 0.05).

Conclusion: Risk of developing CVDs is accumulated throughout the life course but it is evident from the findings that the greatest increase in risks is acquired in adult life. We need to address the link between sedentary lifestyle, unhealthy eating, obesity and other prevailing cardiometabolic risk factors which contributes to high disability rates among the working adult population. Healthy behaviors and intervention at early stage is priority to reduce the risk of developing CVDs in adult life.

PO1.02.11

Joint effect of birth weight and obesity measures on abnormal glucose metabolism at adulthood

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To investigate the joint effect of birth weight and each of obesity measures [body mass index (BMI) and waist circumference (WC)] on abnormal glucose metabolism (including diabetes) at adulthood. Using the historical cohort study design and the convenience sampling method, 1 921 infants who were born in Peking Union Medical College Hospital from June 1948 to December 1954 were selected to do the follow-up in 1995 and 2001 respectively. A total of 972 subjects (627 were followed up in 1995 and 345 were followed up in 2001) with complete information on genders, age, birth weight, family history of diabetes, BMI, WC, fasting plasma glucose(FPG) and 2-hour plasma glucose (2-h PG) met the study inclusion criteria. The ANOVA and Chi-squared tests were used to compare the differences in their characteristics by birth weight group. In addition, multiple binary Logistic regression model was used to investigate the single effect of birth weight, BMI, and waist circumference on abnormal glucose metabolism at adulthood. Stratification analysis was used to investigate the joint effect of birth weight and each of obesity measures (BMI and WC) on abnormal glucose metabolism. There were 972 subjects (male: 50.7%, mean age: 46.0 ± 2.2 years) included in the final data analysis. The 2h PG in low birth weight group was 7.6 ± 3.2 mmol/L, which was higher than that in normal birth weight group (6.9 ± 2.1 mmol/L and high birth weight group (6.4 ± 1.3) mmol/L. F = 3.88, P = 0.021). After adjustment for gender, age, body length, gestation age, family history of diabetes, physical activity, smoking and alcohol consumption, and duration of follow-up, subjects with overweight and obesity at adulthood had 2.73 (95% confidence interval (CI) = 2.06-3.62) times risk to develop abnormal glucose metabolism compared with normal weight ones. Likewise, subjects with central obesity were more likely to develop abnormal glucose metabolism than ones with normal waist (odds ratio (OR) = 3.35, 95% CI = 2.49-4.50). In addition, compared to subjects with normal birth weight and normal BMI at adulthood, ones with normal birth weight and overweight (including obesity) at adulthood were more likely to have abnormal glucose metabolism (OR = 2.60, 95% CI = 1.91-3.49); subjects with low birth weight and overweight (including obesity) at adulthood had the highest risk for abnormal glucose metabolism (OR = 4.70, 95% CI = 1.84-11.99). The attributable proportion of interaction between low birth weight and overweight (including obesity) at adulthood was 48.5%. In addition, compared to subjects with normal birth weight and normal WC at adulthood, one with normal birth weight and central obesity at adulthood were more likely to have abnormal glucose metabolism (OR = 3.18, 95% CI = 2.33-4.32); subjects with low birth weight and central obesity at adulthood had the highest risk for abnormal glucose metabolism (OR = 4.78, 95% CI = 2.01-11.38); subjects with high birth weight and central obesity at adulthood also had high risk for abnormal glucose metabolism (OR = 4.35, 95% CI = 1.38-13.65). We found that the attributable proportion of interaction between low birth weight and central obesity at adulthood was 38.5%, and was 28.3% for interaction between high birth weight and central obesity. There was strong interaction between birth weight and overweight (especially central obesity) at adulthood on abnormal glucose metabolism.
PO1.02.12
Neonatal nutritional deficit in infants with birth weight less than 1500 g and its association with blood pressure in adolescence
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\textsuperscript{1}Maternidad Sardà, BUENOS AIRES, Argentina; \textsuperscript{2}Maternidad Sardà, BUENOS AIRES, Argentina; \textsuperscript{3}Nutricia Bago, BUENOS AIRES, Argentina

Background: VLBW frequently present postnatal malnutrition at hospital discharge. This phenomenon is associated with short- and long-term adverse outcome. Its association with high arterial tension levels in the adolescence has not been reported. Objective: To evaluate the association between higher than 75\% percentile systolic (SBP) and diastolic blood pressure (DBP) in adolescents with VLBW at birth and their nutritional deficits during the first 28 days of life.

Methods: Prospective cohort. VLBW patients enrolled in a follow-up program in the neonatal period and in whom the nutritional follow-up program that in the neonatal period received an intensive nutritional support and in whom the nutritional deficits were prospectively recorded.

Results: 137 patients were followed-up. Pc 75\textsuperscript{th} was

Dec. Intensive early nutritional support and in whom the nutritional follow-up program that in the neonatal period received an intensive nutritional support and in whom the nutritional deficits were prospectively recorded.

PO1.02.13
Hepatitis C virus infection might increase the risk of atrial fibrillation
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Background & Aim: Previous studies indicated that chronic inflammatory conditions might increase the risk of atrial fibrillation (AF). Among patients with Hepatitis C virus (HCV) infection, extrahepatic manifestations are polymorphic, including cardiovascular, renal, metabolic and central nervous system diseases. However, limited data on the association of HCV infection and AF. The aim of this study was to investigate the association between HCV infection and AF.

Methods: We conducted a population-based cohort study by using the Taiwan National Health Insurance Research Database from 1997-2013. 11,806 HCV infected patients were included in our study and each of them was matched by age, gender and socioeconomic status at a ratio of 1:4. Overall, 58,820 patients (11,764 matched sets) were included in the final analysis. Due to higher mortality among HCV infected patient, we used competing risks regression models to compute the hazard ratios (HRs) accompanying 95\% CIs after adjustment for age, sex, socioeconomic status and other comorbidity. Two-tailed p = 0.05 was considered significant.

Much comorbidity has shown positive association with AF. To examine potential effect modifiers, we conducted sensitivity analyses to evaluate the difference and consistency between HCV infection and AF.

Results: There were 2,703 AF incidents during the follow-up period from 1997-2013. The incidence rate (95\% CI) of AF were 340.1(314.3–367.9) and 271.2(259.8–283.1) among patients with and without HCV infection, respectively. In competing risks regression models, the relative hazard of AF was 1.20 (95\% CI, 1.10-1.31) with HCV compared to those without. The sensitivity analysis adjustments exhibited little effect on the estimates of the association between HCV infection and AF according to different models.

Conclusions: HCV infection was associated with an increased risk of AF. Possible mechanisms include chronic systemic inflammation caused HCV infection. Further mechanistic research is required

PO1.02.14
Body parameters at birth and blood pressure in young age
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\begin{table}
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\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Parameter} & \textbf{VLBW} \textsuperscript{a} & \textbf{NBW} \textsuperscript{a} & \textbf{VLBW} \textsuperscript{b} & \textbf{NBW} \textsuperscript{b} & \hline
\textbf{SBP (mmHg)} & n=50 & n=100 & n=30 & n=60 & \\
\textbf{DBP (mmHg)} & n=50 & n=100 & n=30 & n=60 & \\
\hline
\textbf{Inclusion} & & & & & \\
\textbf{BMI (kg/m²)} & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & \\
\textbf{Z-score} & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & \\
\textbf{DBP (mmHg)} & & & & & \\
\textbf{Inclusion} & & & & & \\
\textbf{BMI (kg/m²)} & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & \\
\textbf{Z-score} & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & \\
\textbf{DBP (mmHg)} & & & & & \\
\textbf{Inclusion} & & & & & \\
\textbf{BMI (kg/m²)} & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & \\
\textbf{Z-score} & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & \\
\textbf{DBP (mmHg)} & & & & & \\
\textbf{Inclusion} & & & & & \\
\textbf{BMI (kg/m²)} & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & \\
\textbf{Z-score} & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & \\
\textbf{DBP (mmHg)} & & & & & \\
\textbf{Inclusion} & & & & & \\
\textbf{BMI (kg/m²)} & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & 14.0 (11.9–16.1) & 18.0 (16.9–19.1) & \\
\textbf{Z-score} & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & -0.7 (0.0–1.4) & 0.0 (0.0–1.4) & \\
\textbf{DBP (mmHg)} & & & & & \\
\hline
\end{tabular}
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**Background:** The gestational maturity of the newborn is often listed among the factors determining the development of essential hypertension. Values of blood pressure are affected by a complex interaction of genetic and environmental factors. Among the latter, special attention is given to birth weight, which reflects the conditions during intrauterine development. Numerous epidemiological studies have demonstrated the negative correlation between birth weight and blood pressure in children and adolescents. The aim of the study was to analyse the correlation between the birth length and weight and values of blood pressure in young women, and to assess differences in mean values of systolic and diastolic blood pressure in groups of subjects born with low, average and high body weight and length.

**Materials and methods:** We analysed 101 girls aged 19 years on the day of the study. The study used information from the personal child health record. Examination also included measurement of blood pressure and anthropological parameters. Blood pressure was measured using an oscillometric device. The cuff was placed on the left arm at heart level, and the measurement was taken twice. Obtained values of blood pressure were analysed using percentile tables. Since only 5% of the surveyed girls had birth weight under 2500g, the analysed subjects were grouped in terms of body weight based on terciles, and the same procedure was used for the distribution of body length. Basic descriptive statistics were used for the general characterisation of the analysed quantitative traits. The significance of differences between means for more than two groups and a single independent variable was tested using the analysis of variance (ANOVA).

**Results and conclusions:** The mean birth weight in the study group was 3320 ± 9.3 kg. The mean body mass index was 20.8 ± 3.2 cm. The actual mean body weight of the analysed subjects was 167.1 ± 5.6 cm, and the mean body weight was 58.4 ± 9.3 kg. The mean body mass index was 20.8 ± 2.9 kg/m². The mean recorded values were 114.30 ± 2.9 kg for systolic blood pressure and 73.86 ± 10.40 mmHg for diastolic blood pressure. Girls with high systolic blood pressure had lower mean birth weight and length compared to girls with normal systolic blood pressure. Girls with the lowest mean birth length had high diastolic blood pressure, and girls with the greatest birth length had severe hypertension. The lowest mean birth weight was found in girls with normal diastolic blood pressure and the highest birth weight was found in girls with hypertension, but the differences were not statistically significant (p > 0.05). There was no correlation between birth weight and length and values of systolic and diastolic blood pressure.

Population studies increasingly often suggest that the pathogenesis of coronary heart disease and abnormalities associated with them depend on the number of interactions occurring at different stages of body development. It has been speculated that the negative correlation between birth weight and blood pressure becomes stronger with age, but a longer observational study is required to finally confirm this hypothesis.

**PO1.03 – Epigenetics – Growth and cardio-metabolic health**

**PO1.03.01**

**HIF3α methylation in cord blood associates with cardiovascular measures in early childhood**

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The intrauterine environment influences the risk of later cardiometabolic disease, a process likely mediated by epigenetic changes at relevant disease-modifying genes. Differential methylation at two regions of the hypoxia-inducible factor 3 alpha gene (HIF3α), a negative regulator of adaptive transcriptional responses to hypoxia, has previously been associated with maternal prepregnancy BMI, birthweight, postnatal weight gain and adiposity measures. We investigated the relationship between differential HIF3α methylation and early life cardiovascular risk phenotypes in a large Australian population-derived cohort, the Barwon Infant Study (BIS). Methylation was quantified at 19 CpG units spanning two regions in cord blood samples from 776 infants. Childhood aortic intima-media thickness (aIMT), previously linked to cardiovascular risk in young adults, was measured at one month of age (n = 454). Aortic IMT was adjusted for minimal aortic diameter to account for age-related differences in vessel size. Increased methylation at seven (of 13 units) CpG units at one HIF3α region was associated with mean aIMT (estimated 0.77 μm increase in mean aIMT thickness for every 1% increase in average HIF3α methylation across the region, 95% CI: 0.09, 1.44, p = 0.03), adjusting for sex and birthweight standardised for gestational age. Infant weight, BMI, and the sum of tricep and subscapular skinfold thickness (a measure of adiposity) at one month were associated with mean aIMT (r = 0.25, r = 0.23 and r = 0.17 respectively, p < 0.001 for all) but not HIF3α methylation (r = 0.04, p = 0.53; r = 0.03, p = 0.65; and r = -0.02, p = 0.70 respectively). We are currently analysing equivalent cardiometabolic phenotypes at four years of age. BIS is among the first longitudinal studies of cardiovascular intermediate risk phenotypes from birth into childhood. We provide evidence of a clear association between differential methylation of the HIF3α gene at birth and putative markers of early cardiovascular risk in infancy. These data support a link between epigenetic variation in utero and later cardiovascular risk. Further studies are required to identify antecedents of...
HIF3α methylation at birth and to determine the relationship between HIF3α methylation and gene expression.

PO1.03.02
Physical activity before and during pregnancy and DNA methylation in maternal peripheral blood
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Background: Leisure time physical activity during pregnancy is associated with pregnancy complications and fetal outcomes. Epigenetic mechanisms, such as DNA methylation, potentially play key roles in these associations. Few studies have investigated maternal DNA methylation in relation to physical activity.

Methods: We conducted a cross-sectional study among participants (N = 92) of the Omega study, a pregnancy cohort study based in western Washington state. During a study interview in early pregnancy, participants self-reported leisure time physical activity duration (hours per week) and energy expenditure (MET-hours per week) in the year before pregnancy and during early pregnancy. DNA methylation in selected sites of candidate genes (NSMAF, NXXN, MSGN1, C1orf212, NOS2A, H19, HSD11B2, and F2), selected based on their role in pathophysiologic pathways related to pregnancy complications and outcomes, was profiled in maternal peripheral blood, collected shortly after the study interview (16 weeks gestation, on average). Site-specific linear regression models adjusted for maternal age and gestational age at blood draw were used to determine beta estimates and 95% confidence intervals.

Results: Eighty-seven percent of participants reported any leisure time physical activity in the year before pregnancy, and 77% reported any leisure time physical activity in early pregnancy. Each additional hour/week or MET-hour/week of pre-pregnancy leisure physical activity was associated with hypermethylation of a site in C1orf212 (β = 0.137, P = 0.05 and β = 0.030, P = 0.05, respectively). Each additional MET-hour of early pregnancy leisure time physical activity was associated with hypomethylation of a site in F2 (β = -0.101, P = 0.01). Pre- or early pregnancy leisure time physical activity was not associated with methylation in other evaluated candidate genes.

Conclusions: Maternal leisure time physical activity may be associated with methylation levels of C1orf212, a protein coding gene, and F2, a protein coding gene involved in inflammation, in peripheral blood. Future larger studies conducted in diverse populations are needed to confirm observed associations. Results from such studies will contribute to better understanding the mechanisms underlying associations of maternal physical activity with pregnancy complications and fetal growth.

PO1.03.03
DNA methylation mediates effects of prenatal maternal cognitive appraisal of a disaster on metabolic and immune outcomes: Project Ice Storm
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Background: Research suggest that prenatal exposure to stress is associated with adverse health outcomes, such as type 2 diabetes, hyperglycemia, and insulin resistance, as well as immune disorders, in offspring. DNA methylation is considered one possible underlying mechanism. The 1998 Quebec ice storm provides a unique opportunity to study an independent prenatal stressor on child outcomes. We have already shown that higher prenatal maternal hardship from the ice storm predicts higher insulin secretion in the children at age 13½. The objectives of this study are to determine 1) whether prenatal exposure to disaster-related objective hardship influences children’s C-peptide secretion and whether maternal cognitive appraisal influences children’s insulin and C-peptide secretion at age 13½; 2) whether DNA methylation of diabetes-related genes mediates the effects of prenatal stress on insulin and C-peptide secretion; and 3) whether DNA methylation of NF-kB signaling-related genes in T cells mediates the effect of prenatal maternal cognitive appraisal of the ice storm on Th1 and Th2 cytokine production in these adolescents.

Method: We recruited women who were pregnant during ice storm in January 1998, and they completed questionnaires about their stress in June 1998. We assessed the severity of their objective exposure to the storm, and their subjective distress (PTSD symptoms). To assess their cognitive appraisal we asked how they thought about the consequences of the storm, from very negative to neutral to very positive. Their children’s (n = 32) insulin and C-peptide secretion in response to an oral glucose tolerance test were assessed in blood at 13½ years. DNA methylation levels of selected type 1 and 2 diabetes-related genes were chosen based upon the genes associated with objective hardship and/or cognitive appraisal levels. For immune function, twenty NF-kB signaling-related genes whose methylation levels were associated with maternal cognitive appraisal were selected to test for mediation effects on the children’s cytokine levels. Bootstrapping analyses were performed to determine the mediation effect of DNA methylation.

Results: We found that children whose mothers experienced higher objective hardship exhibited higher C-peptide secretion. Cognitive appraisal was not directly associated with either insulin or C-peptide secretion. DNA methylation of type 1 and 2 diabetes-related genes had a positive mediation effect of objective hardship on both insulin and C-peptide secretion: higher objective hardship predicted both higher insulin and C-peptide secretion through DNA methylation. Negative mediation effects of cognitive appraisal were observed on both outcomes: negative (versus neutral/positive) cognitive appraisal predicted both higher
insulin and C-peptide secretion through DNA methylation. However, only one gene, LTA, remained a significant mediator on C-peptide secretion after Bonferroni correction. For immune function, DNA methylation levels of five CpGs from LTA were significant mediators of the effect of maternal cognitive appraisal on IL-2 secretion after correcting for multiple testing; there were no mediation effects on IFN-γ, and no mediation effects on IL-4 and IL-13 secretion, after Bonferroni correction.

Conclusions: Our findings suggest that DNA methylation could act as an intervening variable between prenatal stress and metabolic outcomes, highlighting the importance of epigenetic mechanisms in response to environmental factors.

PO1.03.04
Impact of a low glycaemic index diet in pregnancy on DNA methylation in 5 year old children: the ROLO Study
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Background: Environmental factors during fetal development have been shown to influence variable DNA methylation patterns which have been implicated in the determination of long-term health for the child. Maternal diet during pregnancy has been shown to influence offspring DNA methylation at birth but research is limited as to whether these changes persist as the child ages or whether the postnatal environment has a stronger influence on the methylome. This study aims to investigate if a dietary invention during pregnancy has a lasting impact on childhood epigenetic profiles at 5 years of age using a genome-wide methylation approach.

Methods: Sixty-three children were selected from the ROLO study (Randomised cOntrol trial of LOw glycaemic index diet versus no dietary intervention). DNA methylation profiles were obtained from saliva samples collected at 5 years of age. DNA methylation was investigated in 771,484 CpG sites using the Illumina MethylationEPIC BeadChip array. Principal component and regression analyses identified 22,181 differentially methylated CpGs (unadjusted \( P \leq 0.01 \)) in children of mothers exposed to the dietary intervention compared to the controls. No specific CpG sites showed significantly different methylation at False-Discovery-Rate corrected \( p \)-value. Principal components analysis found no strong association with the intervention, nor with child birth weight, current weight, BMI or adiposity measures at 5 years of age. Interestingly, gene pathway analysis identified functional clusters that differed between the intervention and control children involved in insulin secretion and resistance, pathways targeted by the intervention. Gene functional clusters involved in cellular functioning and regulation that control multiple cell differentiation processes during embryonic and adult life were also influenced by the intervention.

Conclusions: In this modest-sized discovery sample, we identified preliminary evidence of potentially long-lasting influences of a low glycaemic index dietary intervention in pregnancy on childhood DNA methylation patterns related to insulin secretion and resistance. Larger studies and replication of these findings are required to substantiate whether methylation differences at birth have a long-lasting effect into childhood.

PO1.03.05
A low glycaemic index diet in pregnancy induces DNA methylation variation in blood of newborns: results from the ROLO Study
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Background: The epigenetic profile of the developing fetus is sensitive to environmental influence. Mounting research suggests a role of variable DNA methylation in fetal programming of risk for a range of common non-communicable diseases. Maternal diet has been shown to influence individual DNA methylation patterns in offspring but research in humans is generally limited to observational studies with poorly defined exposures. This study investigates the impact of a dietary intervention during pregnancy on neonatal epigenetic profiles using a genome-wide methylation approach.

Methods: Sixty sex-matched neonates from the ROLO (Randomised cOntrol trial of LOw glycaemic index dietary intervention to prevent macrosomia) study were analysed. DNA methylation was investigated in 771,484 CpG sites in neonatal cord blood. Principal component analysis was undertaken and epigenome-wide associations were examined using linear regression of the methylation values comparing the dietary intervention group to controls. Associations with maternal and offspring factors were also explored.

Results: Principal component and regression analyses identified widespread variation in the DNA methylation profile of newborns of mothers exposed to the dietary intervention, accounting for 11% of total variation within the dataset. Despite this, no specific CpG sites showed significantly different methylation at False-Discovery-Rate corrected \( p \)-value. No association was found with maternal early-pregnancy body mass index, infant sex, or birthweight. Locus-specific replication of a subset of sites in a larger sample failed to replicate the original genome-wide findings. Pathway analysis identified common influences of the...
intervention on multiple aspects of cellular function including pancreatic and immune functioning.

Conclusions: Using a modest sized discovery sample, we identified preliminary evidence of widespread differential methylation in progeny of mothers exposed to a low glycaemic index dietary intervention. This included differential methylation of several genes plausibly linked to pathways targeted by the intervention. Although these findings provide preliminary evidence for dietary interventions in pregnancy modifying the offspring epigenome, limited replication failed to reproduce a subset of the findings, potentially due to the very small effect size. Larger studies are required to fully explore the potential for interventions in pregnancy to break the cycle of transmission of poor metabolic health from mother to offspring via epigenetic variation.

PO1.03.06
Varying influence of cellular heterogeneity on the relation of DNA methylation to adiposity and early life

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Background: DNA methylation is a key indicator of cell differentiation, and DNA methylation profiles differ strongly by cell type. Methylation change can be intrinsic (cell count independent) or extrinsic (cell count dependent). In previous work on Infinium HumanMethylation450K arrays, methylation sites within MSI2 and SLC25A10 were associated with concurrent BMI, after Houseman correction. The current study evaluates interplay of MSI2 and SLC25A10 methylation with adolescent adiposity, early life environmental influences and cell counts.

Methods: Whole bloods from 842 individuals aged 17 years were assayed for MSI2 and SLC25A10 methylation. MSI2 methylation was measured at 3 internal sites (CpGs), and SLC25A10 at two internal CpGs, by pyrosequencing. Methylation levels were investigated for their association with early-life environmental influences, using adjusted linear regression models with and without cell count. Cell counts (CD4, CD8, NK, Granulocytes, B cells and monocytes) were estimated using the Houseman method. Collinearity between CpGs and cell counts was examined using variance inflation factors (VIFs) as measures of collinearity within the terms of the regression.

Results: DNA methylation of MSI2 was associated with log transformed BMI unadjusted for cell count adjustment ($\beta = 0.007$, $p = 4 \times 10^{-6}$), and when adjusted for cell count ($\beta = 0.007$, $p = 2 \times 10^{-6}$). Without cell count adjustment, SLC25A10 methylation was not associated with BMI ($\beta = 0.001$, $p = 0.327$). With cell count adjustment, it was positively associated ($\beta = 0.004$, $p = 0.004$). Early life factors were associated with unadjusted MSI2 methylation (pre-pregnancy BMI ($\beta = 0.11$, $p = 0.003$) and duration of exclusive breast-feeding ($\beta = -0.047$, $p = 0.045$), but these associations were abolished with adjustment for cell counts ($\beta = 0.040$, $p = 0.218$ and $\beta = -0.01$, $p = 0.644$ respectively). Maternal pre-pregnancy BMI was associated with cell count adjusted SLC25A10 DNA methylation ($\beta = 0.129$, $p = 0.005$), but not when unadjusted for cell count ($\beta = 0.030$, $p = 0.552$). VIFs for associations between methylation levels and cell counts were very high (10-125), but reduced with removal of the granulocyte term to all <2. Models were re-run removing collinear covariates with marginal difference in coefficients.

Conclusions: MSI2 and SLC25A10 methylation were associated with BMI after adjustment for cell counts, so the BMI-associated-variance in methylation levels is intrinsic to the cell types. In the case of MSI2, there is also some BMI-associated-methylation-variance that is extrinsic of the cell types. However, a critical point of difference existed in the relationships between methylation levels and early life factors. MSI2 associations occurred without cell adjustment to early life factors, so are likely to pertain to extrinsic variation. SLC25A10 associations to these factors, occurred with cell adjustment and so are likely intrinsic of the cell types measured.

Discussion: This study adds evidence that methylation of specific loci associate with adiposity. These two loci demonstrate starkly that environment-associated DNA-methylation can be intrinsic (cell count independent, e.g. SLC25A10) or extrinsic (cell count dependent, e.g. MSI2), affecting how DNA methylation mediates the association between early life factors and adiposity. Perhaps early environments associated with extrinsic methylation levels affect cell fate and cell mix in the adult; whereas early environments associated with intrinsic methylation affect programming within a cellular subtype. These interpretations can only be made after statistical complexities such as collinearity are resolved.

PO1.03.07
DNA methylation of nos3 promoter in IUGR-guinea pig fetuses does not predict endothelial function and DNA methylation later in life

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Background: Intrauterine growth restriction is associated with endothelial dysfunction and cardiovascular diseases in adult subjects. It has been proposed that changes in the DNA
methylation pattern of key endothelial genes, such as the endothelial nitric oxide synthase gene (\textit{nos3}), which could take place as early a fetal development, would precede the founding of an altered endothelial function. To address this issue, we studied the levels of eNOS expression, \textit{nos3} promoter DNA methylation pattern and ex vivo endothelial function in fetal and adult arteries from IUGR guinea pigs.

**Methods:** Pregnant guinea pigs were submitted at mid-gestation to a surgery for implanting ameroid constrictors at both uterine arteries (IUGR), or a sham intervention (Control). In half of the sows, pregnancy was interrupted at term (~ 60 days) and fetuses were extracted by C-section, dissected and weight, whilst the other half was allowed to breed and the offspring were followed up to adulthood (10 months). Fetal and adult femoral arteries were isolated to assessed vascular function by wire-myography. Primary cultures of endothelial cells were obtained from fetal and adults aorta. In these cells levels of eNOS mRNA were quantified by qPCR and the DNA methylation of 12 CpG sites in \textit{nos3} promoter was determined by pyrosequencing.

**Results:** In term fetuses, IUGR was associated with an increased expression of eNOS mRNA as well as a decrease in the DNA methylation status in CpG -170 (relative to the transcription start site) compared to controls fetuses. In contrast, endothelial-dependent relaxation in IUGR femoral arteries was comparable to controls, but with a reduced sensitivity. Endothelial-independent relaxation to NO was similarly reduced in sensitivity but not in the maximal effect in IUGR femoral arteries. In adult guinea pigs from IUGR pregnancies, eNOS mRNA levels were substantially decreased compared to control adults, and this change was associated with an increased DNA methylation level in CpG -170. Similarly, there was a reduced endothelial dependent relaxation, as well as a reduced sensitivity to NO, in adult IUGR femoral arteries compared to controls.

**Conclusion:** This data suggests that changes in \textit{nos3} promoter DNA methylation observed in IUGR term fetuses would represent the exposure to an adverse intrauterine environment, however, this would not be associated with endothelial dysfunction and DNA methylation pattern on \textit{nos3} in the adult life. Conversely, the adult cardiovascular dysfunction associated with an increased DNA methylation level in CpG -170. Similarly, there was a reduced endothelial depen-

**PO1.03.08**

**Is the low birthweight a determinant factor for epigenetics changes and body composition?**


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**Background:** 22 millions out of 137 millions born with low birthweight, now we known that is a background for the development origin of the adult disease.

**Objective:** To know whether low birthweight is a determinant factor for epigenetic changes and body composition.

**Methods:** The study was approved by the Ethics Committee and informed consent was obtained from parents. We enrolled 60 newborns from Hospital Central Dr Ignacio Morones Prieto in San Luis Potosi, Mexico. Serum samples were taken at the first 24 h after birth; we measured IL-6, IL-1b by ELISA and microRNAs by qRT-PCR, biochemical parameters, anthropometric measurements and by bioelectrical impedance fat mass, lean fat, nutritional index. For statistical analysis we used t student for continuous and categoric by chi square test, \( p < 0.05 \) were considered statistically significant. All calculations were done in SPSS 22 and InStat 5.0.

**Results:** Gestational age for both groups median 37 weeks (IQ 31-40), weight (g) mean eutrophic (2648 ± 732), hipotrophic (1994 ± 475) \( p = 0.001 \), lenght (cm) eutrophic median 49.5 (IQ 38-60) hipotrophic median 45.5 (IQ 34-49) \( p = 0.001 \), head circumference eutrophic median 32 (IQ 26-38) hipotrophic median 29 (IQ 22-32) \( p = 0.002 \), abdominal circumference eutrophic mean (29.7 ± 3.6) hipotrophic mean (25.9 ± 2.8) \( p = 0.001 \). Resistance (\( \Omega \)) by bioelectrical bioimpedance in eutrophic median 442 (IQ 343-922) hipotrophic median 694 (IQ 392-1066) \( p = 0.001 \), reactance (\( \Omega \)) eutrophic median 71.2 (IQ 42-127) hipotrophic median 71.6 (IQ 44.6-129) \( p = 0.001 \), Cholesterol eutrophic mean (5.4 ± 1.9) hipotrophic mean (7.0 ± 2.8) \( p = 0.47 \), IL-6 expression was not different between groups \( p = 0.56 \), IL-1b was significant lower in hipotrophic group \( p = 0.01 \). Both microRNA miR-132 and miR-146 was upregulated in hipotrophic group, the \( p \) value was 0.04 and 0.007 respectively.

**Conclusion:** This is the first report about the relation of low birthweight with epigenetic biomarkers, biochemical and anthropometric parameters, bioelectrical impedance. The results directs us to a field of research in low weight neonates toward the origin of adult disease.

**PO1.03.09**

**Circulating microRNAs expression of newborn associated with overweight and pregestational obesity**

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**No3 DNA methylation pattern and endothelial function in IUGR guinea pigs**
**Conclusion:**

K. Kashima\(^1\), T. Kawai\(^2\), R. Nishimura\(^3\), Y. Shiwa\(^4\), infants during perinatal period

Epigenetic and transcriptomic changes in preterm or SGA diseases. They may be participating in the programming of metabolic and miR-378 are different in all three groups suggesting that epigenetic changes in cord blood and postnatal peripheral blood of preterm or SGA infants using epigenome-wide methylation analysis, and to search for environmental or therapeutic factors that associate with epigenetic changes in these premature babies.

**Methods:** We conducted Illumina 450K methylation microarray analysis using mononuclear cell fraction derived from 127 cord blood and 66 postnatal peripheral blood samples obtained on or around the babies’ due date, whose gestational age ranged from 23 to 41 weeks. For the statistical analysis, we utilized linear regression multivariate analysis, that is, in this model we set the beta methylation level as the dependent variable, gestational age (GA) and birthweight z-score for GA in the Japanese standard (SD-score) as the explanatory variables, adjusted by blood cell fraction, sex, and so on. For adjustment of multiple tests, we utilized corrected p-value using Benjamini-Hochberg method. Moreover, we conducted Agilent expression microarray analysis using 65 cord blood and 48 postnatal peripheral blood samples.

**Results:** [Result1] In the analysis of the cord blood samples, we identified 48,979 differently methylated CpG sites (DMPs) related to GA. On the other hand, there were 454 SD-score-related DMPs. More than half of SD-score-related DMPs overlapped with GA-related DMPs. [Result2] In the analysis of the postnatal blood on or around the due date, there were almost no DMPs associated to either GA or SD-score at birth. [Result3] In the expression microarray analyses, there were the same trends seen in the results of methylation microarray.

**Conclusions:** Drastic epigenetic changes were found in preterm babies’ cord blood, but most epigenetic differences showed a tendency to disappear in preterm infants by their due date. Transcriptome had the same trends regarding gestational age. We confirmed that gestational age is one of the most important factors that affect babies’ epigenetics. We also found some SGA-related epigenetic alterations, most of which similarly disappeared by their due date.

**POI.03.10**

Epigenetic and transcriptomic changes in preterm or SGA infants during perinatal period

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**Background:**

Obesity and overweight have been considered as an important health problem worldwide due to increased prevalence and incidence. Obesity is characterized by an increased in body fat that is associated to metabolic alterations including insulin and leptin resistance, and the inflammatory chronic state have a role in the physiopathology. Overweight and obesity are considered an important factor of risk for metabolic syndrome, diabetes type 2 and cardiovascular diseases and other pathologies as cancer. Consequences of short and long term have a social and economic impact in life. It is known that the environment has a role in the establishment of altered metabolic and inflammatory responses, and could be modulated by microRNAs. The objective of the study was to analyze the expression profile of five circulating microRNAs in pairs: mother and newborn subset normal, overweight and obesity groups.

**Methods:** Pregnant women were included and grouped by pregestational body mass index (35 with normal weight, 23 overweight, and 12 obese women). A peripheral blood sample was obtained from mother and her respectively newborn and used to determine circulating miRNAs expression.

**Results:** There are significant differences in the expression of four microRNAs in mothers and newborns between of three groups: pre-gestational normal weight, overweight and obese: miR-146a \(p = 0.035\), miR-155 \(p = 0.016\) and \(0.0092\), miR-221 \(p = <0.0001\) and miR-378a \(p = 0.003\). An association between maternal BMI and the newborns expression of miR-155 and miR-221 expression was also observed.

**Conclusion:** expression of miR-146, miR-155, and miR-221 and miR-378 are different in all three groups suggesting that they may be participating in the programming of metabolic diseases.

**POI.03.11**

Mother’s pre-pregnancy BMI and placental candidate miRNAs: Findings from the ENVIRONAGE birth cohort

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**Background:**

There is increasing evidence that the predisposition for development of chronic diseases arises at the earliest times of life. In this context, maternal pre-pregnancy weight might modify fetal metabolism and the child’s predisposition to develop disease later in life. The aim of this study is to investigate the association between maternal pre-pregnancy
body mass index (BMI) and miRNA alterations in placental tissue at birth.

**Methods:** In 211 mother-newborn pairs from the ENVIRO-NAGE birth cohort, we assessed placental expression of seven miRNAs important in crucial cellular processes implicated in adipogenesis and/or obesity. Multiple linear regression models were used to test the associations between pre-pregnancy BMI and placental candidate miRNA expression.

**Results:** Maternal pre-pregnancy BMI averaged (± SD) 23.9 (±4.1) kg/m². In newborn girls (not in boys) placental miR-20a, miR-34a and miR-222 expression was lower with higher maternal BMI. In addition, the association between maternal pre-pregnancy BMI and placental expression of these miRNAs in girls was modified by gestational weight gain. The lower expression of these miRNAs in placenta in association with pre-pregnancy BMI was only evident in mothers with low weight gain (<14 kg).

**Conclusions:** The placental expression of miR-20a, miR-34a, miR-146a, miR-210 and miR-222 may provide a sex-specific basis for epigenetic effects of pre-pregnancy BMI.

**PO1.03.12**

**Are preterm survivors aging prematurely?**

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**Background:** Individuals born preterm are at increased risk for the early onset of chronic conditions associated with aging, including hypertension and insulin resistance. This raises the question of whether these individuals may be aging at a faster rate than same-age term-born controls.

DNA methylation at 353 specific CpG sites (i.e., the epigenetic clock; Horvath, 2013) is strongly associated with increased age across individuals, and is reliable enough to predict individual chronological ages. We hypothesized that men and women born at extremely low birth weight (ELBW; birth weight ≥ 1000g) would show more extensive DNA methylation at epigenetic clock sites than matched control participants born at normal birth weight (NBW; birth weight ≥ 2500g).

**Methods:** We examined DNA methylation in buccal epithelial cells from 45 adults born at ELBW and 49 matched controls born at NBW, aged 30 to 35, using the Illumina Infinium Human MethylationEPIC 850k Bead Chip array to probe over 835,000 CpG sites from across the genome. Methylation results were normalized using the SWAN (subset-quantile within array normalization) method (Maksimovic et al., 2012). DNA methylation and chronological age were analyzed for group and sex differences in separate univariate ANOVAs. Pearson correlations between DNA methylation and chronological age were compared by subgroup (Horvath, 2013).

**Results:** After normalization and controlling for common genetic variation, we found that DNA methylation levels at
Methods: Adult (n = 36) and newborn (n = 151) isolated peripheral blood leukocyte subtypes (CD4, CD8, B-cell, NK, monocyte, granulocyte) were harmonized and compared using linear mixed effect models adjusting for age, sex and subject, as a random effect. From the list of significant candidates (Q-value < 0.05), we identified a subset of highly invariant sites. Using a constrained projection/quadratic programming approach we projected the proportion of ESC signature in the samples. We replicated the results using 46 newborns and 200 adult isolated leukocyte samples. The results were further extended to observe if this signature was present in other cells using isolated embryonic an fetal hematopoietic cells (n = 74) vs adult bone marrow cells (n = 49); fetal somatic (n = 247) vs adult somatic tissues (n = 156), and cord blood (n = 60) and peripheral blood samples (n = 993) at different ages (0 to 103 years).

Results: We identified a common set of differentially methylated CpG sites that constitute a lineage invariant and developmentally sensitive methylation signature across the different leukocyte subtypes. The cell fraction displaying the signature was highly dependent upon developmental stage (fetal vs adult) and in leukocytes, it described a dynamic transition during the first 5 years of life. A dramatic loss of the ESC signature occurs in blood following birth with a 50% reduction occurring at approximately 1 year. After age 5 a low but detectable level of ESC occurs in some individuals even into advanced ages. Significant interindividual variation in ESC fraction at birth is partly explained by gestational age. Significant individual variation in the embryonic signature of leukocytes was evident at birth, in childhood, and throughout adult life. The embryonic origin of the newborn cells is supported by the highly concordant methylation signatures they share with embryonic stem cell lines, induced pluripotent cells and fetal liver CD34+ stem/progenitors. Furthermore, multiple non-hematopoietic fetal tissues but not their adult counterparts display the signature, thus confirming it as a marker of embryonic lineage. The ESC methylation signature provides insight into a fundamentally developmental process of immune cell maturation. The genes denoting the signature included transcription factors and proteins intimately involved in embryonic development.

Conclusion: Our DNA methylation signature traces the developmental origin of cells and informs the study of stem cell heterogeneity in humans under homeostatic and pathologic conditions.

PO1.03.14

Caffeine consumption during pregnancies and DNA methylation in the offspring

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Aim: To study the relationship between maternal caffeine consumption during pregnancy and the epigenetic profile of the offspring.

Background: Excessive maternal coffee consumption during pregnancy has been linked to adverse health effects in the offspring, particular ADHD and other neuro-developmental traits. Could some of this risk be mediated through DNA methylation?

Material & Methods: We investigated the association between maternal caffeine consumption during pregnancy and the DNA methylation in umbilical cord blood from the Norwegian Mother and Child Cohort (MoBa). This cohort is a large nation-wide birth cohort, with DNA methylation data for 1009 pregnancies in for discovery cohort and 493 pregnancies in the replication cohort.

Results: Some CpGs were genome wide significant after multiple testing at the false discovery level of 5%. We also replicated several near-significant findings in the independent replication cohort, adjusted for multiple testing. Some of the replicated CpGs were likely to regulating genes involved in anthropometry and in neuro-cognitive traits.

Conclusion: These findings could potentially explain some of the reported associations between high caffeine intake and ADHD.

PO1.03.15

Epigenetic gestational age: associations of family characteristics and perinatal factors with gestational age acceleration


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Background: Gestational age (GA) is associated with a range of medical and neuropsychological outcomes in childhood. Recently, models which use DNA methylation (DNAm) measured in cord blood to predict GA have been developed; inevitably, these predictions differ somewhat from gestational age determined by ultrasound and last menstrual period (LMP). This difference between observed and predicted GA is known as gestational age acceleration (GAA). In children and adults, age acceleration (the difference between DNAm predictions of chronological age) is associated with poor clinical outcomes, including mortality. The aim of this study was to investigate the associations of GAA calculated from DNAm with sex, socioeconomic status (SES), parental behaviours, parental characteristics, and perinatal factors.

Methods: Participants (n = 863) from the ARIES sub-cohort of Avon Longitudinal Study of Parents and Children (ALSPAC) formed the sample. GAA was calculated using the residuals of a regression of predicted GA (using cord blood methylation at 96 CpG sites) on GA (determined by ultrasound and LMP). The method for predicting GA was based on a model developed by Bohlin et al. (2016). A series of linear
regressions were employed to determine associations of child sex, parental SES (social class, parental education, housing tenure and financial difficulties), parental behaviours (smoking, alcohol use), parental characteristics (mental health, relationship status, parity, body mass index [BMI] and age) and perinatal factors (delivery method, pregnancy complications, birthweight, birth length, head circumference, and APGAR scores at 5 minutes) with GAA. Analyses were completed on 100 multiply imputed data sets.

**Results:** Mothers who were overweight and obese (as indicated by self-reported pre-pregnancy BMI) had children with later than predicted GA (mean difference $[MD] = 1.61$ days, 95% CI 0.64 to 2.55 days; $MD = 2.80$ days, 95% CI 1.22 to 4.35 days respectively, $p < .001$) compared to mothers who were underweight or had a normal pre-pregnancy BMI. Higher birthweight, birth length and head circumference of the child were similarly positively associated with GAA ($MD = 1.82$ days per kg of birthweight, 95% CI 1.12 to 2.47 days, $p < .001$; $MD = 0.35$ days per cm of birth length, 95% CI 0.19 to 0.50 days, $p < .001$; $MD = 0.49$ days per cm of head circumference, 95% CI 0.22 to 0.71 days, $p < .001$). There was weak evidence to support associations of sex, parental relationship and delivery method with GAA. Other variables were not associated with GAA.

**Conclusions:** Parental factors and perinatal factors, specifically maternal pre-pregnancy BMI, birthweight, birth length and head circumference, are positively associated with GAA and should be considered when predicting GA based on DNAm. The association between maternal overweight/obesity and higher GAA may imply that overweight and obesity is associated with more rapid development of the fetus in utero; however, these positive associations with factors linked to both positive and negative health outcomes suggest that the health implications of GAA are likely complex.

**POI03.16**

Maternal obesity predisposes adult male rat offspring to increased adiposity via epigenetic modifications in a depot-specific manner.


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According to the Developmental Origin of Health and Disease (DOHaD) concept, maternal obesity and accelerated growth in neonates predispose offspring to white adipose tissue (WAT) accumulation. The mechanisms underlying the phenomenon known as developmental programming are poorly understood. In order to unravel the underlying mechanisms, we have developed a rat model of maternal obesity using a high-fat (HF) diet prior and throughout gestation and lactation. We evaluated the potential programming effects of maternal obesity on offspring’s WAT at two stages of lactation (postnatal days 12 (PND12) and 21 (PND21)) and in adulthood (9 months). At birth, newborns from obese dams (called HF) were normotrophs. HF neonates exhibited a rapid weight gain during lactation, a key period of adipose tissue development in rodents. The expansion of WAT was correlated with increases in both adipocyte size (hypertrophy) and number (hyperplasia) in visceral perirenal (pWAT) and subcutaneous inguinal (iWAT) deposits. 9-month-old HF offspring displayed persistent increased adiposity. However, among iWAT and pWAT, only the latter showed a persistent “expandable” phenotype (i.e. higher fat mass, hypertrophy and hyperplasia). Maternal obesity led to changes in adipogenic and lipogenic gene expression in HF offspring’s WAT from neonatal period to adulthood. In particular, HF offspring showed persistent increased leptin and decreased PPARg mRNA contents in a depot-specific manner, consistent with persistent elevated plasma leptin levels as well as modified cellularity. We hypothesized that long-term modifications of gene expression occur, at least in part, via epigenetic malprogramming which may take place during the early postnatal period. Epigenetic marks may serve as a memory of exposure, in early life, to inappropriate environments. These persistent marks may ultimately induce long-term changes in gene expression. Here, we focused on epigenetic modifications (i.e., DNA methylation, DNA hydroxymethylation and histone modifications) of regulatory sequences involved in leptin and PPARg gene expression in both deposits. PND12 is an active period for epigenomic remodeling within regulatory sequences of both genes in HF offspring, consistent with modified hormonal status and enzymatic components of the epigenetic machinery. Some of these epigenetic modifications were still visible in weaned HF offspring. Retained marks were observed in 9-month-old HF rats. The long-term epigenetic malprogramming was correlated with long-lasting modified gene expression and depot phenotype. Overall, we showed that editing of epigenetic marks takes place early in life during WAT’s development and might persist throughout life in a depot-specific manner. Consistent with the DOHaD hypothesis, persistent epigenetic remodeling occurs at regulatory regions of key lipogenic genes that might account for increased adiposity in adult HF offspring.

**POI03.17**

Infants born small-for-gestational age have different placental expression of microRNAs

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**Background:** Normal placental function is essential for optimal fetal growth and development. The expression of
microRNAs can be influenced by the environment. The objective of this study was to investigate the placental microRNA expression profile in infants born small-for-gestational age (SGA) and exposed to low maternal gestational weight gain (GWG).

Methods: 13 full-term newborn babies with birth weights < -2 SD from the population mean exposed to maternal GWG ≤ 10 kg (group 1) were identified in a placental biobank. 9 children with birth weights < -2 SD and GWG 11.5–16.0 kg constituted group 2. 20 children with normal birth weights but GWG ≤ 10 kg constituted group 3 and 26 children with both normal birth weights and GWG constituted group 4. The infants in groups 2–4 were matched with group 1 with respect to gender, gestational age, maternal parity, and maternal age. Total RNA were extracted from the placental biopsies. After microRNA preparation, next generation sequencing using Illumina technology was performed. Comparisons between the groups were done with ANOVA for unequal variances and Benjamini-Hochberg’s correction for multiple testing.

Results: The mean (SD) birth weight and maternal GWG in group 1 were 2,834 (296) g and 9.2 (1.2) kg, respectively. The corresponding numbers in group 2 were 2,636 (211) g and 13.6 (1.0) kg, respectively, in group 3 3,696 (355) g and 9.1 (1.0) kg, respectively, and in group 4 3,747 (356) g and 15.0 (1.2) kg, respectively. 48 of the 68 children were boys. The minimum reads/sample were 9.2 millions. The expression of 16 microRNAs differed significantly between group 1 and group 2. The expression of 12 microRNAs differed significantly between group 2 and 4. Ten of the differentially expressed microRNAs differed in both comparisons (miR-3679-5p, miR-4532, miR-335-3p, miR-379-3p, miR-380-3p, miR-369-5p, miR-330-5p, miR-519e-3p, miR-105-5p, and miR-3065-5p).

Conclusions: The mechanism behind poor fetal growth may involve differential expression of microRNAs in the placenta. Low maternal weight gain during the pregnancy seems to influence the placental microRNA expression in children born SGA but not in children with normal birth weights.

PO1.04 – Gestational diabetes

PO1.04.01

Relationship between Glycated Hemoglobin in Early Type2 Diabetic Pregnancy and Adverse Pregnancy Outcomes

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Background: The prevalence of type2 diabetic pregnancy has increased worldwide in the past decade along with the prevalence of type2 diabetes. Many studies including the HAPO study had revealed the fact that hyperglycemia is associated with many adverse pregnancy outcomes such as spontaneous abortion, malformation, cesarean delivery, and many neonatal complications. Some studies showed that among type 1 diabetic pregnancy and undiagnosed diabetes pregnancy women, high level of HbA1c in the 1st trimester was related to abortion, stillbirth and malformation in early pregnancy. However, the relationship between early HbA1c level and adverse outcomes other than congenital malformation in type2 diabetic pregnancy reminds unclear.

Method: 384 pregnant women with type2 diabetes from Jan 2005 to Jan 2017 were recruited. Adverse pregnancy outcomes were preterm birth (< 37 weeks), cesarean delivery, complicated with preeclampsia, SGA and LGA. Neonatal complications including neonatal hypoglycemia, NICU admission and stillbirth. The results were analyzed by t-test and ROC curve.

Results: Patients with LGA and NICU admission had a higher FPG level in the 1st trimester, and patients with preterm birth, LGA, neonatal hypoglycemia and NICU admission had a higher HbA1c level in the 1st trimester. Moreover, HbA1c in the 1st trimester had a predictable value towards preterm birth, LGA (P<0.01) and NICU admission (P<0.05) with a cut-off value of 6.45%, while the cut-off value to predict neonatal hypoglycemia (P<0.01) was 6.65%.

Conclusion: Elevated HbA1c and FPG level in the 1st trimester was associated with several adverse pregnancy outcomes in type 2 diabetic pregnancy. With an HbA1c level above 6.45% in the 1st trimester suggested increased risk of preterm birth, LGA, neonatal hypoglycemia and NICU admission.
epigenetic factor that predisposes offspring to metabolic and cardiovascular diseases. However, the mechanisms via which maternal hyperglycemia affects the development of these diseases in offspring has not been thoroughly studied yet. Mammalian tribbles homologue 1 (TRIB1) gene is associated with coronary artery disease (CAD) and plasma lipid concentrations in humans. According to animal studies TRIB1 deficiency increases plasma cholesterol and triglyceride levels in mice. Our aim was to study the effect of the degree and duration of maternal hyperglycemia on the level of TRIB1 expression in human umbilical vein endothelial cells (HUVECs) of newborns from women with gestational diabetes mellitus.

**Materials and methods:** The study included 41 women with GDM treated for GDM starting before 30-th week of gestation (GDM1), 9 women treated for GDM after 34-th week of gestation (late treatment group or GDM2) and 17 women without GDM (control group). The diagnosis of GDM was based on International Association of Diabetes and Pregnancy Study Groups criteria. HUVECs were isolated and expanded in vitro up to passage 2 and tested for viability and replicative senescence. Samples with viability > 85% and low level of senescent cells (<10%) were used. Immunophenotype was determined by Flow Cytometry analysis. The level of TRIB1 expression was determined by RT-PCR. Women with GDM kept electronic nutrition and glycemic control diaries with the help of a specially developed mobile application and sent data to the doctor. According to the personal diaries automatic calculations of the integral indicators characterizing the self-control of glycemia (mean fasting and postprandial glycemia, the frequency of exceeding the target levels of glycemia) and food intake (amount of carbohydrates, proteins, fat and calories) were accomplished. Statistical analysis included Kruskal-Wallis test, Mann-Whitney test and Spearman correlations.

**Results:** The level of TRIB1 expression in GDM2, GDM1 and control groups amounted to 2.6 ± 0.9, 4.9 ± 2.9, 7.5 ± 5.4, respectively (p = 0.003) (Figure 1). Notably, TRIB1 expression was significantly lower in GDM2 compared to GDM1 group (p = 0.006) and controls (p = 0.005). The difference in TRIB1 expression between GDM1 and control groups was not significant (p = 0.060). Age and pregestational BMI did not differ among the three groups. Some negative correlations have been observed between the level of TRIB1 expression and following parameters: gestational age when treatment for GDM started (r = -0.303, p = 0.036); total amount of carbohydrates consumed a day (r = -0.388, p = 0.041) and plasma glucose level 1 h and 2 h in OGTT (r = -0.291, p = 0.027 and r = -0.298, p = 0.023 respectively).

**Conclusion:** TRIB1 expression appeared to be lower in HUVECs of newborns from women with late start of treatment for GDM compared to controls. The difference was attenuated if treatment had been started before 30th week of gestation. The data obtained confirm the potential influence of intrauterine hyperglycemia on the TRIB1 expression that is likely to epigenetically program predisposition to CAD in offspring.

Relative expression of TRIB1 gene in human umbilical vein endothelial cells of newborns from women with GDM and control group

**PO1.04.03**

**Can we develop a successful risk score for gestational diabetes?**

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**Background:** The global epidemic of type 2 diabetes and gestational diabetes (GDM) requires methods for early detection of individuals at risk. Risk scores have been successfully developed for type 2 diabetes, but the GDM scores are not performing equally well. The aim of this study was to investigate the risk profiles of GDM women, taking simultaneously into account the marked heterogeneity of GDM.

**Methods:** This is a secondary analysis of the RADIUS (Finnish Gestational Diabetes Prevention) study including 510 women at high GDM risk (BMI ≥ 30 kg/m² and/or previous GDM) recruited either in pre-pregnancy or in first trimester. We divided the participants according to BMI, parity and GDM history: nulliparous obese (group A), multiparous obese (group B), non-obese with prior GDM (group C), and obese with prior GDM (group D). Age, weight, family history of diabetes and first trimester markers of inflammation, lipid and glucose metabolism served as potential predictors for GDM. We also tested in all groups the performance of a GDM risk score by van Leeuwen et al, where probability of GDM = 1/ [1 + exp(-β)], in which β is calculated as [-6.1 + (0.83 x non-Caucasian ethnicity) + (0.57 x positive family history of diabetes mellitus) - (0.67 x multipara without history of GDM) + (0.5 x multipara with history of GDM) + (0.13 x BMI)].

**Results:** The cumulative GDM incidence was 37.4% (95% CI: 33.2 to 41.8) in the first trimester and 49.4% (95% CI: 45.0 to 53.9) in the second trimester.
53.8) in the second trimester. Among the non-obese (BMI < 30 kg/m²) women with a history of previous GDM (group C), the cumulative incidence in the second trimester was 59% and among obese women with previous GDM (group D) 74%. Obese primiparous women (group A) showed an increased GDM risk with higher fasting glucose values increasing GDM risk OR 3.76 (95% CI: 1.48 to 9.53) but in the other subgroups there were no risk predictors. The estimated probability of GDM calculated by Van Leeuwen risk score was lower than the true incidence of GDM (Figure 1), especially among the non-obese women with previous GDM (group C).

Conclusions: Our “risk model”, simply based on degree of adiposity and history of previous GDM, performed as well as more complicated/sophisticated models in identifying a high GDM-risk group already in the first trimester. Due to the heterogeneity of GDM, it might be impossible to achieve a universal risk score; instead, focus should be on universal OGTT screening.

PO1.04.04
Cardio-metabolic risk factors in offspring of diabetic mothers (ODM) in India.
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Background: Maternal diabetes is a risk factor for obesity and glucose intolerance in the child. Only sparse data is available in India. We followed children born to gestational diabetic and non-diabetic mothers 2-26 years after delivery to assess their body size and composition, and cardio-metabolic risk factors.

Methods: Of 916 women diagnosed and treated for diabetes in pregnancy at the Diabetes Unit, KEM Hospital, Pune (1986–2014), we traced 364 mothers and studied 200 children by January 2017 (ODM). We also studied 154 children whose mother was not diagnosed diabetic during pregnancy (ONDM), matched for age, gender and socioeconomic status (usually a friend, neighbour or classmate). We measured anthropometry, body composition (DXA) and either capillary blood glucose (<10 years age, 118 ODM and 72 ONDM) or a 1.75g/kg OGTT with venous blood collection (>10 years age, 82 ODM and 82 ONDM). Overweight was diagnosed by IOTF (< = 18 years) or WHO criteria (> = 18 years). Glucose tolerance was classified by the ADA 2014 criteria (DM: fasting plasma glucose ≥ 126 mg% or 2 hour plasma glucose ≥ 200 mg%, IGT: 2 hour plasma glucose ≥140 mg% and < 200 mg%, IFG: fasting plasma glucose ≥100 mg% and <126 mg%). We compared ODM with ONDM by calculating age and gender specific SD scores (reference ONDM) for various measurements.

Results: Three (4%) ODM were already diabetic at the time of follow up (diagnosed at 16, 14 and 23 years of age, two on OHA and one on insulin treatment) and one more was diagnosed on testing. ODM had higher prevalence of pre-diabetes (37% vs. 22%, p = 0.031) and higher prevalence of overweight + obesity (24% vs. 15%, p = 0.041) compared to ONDM. SD scores showed that the ODM had higher BMI, sum of skinfolds and body fat percent, circulating glucose, fasting insulin, cholesterol, LDL cholesterol and triglyceride concentrations. They also had higher HOMA-IR and pulse rate but lower disposition index and diastolic blood pressure (Figure 1).

Conclusions: We confirm elevated risk of obesity, adiposity, diabetes and other cardio-metabolic risk factors in the young children of Indian diabetic mothers. This could represent genetic and/or fetal programming effects. Despite following the current standards of practice for management of GDM, the offspring continue to have high risk of diabetes. This suggests a need for reevaluation of current standards of care which overlook the peri-conceptional period.
PO1.04.05

Predictors of neonatal adiposity at birth in Gestational Diabetic and Normal Glucose Tolerant Mothers


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Introduction: Maternal hyperglycemia during pregnancy is known to be associated with fetal macrosomia and adiposity in adult life; however, there are only a few studies exploring effect on body composition at birth. We studied neonates of mothers with gestational diabetes (GDM) and normal glucose tolerance (NGT) for body composition measurements at birth and explored association between maternal parameters during pregnancy and neonatal adiposity at birth.

Methods: In a hospital based prospective study mothers were tested for GDM with a 75gm OGTT and IADPSG criteria (FPG ≥ 92mg%, 1hPG ≥ 180,2hPG ≥ 153). Paternal and maternal anthropometry and biochemical parameters (glucose, lipids) were studied. Neonatal size (anthropometry) and composition (DXA) were measured by trained staff. We compared maternal and neonatal birth size and body composition measurements in GDM and NGT mothers. Fat and Lean Mass Index were calculated as mass in kg divided by height in meter^3.

Results: We analyzed 121 GDM and 175 NGT mother-child pairs (53% boys in GDM, 45% in NGT). As compared to NGT mothers, GDM mothers were older (27.8 Vs 25.2 y) and heavier (pre-pregnancy weight 58.6 Vs 52.4 kg), weight gain during pregnancy was similar. GDM mothers had higher plasma glucose and triglycerides (fasting glucose 85.3 Vs 75.7 mg/dl, 120 min glucose 140.2 Vs 111.5 mg/dl, triglycerides 154.6 Vs 130.2 mg/dl, p < 0.05, all) but lower HDL and similar cholesterol as compared to NGT mothers. GDMs were treated as per current standards of practice. Fifty percent of mothers were delivered by caesarean section, 14% GDM and 10% NGT delivered preterm.

Neonates of GDM mothers were heavier (2.9 Vs 2.7 kg), taller (length 49 Vs 48 cm) and more adipose (subscapular 4.8 Vs 4.2 mm, fat mass 0.6 Vs 0.5 kg, fat % 19 Vs 16%, Fat mass index 4.8 Vs 4.1 kg/m^3 p < 0.05 All) compared to those of the NGT. When we plotted Fat Mass Index against Lean Mass Index, the relative fat mass deposition in relation to lean mass was exaggerated in GDM neonates than NGT (Figure 1). Girls were shorter, more adipose and had lower lean mass index. Using INTERGROWTH standards 24% of GDM and 40% of NGT neonates were SGA, and 3% of GDM but none of the NGT neonates were LGA. After adjustment for the difference in gestational age and gender, the difference between birth weight and fat % in GDM and NGT babies was ascribable to the effect of maternal age, weight, height and father’s weight.

Lipids and blood pressure were not associated. The difference between neonatal fat % between the groups was ascribable to maternal weight and plasma cholesterol and HDL concentrations.

Conclusion: We confirm the excess adiposity of babies born to GDM mothers, which show an exaggerated “thin-fat: phenotype. Unlike in the western population, 24% of babies of Indian GDM mothers were still SGA and only 3% were LGA. This necessitates a re-evaluation of the current standards of diagnosis and treatment of GDM in LMIC.

PO1.04.06

Sedentary behaviour and shorter duration of walking in early pregnancy is associated with gestational diabetes among obese women

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Background: Randomised controlled trials of lifestyle modification in obese pregnant women to reduce the incidence of gestational diabetes mellitus (GDM) have not shown consistent benefits, possibly because any interventions provided were not able to achieve desired increase in physical activity and reduction in gestational weight gain. There is a scarcity of data available about the actual physical activity and sedentary behaviour of women during pregnancy and their impact on maternal glycaemia.

Methods: A sub-study on physical activity (PA) was conducted within the longitudinal PRiDE study which recruited women at high risk of GDM. Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) and detailed medical history and anthropometric data collected. 2-hour glucose tolerance tests were conducted in the early 3rd trimester (mean gestation 26 + 6 weeks).

Results: PA data were available from 3494 women in the late 1st trimester (mean12 + 3 weeks), of whom 24.6%, 18.6% and
56.8% were in the normal body mass index (BMI), overweight and obese categories respectively. Women with a diagnosis of GDM were older, had a higher BMI, waist circumference and less likely to smoke than those without GDM (p < 0.05 for all). The following are the mean (±SD) of PA parameters per week in pregnant women in the 1st trimester: vigorous PA 61 (±288) minutes, moderate PA 177 (±546) minutes, walking 495 (±828) minutes, metabolic equivalent of task (MET) 2800 (±4833) minutes. They spent 341 (±205) minutes a day in sedentary behaviour. 86.3%, 70.5% and 24.1% of women reported doing no vigorous PA, moderate PA or walking per week. In obese women, every hour of increased sedentary time per day in early pregnancy was associated with a higher post-challenge glucose of 0.06mmol/l in the early 3rd trimester, after correcting for age, ethnicity, smoking, BMI, waist circumference, gestational weight gain, duration of walking and fasting glucose (standardised β-coefficient 0.08, p = 0.027). However in the same model, fasting glucose was only associated with maternal age, BMI and ethnicity. There was no association between glucose measures and any of the physical activity or sedentary time parameters in women with a BMI <30kg/m². Among obese women who walked below the median of 180 minutes a week, 16.3% had a diagnosis of later GDM compared to 12.2% who walked longer. This lower duration of walking in the 1st trimester was associated with a 1.56 higher risk of later GDM compared to 12.2% who walked longer. This model was adjusted for confounders (95% CI 1.07, 2.27, p = 0.021).

**Conclusion:** This large cohort study showed that around three quarters of pregnant women do not undertake PA in early pregnancy and spend over 5.5 hours per day in sedentary behaviour. In obese women the latter was independently associated with higher post-prandial glycaemia later on in pregnancy and shorter duration of walking was predictive of GDM. Future trials should aim to reduce time spent in sedentary behaviour and encourage longer duration of lower intensity PA (eg. walking) to reduce the incidence of GDM.

**PO1.04.07**

Can adverse effects on kidney in GDM newborn be prevented?

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**Background:** Gestational Diabetes (GDM) has reached epidemic proportions worldwide and dysregulation of glucose metabolism is found in up to 15% of pregnancies, according to the International Association of Diabetes in Pregnancy Study Group and the World Health Organization. Investigations with animal models have demonstrated that exposure to maternal hyperglycaemia during *in utero* development can detrimentally affect nephrogenesis which, in turn, would represent a risk factor for the onset of chronic renal disease and hypertension in adulthood. Studies on renal physiology in GDM neonates at the early stage of postnatal age are scarce and no reports concerning the correlation between nephron number-data and renal function in this group have been performed yet. We here examined the effect of GDM on kidney development and physiology at the postnatal age of 30–40 days in 170 newborns (sub-classified in no- and well-managed GDM) versus 65 matched healthys.

**Methods:** Biochemical parameters of glomerular and tubular function or impairment/injury (i.e albumin, b-2 microglobulin and the activity of N-acetyl-b-D-glucosaminidase, cathepsin B, glucuronidase and legumain) were evaluated in the urine of the two GDM groups and compared to results from the healthy control neonate population. Data were then associated with predominant susceptibility factors of renal damage related to low nephron number, such as birth weight, total renal volume and renal cortex volume. Renal volumes were estimated using 3D-ultrasounds (VOCAL II, GE Ultrasounds, USA).

**Results:** Compared to control, the well-managed GDM group did not show significant differences in all biochemical and anatomical parameters tested whereas the no-managed GDM neonates exhibited significant higher levels of cathepsin B and N-acetyl-b-D-glucosaminidase activity as well as significantly reduced values of total renal volume and cortical volume.

**Conclusions:** Our data indicate that, at the early stage of postnatal age, GDM correlates with impairment of both kidney’s development and function. Conversely, an appropriate management of this disease may counteract these effects. Data also indicate that, at this postnatal age, GDM affects renal tubule and cathepsin B and N-acetyl-b-glucosaminidase may be suggested as early indicators of such condition. Our findings support the efficacy of global actions about GDM.

**PO1.04.08**

Gestational diabetes-associated foeto-placental endothelial dysfunction is still present in mothers treated with insulin therapy

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Background: Gestational diabetes mellitus (GDM) occurs with maternal hyperglycaemia and foeto-placental endothelial dysfunction. Women with GDM subjected to diet (GDMd) present with normal glycaemia at term; nevertheless, foeto-placental endothelial dysfunction is still present. Some of the women with GDMd fail to control glycaemia and are subjected to insulin therapy (GDMI).

Aim: To assess whether maternal insulin therapy reverses foeto-placental endothelial dysfunction in GDMI.

Methods: Primary cultures of human umbilical vein endothelial cells (HUVECs) were isolated from normal, GDMd, or GDMI pregnancies to assay L-arginine transport kinetics, endothelial nitric oxide synthase (eNOS) and cationic amino acids transporter isoform 1 (hCAT-1) expression and activity, endothelial nitric oxide synthase (eNOS) and cationic amino acids transporter isoform 1 (hCAT-1) expression and activity, p44/42 mapk and protein kinase B/Akt activation, and insulin receptor isoforms A (IR-A) and B (IR-B) mRNA expression. Experiments were performed in the presence or absence of insulin (1 nmol/L, 8 h). Vascular reactivity assays were in umbilical vein rings challenged with insulin (0.1-1000 nmol/L) and calcitonin gene-related peptide (CGRP, 0.1-1000 nmol/L).

Results: In the absence of insulin a higher maximal transport capacity (Vmax/Km) for L-arginine, NOS-generated L-citruline, and NO level was found in cells from GDMd and GDMI compared with normal pregnancies. Insulin reversed the GDM effects in both groups. Similar results were found for protein abundance and mRNA expression for eNOS, hCAT-1, p44/42 mapk, IR-A mRNA, but not Akt activator phosphorylation or IR-B mRNA expression. Insulin and CGRP caused concentration-dependent relaxation in umbilical vein rings from normal pregnancies, an effect that is impaired in GDMd and GDMI.

Conclusion: Insulin therapy is not enough to restore GDM-associated human foeto-placental endothelial dysfunction.

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PO1.04.09
Gestational diabetes and body composition of newborns

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Background and objective: The clinical and public health relevance of gestational diabetes mellitus-GDM is widely debated due to its increasing incidence. Obesity, a pandemic in developing and developed countries contributes to the higher risk of GDM. Fetal exposure to this altered metabolic intrauterine environment probably leads to increases in fetal adiposity, affecting growth pattern and development later in life. The objective of this study was to investigate the relationship between GDM and fat mass percentage-FM% of the newborns.

Methods: A cross-sectional study involving 72 mothers, previously diagnosed with GDM and 139 apparently healthy mothers and respective newborns was conducted in a large maternity in Sao Paulo, Brazil. Exclusion criteria were adolescence, multiple pregnancies, hypertension, hormonal disorders, infectious diseases, drug and/or alcohol consumption, preterm (<37 weeks) and post-term (≥42 weeks) delivery, low birth-weight (<2500g), apgar score < 3, and genetic disorders of the newborn. Maternal height was measured by a stadiometer (Tonelli 120A®), Brazil), and weight and body composition by a bioelectrical impedance analyzer (InBody 370®, Biospace Co., Korea). Newborn weight and body composition were assessed by air-displacement plethysmography (PEA POD, Cosmed, USA). Associations between the outcome (newborn FM%) and the independent variables investigated (GDM, maternal age, ethnicity, socioeconomic score, parity, pre-pregnancy BMI, gestational weight gain and sex) were assessed by multiple linear regression analysis, considering p ≤ 0.05.

Results: There were statistically significant associations between gestational weight gain (p = 0.002), pre-pregnancy BMI (p = 0.001) and sex (p = 0.001) with FM% of the newborn.

Conclusion: Those findings did not show an association between GDM and FM%, probably in view of the maternal control of the GDM, but endorsed the interplay between pre-pregnancy BMI and weight gain in pregnancy. As expected, there was an association between female sex and FM%.

PO1.04.10
Increased risk of overweight during school age in children born to mothers with GDM

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Background and aims: Globally, gestational diabetes mellitus (GDM) affects approximately one out of seven pregnancies amounting to approximately 8 million live births yearly. Children of GDM mothers (GDM-F1) are at increased risk of becoming overweight and developing metabolic disease in later life. We conducted a narrative review of the literature aiming to understand the growth characteristics of children born from GDM pregnancies with focus on growth after the adiposity rebound period to provide insights relevant across childhood.

Methods: Medline was searched for articles published from 1995 to Feb 2016 with selected search terms related to growth of GDM offspring. We identified 877 articles of which 12 studies were included for review using a priori chosen inclusion and exclusion criteria for eligibility based on longitudinal assessment of growth as well as data reporting in children older than 7 years of age.
Results: Three studies were conducted among GDM-F1 only, 4 studies compared GDM-F1 with non-GDM offspring and the remaining papers (n = 5) compared GDM-F1 with other reference populations which included healthy, T1DM or T2DM pregnancy offspring (Table 1). Studies among GDM-F1 only (n = 3) showed an increase in BMI z-score at 7 years of age compared to reference data. When compared between GDM and non-GDM offspring, 2 out of 5 the studies reported an increase in weight, height and BMI at 7 years of age among GDM-F1, while the rest reported no significant differences. Compared to other reference populations, only GDM-F1 boys were reported to have larger waist circumference at 7 and 9.5 years of age and BMI was increased in GDM-F1 at 18 years. Increased BMI and waist circumference are considered as a proxy of increased risk of overweight/obesity.

Conclusions: Although information on childhood growth characteristics appeared to be limited, GDM-F1 appears to have an increased risk of overweight, with higher BMI and larger waist circumferences at 7 years of age, which could persist into adulthood.

Table 1. Timing of anthropometrics and body composition deviation of off-spring of GDM.

<table>
<thead>
<tr>
<th>Time points</th>
<th>Weight gain</th>
<th>Adiposity</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 years</td>
<td>1.2</td>
<td>NA</td>
<td>1.4</td>
</tr>
<tr>
<td>6-8 years</td>
<td>1.5</td>
<td>NA</td>
<td>1.7</td>
</tr>
<tr>
<td>8-10 years</td>
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<td>NA</td>
<td>1.8</td>
</tr>
<tr>
<td>9-11 years</td>
<td>NA</td>
<td>Skinfold &amp; Waist Circumference (boys)</td>
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</tr>
<tr>
<td>9-13 years</td>
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<td>NA</td>
<td>2.0</td>
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<tr>
<td>18 years</td>
<td>Growth Velocity</td>
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<td>2.1</td>
</tr>
</tbody>
</table>

PO1.04.11

Exposure to metals during pregnancy and the association with gestational diabetes mellitus: Results from EDEN mother child cohort

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Background: Metals remains a public health concern for longtime because they persist in the environment and may be able to induce toxicity even at low level of exposure. Epidemiological studies has shown the association between heavy metals and gestational diabetes mellitus (GDM), however they are not enough to draw reliable conclusions. The objective of the present study was to evaluate the association between maternal exposure to metals during pregnancy and GDM in mothers from the French EDEN (Étude des Détérminants pré et post nataux du développement de la santé de l’Enfant) mother-child cohort study.

Methods: 2,002 women without pre-existing diabetes were initially included. The GDM was assessed by a gynecologist during consultations after blood analysis. Selenium (Se), lead (Pb), cadmium (Cd) and manganese (Mn) were measured in second-trimester plasma samples. Associations between metals and GDM were examined using multiple logistic regression analysis. Models were adjusted for potential confounders.

Results: 623 had GDM diagnosis available and bio-monitoring data measured. 7.06% had a GDM diagnosis. Mean (median) levels were 100.12 ± 26.18 μg/L (98.4 μg/L) for Se, 18.72 ± 10.44 μg/L (17 μg/L) for Pb, 0.91 ± 0.62 μg/L (0.8 μg/L) for Cd and 10.56 ± 4.76 μg/L (10 μg/L) for Mn. Pb and Cd were significantly (P-value < 0.08) related to GDM: OR (odds-ratio) = 1.99 (95% Confidence Interval: 0.91-3.99) and OR 1.92 (95% CI 1.03-3.60) respectively after adjusting for confounding factors. No statistical significant associations were observed between GDM and Se or Mn.

Conclusions: Our findings add to the growing evidence supporting the role of maternal exposure to heavy toxic metals as a risk factor for GDM through their involvement in the disruption the glucose uptake and the alteration of the related molecular mechanism in glucose regulation.

PO1.04.12

ANGPTL4 expression is altered in human umbilical vein endothelial cells in patients with gestational diabetes mellitus.


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Background: Angiopoietin-like protein 4 (ANGPTL4) is multifunctional signal protein expressed in many tissues. ANGPTL4 is involved in regulation of multiple physiological processes, including plasma glucose level and tolerance regulation, angiogenesis, fat storage, lipid metabolism, food intake regulation, vascular permeability in experimental models of acute myocardial infarction. It was demonstrated on rat models that induction of ANGPTL4 during pregnancy and lactation could be related to metabolic adaptations. It is known that type 2 diabetes patients have significantly lower plasma ANGPTL4 levels than healthy subjects, which indicate a role for ANGPTL4 in diabetes. To date there is no data on the role of
ANGPTL4 in gestational diabetes mellitus (GDM), and the data on the role of ANGPTL4 in endothelium function are limited. Here, we sought to investigate if ANGPTL4 expression in human umbilical vein endothelial cells (HUVECs) could be associated with GDM.

**Materials and methods:** HUVECs were collected from 10 healthy women (Control), 22 women treated for GDM starting before 30-th week of gestation (GDM1) and 6 women treated for GDM after 34-th week of gestation (GDM2). The diagnosis of GDM was based on International Association of Diabetes and Pregnancy Study Groups criteria. Age and pregestational body mass index did not differ between groups. HUVECs were isolated end expanded in vitro up to passage 2 and tested for viability and replicative senescence. Samples with viability >85% and low level of senescent cells (<10%) were used. Immunophenotype was determined by Flow Cytometry analysis. The level of genes expression was determined by RT-PCR. Statistical significance was assessed by Mann Whitney test using the Graph Pad software (San Diego, CA, USA), results were considered significant for a p-value < 0.05.

**Results:** HUVECs demonstrated characteristic endothelial morphology and immunophenotype CD45-/CD144+ /CD31+/CD146+/CD105+ in all groups. Furthermore, samples derived from all groups did not differ in the level of expression of endothelial markers VEGF (5.1 ± 1.4 vs 3.0 ±0.2 vs 2.5 ±0.15 / control vs GDM1 vs GDM2) and HIF1a (5.9 ± 1.2 vs 3.4 ± 0.5 vs 2.2 ± 0.3 / control vs GDM1 vs GDM2). However, the ANGPTL4 expression differed significantly between control and GDM groups: 42.4 ± 11.6 vs 4.0 ± 1.0 (control vs GDM1; p < 0.03), and 42.4 ± 11.6 vs 6.9 ± 1.4 (control vs GDM2; p < 0.01) while no substantial difference between GDM1 and GDM2 groups was observed.

**Conclusion:** ANGPTL4 expression in HUVECs from GDM patients was found out to be lower compared to controls. That may explain a potential mechanism of the intrauterine hyperglycemia influence on the development of predisposition to metabolic and cardiovascular diseases in offspring. Further investigations are required to prove a causal relationship and to determine whether it is systemic or tissue-specific alteration in GDM. The work was funded by Russian Science Foundation (project n.15-14-30012)

**PO1.04.13**

**Equilibrative nucleoside transporter 1 expression in human umbilical vein endothelial cells from gestational diabetes mellitus is restored by insulin therapy**


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**Background:** Human umbilical vein endothelial cells (HUVECs) from diet treated mothers with gestational diabetes mellitus (GDMd) exhibit reduced C/EBP homologous protein 10 (hCHOP)-dependent human equilibrative nucleoside transporter 1 (hENT1) expression triggered by nitric oxide (NO). In mothers who do not meet an optimal glycaemic control, insulin therapy (GDMi) is required to achieve this goal. Exogenous insulin normalizes GDMd-reduced hENT1 expression in HUVECs. However, whether insulin therapy restores GDMd-reduced hENT1 expression via hCHOP in HUVECs is unknown. We hypothesize that insulin restores hENT1 expression in HUVECs from GDMi or GDMd involving hCHOP.

**Objective:** To determine the insulin effect on hENT1 and hCHOP expression in HUVECs from GDMd and GDMi.

**Methods:** HUVECs were isolated from GDMi or GDMd pregnancies from the Hospital Clínico UC-CHRISTUS and Hospital San Juan de Dios (Santiago de Chile). hENT1 and hCHOP expression was evaluated by Western blot in the absence or presence of insulin (1 nmol/L, 8 h) and Nω-nitro-l-arginine methyl ester (L-NAME, 100 μmol/L, 8 h).

**Results:** HUVECs from GDMi exhibit a normal hENT1 protein abundance, whereas it was reduced (34 ± 6%) in cells from GDMd compared with cells from normal pregnancies. Incubation with exogenous insulin did not modify hENT1 expression in cells from normal, GDMi, or GDMd pregnancies. NO synthase inhibition by L-NAME restored hENT1 protein abundance in cells from GDMd and incubation of cells with insulin + L-NAME resulted in reduced hENT1 protein abundance in cells from GDMd (40 ± 11%), hCHOP protein abundance was similar in cells from normal, GDMi, or GDMd pregnancies and remained unchanged in all groups after incubation with exogenous insulin and L-NAME. However, cells exposed to insulin + L-NAME show reduced hCHOP protein abundance in GDMi (53 ± 10%) and GDMd (35 ± 12%). hENT1 mRNA in HUVECs was decreased in GDMi (94 ± 3%) and GDMd (93 ± 3%). On the other hand, hCHOP mRNA was highly increased (60 ± 27 fold) in GDMd HUVECs.

**Conclusion:** Maternal insulin therapy results in a normalization of hENT1 protein expression, despite the maintenance of mRNA level alterations, likely via a hCHOP-independent mechanism in human umbilical vein endothelium.

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**PO1.04.14**

**The bangalore nutrition gestational diabetes lifestyle study**

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**Background:** Indian women are at a higher risk for developing Gestational Diabetes (GDM) than their western counterparts. GDM puts both mothers and babies at increased risk of future diabetes, setting up a vicious cycle. Diet and lifestyle are important modifiable risk factors for GDM but, have been little studied in India. Most studies have focussed on single nutrients rather than overall dietary patterns. BANGLES began in June 2016 aiming to study diet, lifestyle and blood micronutrient levels in early pregnancy as predictors of GDM risk in urban Bangalore.

**Methods:** We have planned to recruit 1000 women (based on a mean GDM prevalence of 20 percent) from antenatal clinics of 2 hospitals serving lower, middle and upper income groups in Bangalore (Bangalore Baptist Hospital and Cloudnine Hospitals). In early pregnancy (<16 weeks gestation) data are collected in the domains of: Diet (quantified 230 item Food Frequency Questionnaire, a 24-hour recall and a culture, attitudes and beliefs questionnaire), Physical activity level (short International Physical Activity Questionnaire [IPAQ]), General health, Socio Economic Status (Standard of Living Index) and blood sample to assess vitamin D, B12 and folate levels. GDM incidence is assessed using a 75-gram Oral Glucose Tolerance Test, applying WHO 2013 criteria, carried out at 24 - 28 weeks’ gestation. Newborn Anthropometry and delivery complications will be recorded. We will examine associations of GDM with frequency of intake of individual food groups, existing ‘healthy eating’ indices, and (dietary patterns) principal components derived from the FFQ.

**Results:** 505 women have been recruited so far and GDM incidence is 18% among the 300 women who have completed the OGTT. Difficulty with identifying and recruiting early pregnancy patients was dealt with by engaging with HIV counselling centres, clinic nurses, trainee doctors and obstetricians to identify expected delivery date lists, and with scan room staff for fetal scan appointment lists. To help the obstetricians to track and refer participants, we stuck enrolment stickers on antenatal cards after recruitment. To engage participants, we provided snacks, drinks, water bottles, gifts, blood tests, nutrition counselling, pamphlets and recipe ideas. The development of a manual in regional languages has been useful for collecting consistent data. Inviting posters, highlighting the importance of nutrition, were also useful.

**Conclusions:** New experiences and challenges faced during data collection could be useful check points for future studies. The data collection is ongoing and recruitment will continue for 7 months, to target 1000 pregnant women. The knowledge from this project will be useful to understand the dietary and lifestyle factors and their related risk to GDM in India. This will be valuable to develop culture-appropriate nutrition awareness and education programs and intervention studies, in reproductive-aged women, who are exceptionally motivated to healthful behaviours that might extend beyond pregnancy.

**PO1.04.15**

Dysregulated hypothalamic-pituitary-adrenal axis (HPA) activity is linked to glucose intolerance in pregnancy in South Asians (SA)

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**Background:** SA have a higher risk of gestational diabetes (GDM), type-2 diabetes and metabolic syndrome than White Caucasians (WC). Dysregulated HPA activity is a plausible candidate mechanism. We hypothesised that HPA axis activity would be increased in SA in pregnancy compared to WC and would associate with hyperglycaemia in pregnancy. We aimed to study whether there were ethnic differences in HPA activity in early pregnancy women in a high-risk pregnancy cohort and test associations with glucose tolerance in later pregnancy.

**Methods:** SA and WC women (n=52 per group) were recruited from the PRiDE study <16 weeks gestation. Saliva was collected at waking, 30 min after, 4pm and bedtime before 16 weeks of pregnancy along with 24 hour urine. Salivary cortisol and cortisone was analysed using mass spectrometry and urinary glucocorticoid (UGC) analysis using gas chromatography. Analyses were adjusted for BMI, age, smoking and gestation.

**Results:** In adjusted analyses, SA had higher cortisone awakening response (β = 0.40, p = 0.034) than WC. Despite significantly lower BMI, total UGC excretion in SA was similar to WC. Total UGC excretion was independently related to increased BMI only in WC (β = 0.02) but to waist circumference (p = 0.005) and skin fold thickness (p = 0.038) in SA. UGC metabolites indicated increased 11bHSD2 activity (β = 0.069, p = 0.045) and lower 5a-reductase activity (5AR) (β = -0.154, p = 0.013) in SA. Both waking (β = 1.469, p = 0.019) and peak cortisone (30 min) (β = 0.591, p = 0.035) at 12 weeks independently predicted fasting plasma glucose at 24-28 weeks gestation.

**Conclusion:** Early pregnancy salivary cortisone is an independent marker of glycaemia in pregnancy. SA have higher awakening cortisone responses than WC with increased activation of 11βHSD and reduced 5AR. Altered diurnal variation and clearance of cortisol could explain higher risk of GDM in SA. Adiposity, not BMI is related to cortisol metabolism in SA.

**PO1.04.16**

Neonatal outcomes among offspring of obese women diagnosed with gestational diabetes mellitus in early versus late pregnancy

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**Background:** Obesity during pregnancy is associated with adverse pregnancy outcomes. The aim of this study was to assess the relationship between maternal obesity diagnosed in early versus late pregnancy and antenatal and neonatal outcomes.
Introduction: Gestational diabetes mellitus (GDM) diagnosed early in pregnancy (early GDM) may be regarded as a marker of an increased metabolic burden possibly affecting the fetus for a longer period compared with GDM diagnosed later in pregnancy (late GDM). The aim of this study was to characterize obese women according to timing of GDM diagnosis, and to assess the impact of the timing of GDM diagnosis in relation to neonatal outcomes.

Material and methods: Women over 18 years of age with a pre-pregnancy body mass index (BMI) ≥ 30 kg/m² were grouped according to the results of a 75g two-hour oral glucose tolerance test (OGTT) performed at 13.1 weeks of gestation and repeated at 23.4 weeks if normal at first testing. Primary outcomes were offspring birthweight and large for gestational age (LGA). Secondary outcomes were Apgar scores, birth injuries, neonatal hypoglycemia, and need for intensive neonatal care.

Results: Out of a total of 361 high-risk women, 164 (45.4%) were diagnosed with GDM. Of these, 133 (81.1%) were diagnosed with early GDM and 31 (18.9%) with late GDM. We detected no differences in offspring birthweight or risk for LGA between early and late GDM. Instead, risk for LGA was positively associated with gestational weight gain (GWG) (p < 0.01).

Conclusions: No significant differences in neonatal outcomes were observed between early and late GDM. The fetal exposure associated with early GDM might be counteracted by early treatment of hyperglycemia and confounded by maternal adiposity and gestational weight gain.

Offspring birthweight and standardized birthweight according to timing of GDM diagnosis.

PO1.04.17
Intrauterine hyperglycemia induced the inflammatory signalling in the cardiac muscle of the infants of diabetic mother rats

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Background: Studies have demonstrated that intrauterine foetal exposure to hyperglycaemia during pregnancy was associated with cardiovascular complications, such as cardiomyocyte hypertrophy, in infants of diabetic mothers (IDMs). We recently developed an animal model of hyperglycaemia during pregnancy to investigate the molecular mechanisms underlying cardiac abnormalities observed in IDMs. Furthermore, we explored the diet that should be consumed to improve the abnormalities by a molecular nutritional study and investigated the potential molecular pathway for this effect in the animal model. Assessment of newborn rat hearts revealed that impaired insulin signalling-induced insulin resistance by inhibiting the Akt/ mTOR pathway, which was improved in the offspring of rats that were fed a fish oil-rich diet. Nevertheless, specific ingredients of fish oil that are responsible for improving impaired insulin signalling remain unclear. Fish oil is present in many types of seafood, particularly fatty fish, and contains high docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) levels, both of which are omega-3 polyunsaturated fatty acids. Consuming fish oil lowers plasma triglyceride levels, resting heart rate and blood pressure and reduces inflammation and improves vascular function. Consuming EPA is also associated with improvements in patients with cardiovascular diseases. Herein, we investigated whether the EPA found in fish oil can be used to attenuate diabetes associated impairments in cardiomyocyte signalling.

Method: Pregnant diabetic rats were administered streptozotocin before receiving EPA or water, and their infants were designated IDM/EPA, IDM/W. We assessed the potential molecular pathway for this effect in the primary cardiac cell from newborn rat hearts by reactive oxygen species (ROS) detection, western blotting, real-time PCR.

Results: Insulin resistance as determined by diminished Glut4 translocation following insulin stimulation, the levels of Advanced Glycation End products (AGEs) and ROS were elevated in the neonatal hearts of IDM/W compared with that seen in the offspring born from non-diabetic control animals. Similarly, the receptor of AGEs mRNA levels, ROS and the amount of nuclear factor-κB, tumor necrosis factor-α, and interleukin 6 mRNA were higher in the hearts from the IDM/W group when compared to that observed in the hearts of offspring born to non-diabetic animals. These deleterious effects of gestational diabetes were significantly

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EPA supplementation during pregnancy improved the impaired signalling via intrauterine hyperglycemia in the heart of IDM.

**POI.05 – Respiratory and atopic disease**

**POI.05.01**

Genetic ancestry modifies risk of asthma following early-life chest illness


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**Rationale:** Epidemiological studies have made clear the strong relationship between asthma development and early-life viral respiratory illnesses, including infection with respiratory syncytial virus (RSV). Genetic predisposition and environmental exposures may affect viral infection-driven asthma outcomes. These observations suggest a complex interaction between host genetics, viral species, and environmental exposures in determining asthma risk. The proportion of African genetic ancestry varies between African Americans, Mexicans, and Puerto Ricans and is known to increase asthma susceptibility. We therefore examined whether African genetic ancestry modifies the association between chest illness and asthma.

**Methods:** We used logistic regression to examine the association between reported chest illness in the first two years of life and physician-diagnosed asthma onset after 2 years of age among participants from the GALA II (Genes-Environments and Admixture in Latino Americans) and SAGE (Study of African Americans, Asthma, Genes, & Environments) studies. Covariates included sex, birth weight, maternal smoking during pregnancy, breastfeeding status, presence of older siblings, and indicators of socioeconomic status (maternal education, family income, and insurance status). Analyses were stratified by race/ethnicity and secondary analyses were also stratified by high versus low African genetic ancestry (median split). African genetic ancestry was determined using the program ADMIXTURE based on genome-wide genotyping data (Axiom LAT1 array).

**Results:** Our sample of 2,602 participants was 26% African American, 30% Mexican, 32% Puerto Rican, and 13% other Latino. Mean age was 13.3 years (SD 3.3) and 52% were female. The proportion of children with asthma who reported bronchiolitis/RSV was 4- to 9-fold higher among Puerto Ricans (10.5%) than African Americans (2.6%) and Mexicans (1.2%). The odds for asthma were greatly increased for a variety of chest illnesses and were consistently highest among Puerto Ricans compared with Mexicans and African Americans (Figure). The difference in risk estimates by race/ethnicity was greatest among children who reported bronchiolitis or RSV-related illness. When stratified by genetic ancestry, asthma odds were higher among Puerto Ricans with high African ancestry (OR = 9.8, 95% CI: 3.4-35.6) compared with Puerto Ricans with low African ancestry (OR = 4.8, 95% CI: 1.7-14.8). African ancestry for African Americans and Mexicans did not appear to modify risk estimates, suggesting that GxE interactions may be population-specific.

**Conclusions:** Puerto Ricans are disproportionately affected by early-life respiratory illnesses. The association between early-life respiratory illnesses and asthma risk appears to be modified by African genetic ancestry in Puerto Rican children. The endemicity of RSV infection in Puerto Rico warrants further investigation.
Asthma odds following a variety of respiratory infections during the first two years of life are highest for Puerto Ricans.

**PO1.05.02**

*Preterm and early term births are associated with higher risk of asthma (asthma medication entitlement): The Finnish 1987-90 Birth Cohort*


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**Background:** Preterm birth is associated with a higher asthma risk in adults. Whether this risk extends to the large group of infants born late preterm: 34 < 37 weeks (wks) or early-term: 37 < 39 wks, is unclear.

**Objective:** We examined the risk of asthma (based on Medical reimbursement) within gestational age (GA) groups: <28wks, 28 < 32wks, 32 < 34wks, 34 < 37wks, 37 < 39wks, (ref) 39 < 42wks, ≥42wks.

**Methods:** Data on all births in Finland (1/1/1987-30/9/1990), from the Finnish Medical Birth Registry (n = 235624, GA: 98.7%) were linked with the Medical Reimbursement Register (Birth-31/12/2013). In Finland, the entitlement for special medication reimbursement is granted, based on physician’s statement following the criteria: need for continuous treatment (>6 months); reversible airflow obstruction (spirometry). Association between GA and asthma were examined using binary logistic regression (adjs. highest parental education, maternal smoking during pregnancy, parity, birth-weight-z-score (BWSD), maternal (biological/adoptive) asthma (ICD8, ICD9 and ICD10).

**Results:** Preterm birth accounted for 5.2% of the cohort and 6.1% received asthma medication reimbursement (Table 1). Linear dose-dependent relationship between preterm birth (GA < 37wks) and asthma was identified: shorter gestation indicated higher asthma risk. Early term born (37 < 39wks) had higher asthma risk. Male sex, lower parental education, asthma history of biological mother as well as biological fathers asthma history, young maternal age, nulliparity and lower BWSD, predicted asthma. The relationship between preterm and early-term birth, and asthma, remained unchanged, despite adjusting for the covariates.

**Conclusions:** Preterm birth and early-term birth are associated with asthma, as indicated by the receipt of asthma medical reimbursement. Asthma histories of biological parents are strong predictors of asthma in this population study. Our results underscore the importance of careful respiratory follow-up of children and adolescents born preterm and early term.

**Table 1.**

<table>
<thead>
<tr>
<th>GA</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28wks</td>
<td>1.13 (1.05-1.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>28-31wks</td>
<td>1.15 (1.07-1.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>32-34wks</td>
<td>1.20 (1.12-1.29)</td>
<td>0.001</td>
</tr>
<tr>
<td>34-37wks</td>
<td>1.31 (1.23-1.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>37-39wks</td>
<td>1.25 (1.17-1.33)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥42wks</td>
<td>Reference</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**PO1.05.03**

*Associations of birth weight and prematurity with late adolescent lung function in Hong Kong’s ‘Children of 1997’ Birth Cohort*

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**Background:** Fetal growth may be associated with lung function in later life via intruterine lung development. Observationally lower birth weight and prematurity are associated with poorer lung function, but this relation may be confounded by social-economic position. Here we assessed the relation of birthweight and gestational age with lung function at ~ 17 years in a developed setting with the little social patterning of prematurity or birth weight.

**Methods:** The adjusted associations of sex- and gestational age-specific birth weight z-score, gestational age, preterm birth (<37 weeks) and small size for gestational age (birth weight <10% gestational age- and sex-specific percentile) with Global Lung Initiative reference age-, sex- and height-specific z-score for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and forced expiratory flow at 25-75% of the pulmonary volume (FEF25%-75%) was assessed in 3,033 - 17
years old from a population-representative Chinese birth cohort in Hong Kong “Children of 1997”.

**Results:** Higher birth weight z-score was associated with higher FEV$_1$ z-score (0.07, 95% confidence interval (CI) 0.03 to 0.11), FVC z-score (0.07, 95% CI 0.03 to 0.11), and FEF$_{25\%-75\%}$ z-score (0.06, 95% CI 0.01 to 0.11) adjusted for social-economic position, birth order, parent’s birth place, maternal age, maternal smoking and prenatal exposure to second-hand smoking. Similarly adjusted, being small for gestational age was associated with lower FEV$_1$ z-score (-0.24, 95% CI -0.38 to -0.11), and FVC z-score (-0.18, 95% CI -0.32 to -0.04) but not FEF$_{25\%-75\%}$ z-score (-0.24, 95% CI -0.40 to 0.08). Gestational age was not associated with FEV$_1$ z-score (0.01, 95% CI -0.02 to 0.03), FVC z-score (-0.001, 95% CI -0.03 to 0.02) or FEF$_{25\%-75\%}$ z-score (0.02, -0.004 to 0.05). Preterm birth was also unrelated to FEV$_1$ z-score (-0.07, 95% CI -0.26 to 0.11), FVC z-score (0.07, 95% CI -0.11 to 0.26) and FEF$_{25\%-75\%}$ z-score (0.06, 95% CI 0.01 to 0.11).

**Conclusions:** Our findings suggest that lower birth weight and being small for gestational age are associated with poorer lung function in late adolescence, but gestational age is not. Identification of factors driving this association between birth weight and lung function might prevent adult disease.

**PO1.05.04**

**Associations of agricultural pesticide exposure with asthma prevalence in adolescence: the PIAMA birth cohort.**

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**Background:** Asthma is the most common chronic disease among children. Children living close to agricultural fields have been found in some studies to be at an increased risk for developing asthma as well as other respiratory symptoms possibly due to increased pesticide concentrations in their homes as a result of the transfer of pesticides from treated fields to the homes.

**Objectives:** The aim of this study was to investigate the associations of residential proximity to agricultural fields as well as estimated amounts of pesticides applied in selected buffers around the home with the prevalence of asthma and related respiratory symptoms at the ages of 14 and 17 years within a Dutch birth cohort study.

**Methods:** We included participants of the PIAMA birth cohort study with data on residential proximity to agricultural fields at the time of the 14-year follow-up and information on asthma, shortness of breath, and/or dry night cough in the past 12 months at the ages of 14 (N = 2,290) and 17 years (N = 1,696) from parent completed questionnaires. We focused on the 100 m buffer to investigate associations with exposure at short distances and the 500 and 1,000 m buffers to investigate associations with exposure at longer distances. For the presence of specific crops within 500 and 1,000 m of the homes, we selected crops that were likely treated with pesticides and that were present for at least 10% of the study participants in the respective buffers in order to have sufficient numbers of exposed children. In addition, we used estimated amounts of specific pesticides with known irritant properties for the respiratory system applied within distances of 500 and 1,000 m for at least 10% of the population under study. The associations were presented as odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for potential confounders.

**Results:** For participants living within 100, 500 and 1,000 m of fields with crops likely treated with pesticides, we did not find a higher risk of asthma, shortness of breath or dry night cough at ages 14 and 17 years. For instance, for participants living within 100 m of fields with any crops likely treated with pesticides the adjusted odds ratios for prevalent asthma at age 14 and 17 years were 0.43 (95% CI 0.15-1.21) and 1.04 (95% CI 0.42-2.59), respectively. Likewise, there was no higher risk of asthma at age 14 and 17 years in participants living within 100 m of agricultural fields treated with any pesticides with known irritant properties for the respiratory system [odds ratios 0.52 (95% CI 0.18-1.47) and 0.77 (95% CI 0.26-2.26), respectively]. There was no association between estimated amounts of specific pesticides (chlormequat, chlorothalonil, diquat, dichloridobromide, florasulam, iodosulfuron-methyl-sodium, mancozeb, mecoprop-p, mesosulfuron-methyl, metsulfuron-methyl, nicosulfuron, prosulfocarb, terbuthylazine, triadimefon and sulphur) within 500 and 1,000 m of the homes and the health outcomes studied.

**Conclusions:** There was no association between living near agricultural fields likely treated with pesticides and asthma, shortness of breath and dry night cough among our study participants.

**PO1.05.05**

**Prenatal exposure to airborne pollutants and the respiratory health through childhood - lessons from Krakow birth cohort.**

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**Background:** Cohort studies are extremely important in assessing the relations between early factors affecting child’s health, and to investigate its casual role in terms of life course approach. The aim was to summarize previous results on the impact of exposure to high levels of airborne pollutants (fine particulate matter -PM2.5 and polycyclic aromatic
Background: Infants with atopic eczema have an increased risk of impaired growth; this a clinical concern that has led to incorporation of growth monitoring into clinical care. Proposed origins for this growth impairment include effects of the inflammatory process, corticosteroid treatment, poor nutrition as a result of an inappropriately restrictive diet, and eczema-associated sleep disturbance. To date, little attention has been paid to the possibility of pre-morbid changes in growth trajectory in infants with atopic eczema.

The aim of the current study was to examine whether the increased risk of impaired postnatal growth in infants with atopic eczema reflects a premorbid alteration in growth trajectory, rather than being secondary to the postnatal inflammatory process or its treatment.

Methods: Within a prospective mother-offspring study: the UK Southampton Women’s Survey, 1759 mother and term-born-offspring dyads had longitudinal fetal and infant anthropometric measurements, along with known menstrual data and assessments of atopic eczema at ages 6 and/or 12 months. Fetal and infant linear, head and abdominal size and growth velocity standard deviation scores were derived from anthropometric measurements at 11, 19, and 34 weeks’ gestation, birth and ages 6 and 12 months. Atopic eczema at ages 6 and 12 months was ascertained using modified UK Working Party diagnostic criteria for the definition of atopic eczema utilising questionnaire and examination data.

Results: The prevalence of atopic eczema was 9.5% at age 6 months and 10.0% at 12 months. Shorter femur length, smaller abdominal circumference and higher head to abdominal circumference ratio at 34 weeks’ gestation were associated with increased risks of eczema at age 6 months (eczema odds ratio per standard deviation (OR /SD) increase 0.81 (95%CI 0.69-0.96), p = 0.017; 0.78 (0.65-0.93), p = 0.006; 1.37, (1.15-1.63), p = 0.001, respectively). Lower velocities of linear growth from 11 weeks’ gestation to birth, and birth to age 6 months were associated with eczema age 6 months (eczema OR /SD increase 0.80, 95% CI 0.65-0.98, p = 0.034; 0.81, 95%CI 0.66-1.00, p = 0.051, respectively) (Figure). Infants with atopic eczema age 12 months had a larger head circumference in early gestation and faltering of abdominal growth velocity from 19-34 weeks’ gestation (eczema OR /SD increase 0.67 (0.51-0.88), p = 0.003).

Conclusions and Relevance: Infants with atopic eczema demonstrate altered patterns of fetal growth, including faltering of linear growth in utero, prior to the clinical onset of eczema. The findings suggest that growth falters prior to the start of the inflammatory process and its treatment, and provide additional support for important prenatal influences on this common skin condition.
Linear growth velocities in relation to atopic eczema at ages 6 months.

PO1.05.07

The role of maternal bulimia nervosa and anorexia nervosa before and during pregnancy in early childhood wheezing

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Background: Mental disorders during pregnancy, namely depression and anxiety, have been associated with childhood wheezing and asthma. To our knowledge, no previous studies have evaluated maternal eating disorders in association with infant respiratory outcomes. We aimed at evaluating whether maternal bulimia nervosa and anorexia nervosa before and during pregnancy are associated with the risk of infant wheezing, as well as the associations of bulimia nervosa and anorexia nervosa with several well-known wheezing determinants.

Methods: The study included 4984 singletons from the NINFEA birth cohort. Maternal bulimia nervosa and anorexia nervosa diagnoses, and purging behaviours were assessed from the questionnaires completed during pregnancy and six months after delivery and analysed as: lifetime diagnosis, disorder active during pregnancy, and disorder present only before pregnancy. The outcome was defined as at least one episode of wheezing occurring between 6 and 18 months of age. Children born to mothers with bulimia nervosa were at an increased risk of developing wheezing irrespective of exposure timing (lifetime diagnosis ORadj 2.39; 95% CI: 1.37-4.16). An increased risk of wheezing was observed in children born to mothers with anorexia nervosa if the disease was present during pregnancy (3.49; 1.21-10.07). Similar results, though lower in magnitude, were observed also for purging behaviours, as well as for purging behaviours without previous bulimia nervosa and/or anorexia nervosa diagnosis. These associations were not entirely explained by concomitant maternal depression or anxiety diagnosis. Several risk factors for wheezing (maternal BMI, smoking during and after pregnancy, caesarean delivery, birth weight, breastfeeding, and day-care attendance) were associated with maternal bulimia nervosa and anorexia nervosa during pregnancy.

Conclusions: Maternal eating disorders, namely bulimia nervosa and anorexia nervosa are associated with childhood wheezing independently of comorbid maternal psychopathology. Maternal lifestyle, perinatal events and child-care practice might be involved in these associations.

PO1.05.08

Maternal depressive symptoms over time and asthma in 3-year-old children: findings from a longitudinal Canadian based pregnancy cohort

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Background: Approximately 10% of Canadian children aged 2-7 years are diagnosed with asthma and is one of most common chronic disease among children. Asthma can have long term effects on children’s health and has a huge economic burden on the health care resource. There is a growing evidence corroborating to links between early exposures of early life stressors including maternal depression and childhood asthma. However, evidence is limited to small, genetically high risk samples. Existing literature on maternal depression has focused depression on one time point either pre-natal or post-natal and its association with childhood asthma. However, limited studies have investigated maternal depression over time and its relationship with asthma in a large community based cohort.

Objective: The aim of this study is to examine the relationship of maternal depressive symptoms across the early childhood period and childhood asthma at age 3 years.

Methods: The All Our Families (AOF) study is an ongoing prospective pregnancy cohort of approximately 3300 mothers and children in Alberta, Canada. A total of 1983 participants met all eligibility criteria and were included in the current study. Study participants completed three questionnaires spanning pregnancy to four months postpartum and participated in the follow up study, when their children turned one,
two and three years’ old. Maternal depression was assessed using self-reported Edinburgh Postnatal Depression Scale (EPDS). Child asthma diagnoses was maternal reported at the 3-year follow up visit. Latent class analysis (LCA) was conducted to identify trajectories of women’s depression across four time points (two during pregnancy and one each at 4 and 12 months postpartum). A multivariate regression model was used to explore the relationship between the maternal depression trajectories and asthma while adjusting for covariates.

Results: The majority of mothers were between 25-34 years (73%), had some post-secondary education (92%), had family incomes ≥ $80,000 (73%) and spoke English at home (90%). Mothers who smoked and took anti-depressants during pregnancy were 9% and 3%. At the 3-year follow-up, 82 mothers (4%) reported that their children have had a diagnosis of asthma. LCA identified four distinct trajectories of maternal depressive symptoms over time: minimal symptoms (n = 1282, 64.7%); early-postpartum symptoms (n = 216, 10.9%); sub-clinical symptoms (n = 372, 18.8%); and persistent high symptoms (n = 112, 5.6%). Logistic regression revealed that mothers having persistent high depressive symptoms were associated with a 2 fold increased risk of childhood asthma, after adjusting for covariates significantly associated with asthma ta the bivariate level. In addition to persistent high depressive symptoms, the strongest predictors of asthma were maternal asthma and pre-term birth.

Conclusion: With more than 25% of women experiencing poor mental health from conception to one year postpartum, identifying those with persistent high symptoms may reduce the burden of disease from childhood asthma.

PO1.05.09

Influence of maternal and fetal 25-hydroxyvitamin D levels on lung function and atopic disease development

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Background: Exposure to low levels of vitamin D in fetal life might be a risk factor for childhood asthma and allergy. We will examine whether 25-hydroxyvitamin D levels in mid-gestation and at birth are associated with lung function, allergic sensitization, asthma and allergy in school-age children.

Methods: We will perform a population-based prospective cohort study among approximately 5,500 mothers and their children. Maternal blood samples in mid-gestation and umbilical cord blood samples at birth were used to determine 25-hydroxyvitamin D levels. At age 10 years, lung function was measured by spirometry (forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow at 25-75% of FVC (FEF25–75%) and forced expiratory flow at 75% of FVC (FEF75%), inhalant allergic sensitization by a skin prick test, and physician-diagnosed asthma and inhalant allergy by a postal questionnaire. For associations analyses, multivariate linear and logistic regression models will be applied.

Results: We will present results of associations of continuous and categorical (low, middle, high) maternal levels of 25-hydroxyvitamin D in mid-gestation and child’s levels of 25-hydroxyvitamin D at birth with lung function measures, allergic sensitization, asthma and allergy. We will also take child’s current 25-hydroxyvitamin D level into account.

Conclusion: Main conclusions and clinical relevance will be provided during the congress.

PO1.05.10

Exploring obesogenic pathways linked to asthma in adult life: 1978/79 Ribeirao Preto Cohort, Brazil

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Background: To analyze the obesogenic pathways throughout the life cycle and its association with asthma in adults.

Methods: Birth cohort study from 1978/79, Ribeirao Preto, Brazil (n = 2063). This cohort was studied in three stages: birth (baseline), school age (1st follow-up) and adult age (2nd follow-up). A theoretical model was proposed to analyze the obesity pathways and its association with asthma in adults, through structural equation modeling. The following variables were used: baseline: family socioeconomic status – SES at birth (construct formed by maternal education, maternal occupation and family income), type of delivery and adequacy of birth weight for gestational age; 1st follow-up: BMI z-score at 7-8 years; 2nd follow-up: current adult SES (construct formed by adult education, adult occupation and monthly family income), current BMI, history of parental obesity and asthma in adults (construct formed by medical diagnostic of asthma, wheezing in the last 12 months and bronchial hyperresponsiveness).

Results: Higher SES at birth (CP = 0.155; p < 0.001) and cesarean section (CP = 0.079; p = 0.039) were associated with having been born large for gestational age. Higher SES at birth (CP = 0.178; p < 0.001), parental obesity (CP = 0.171; p = 0.001) and cesarean section (CP = 0.146; p = 0.002) were associated with being overweight at 7-8 years. In adult life, lower adulthood SES (CP = -0.212; p = 0.003), caesarean delivery (CP = 0.126; p < 0.001), having been born large for gestational age (CP = 0.092; p = 0.006), parental history of obesity (CP = 0.229; p < 0.001) and being overweight at school age (CP = 0.549; p < 0.001) were associated with higher adult BMI. Parental obesity (CP = 0.104; p = 0.047) and to be born small for gestational age (CP = -0.094; p = 0.039) were the variables of the obesogenic pathway that were associated
with asthma in adults; while the higher SES in adult life (CP = -0.106; p = 0.009) was protective of adult asthma.

**Conclusions:** Obesogenic pathways starting from parental obesity are associated with higher weight over the life cycle and asthma.

**PO1.05.11**

Fetal growth and childhood lung function in the STOPPA twin study

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**Background:** Fetal growth restriction has been suggested to be associated with lung development and potential subsequent reduced lung function. Low birth weight and prematurity, both related to fetal growth restriction, have independently been associated with reduced lung function in childhood. However, it is unclear whether the associations are driven by gestational age, fetal growth, or both. Associations between fetal growth restriction and lung function impairment could also be due to shared (familial) genetic and environmental confounding factors.

We aimed to study the association between fetal growth and childhood lung function before and after bronchodilator treatment, while taking gestational age, familial factors, and asthma into account, using objective measures of birth weight, gestational age and lung function.

**Methods:** Based on the Swedish Twin Registry, we recruited 752 twins aged 9-14 years to the Swedish Twin study On Prediction and Prevention of Asthma (STOPPA). Three groups of monozygotic and dizygotic twin pairs of same gender where one (asthma discordant), both (asthma concordant), or none of the twins had a history of asthma (healthy concordant) were identified. Maximal values of forced expiratory volume in the first second (FEV$_1$) and forced vital capacity (FVC) before (pre) and after (post) bronchodilator treatment (Terbutaline 0.5 mg), were used for the analyses. Information on twin’s birth weight and gestational age was collected from the Medical Birth Register (MBR). Potential confounders and other covariates of interest were recognized based on prior literature and directed acyclic graphs and identified from the MBR and a parental questionnaire answered at the clinical examination. Firstly, full cohort analyses of twins were performed to study the association between birth weight, gestational age and fetal growth and FEV$_1$, FVC and FEV$_1$/FVC in z-scores before (n = 520) and after (n = 539) bronchodilator treatment. Secondly, to control for gestational age and familial factors, within-twin pair analyses were performed.

**Results:** In the full cohort post-bronchodilator treatment, FEV$_1$ was significantly associated with a decrease in birth weight (-0.16 z-score per 500 g, 95% CI -0.28 to -0.04) and fetal growth (-0.15 z-score per 1 SD decrease, -0.26 to -0.04) and similar and significant associations were also seen for FVC with birth weight and fetal growth. Non-significant associations were found for FEV$_1$ and FVC with gestational age. The direction of effect was similar in pre-bronchodilator analyses, although with somewhat less strong and non-significant effect estimates for both FEV$_1$ and FVC with fetal growth. No associations were found between any of the exposure variables and FEV$_1$/FVC, pre- or post-bronchodilator. In the within-twin pair analyses, the direction of effect appeared similar to the whole cohort but the confidence intervals were wider.

**Conclusions:** Our results suggest that there is a significant association between restricted fetal growth and post-bronchodilator FEV$_1$ and FVC, but not FEV$_1$/FVC, in childhood that may be independent of gestational age and shared familial factors.

The association between birth weight, gestational age and fetal growth as continuous predictors for lung function in the full cohort of twin

**PO1.05.12**

Does lung function growth trajectories depend on prenatal or postnatal exposure to airborne pollutants? - Krakow birth cohort study

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**Background:** There are variety of factors associated with both the environment and life style, present from prenatal period to adulthood, that may affect or modulate lung function growth. Recent cohort studies showed that spirometry values at 4-6 years of age affect the height of a plateau achieved at age 20-25 years, and hence the starting point for its decline. The aim of this study was to investigate the individual growth trajectories of children’s lung functions as they get older by prenatal and postnatal levels of exposure to airborne pollutants, which were both hypothesized to decline studied parameters, with stronger effect of postnatal exposure.

**Methods:** Study group included non-asthmatic, children from birth cohort in Krakow, who went regular spirometry testing at
the ages 4 – 9 years. Personal airborne measurement of fine particulate matter (PM2.5) and polycyclic aromatic hydrocarbons (PAHs) were performed in the second trimester of pregnancy and this was indicator of prenatal exposure. The same pollutants were reassessed when children where 3 years old with measurement done indoor and outdoor, and were considered as postnatal exposures. Growth trajectories of children’s lung functions were adjusted by polynomial multilevel mixed models. All statistical analyses were carried out with STATA 13.1.

Results: Significant lung function impairment (decrease in both FVC and FEV1) was observed from 4 through 9 years among subjects prenatally exposed to higher levels of prenatal PM2.5 or PAH, however none differences were observed in the rate of increase between lower and higher levels of studied airborne pollutants. Neither PM2.5 nor PAHs levels of postnatal exposure differentiate lung function trajectories is the studied period. Effect of prenatal airborne exposure to pollutants on lung function trajectories remained significant after adjustment to postnatal levels of exposure.

Conclusions: Prenatal levels of airborne pollutants might be associated with impaired individual lung growth trajectories, but the impact of postnatal exposure was not observed.

PO1.05.13
Maternal butter intake during lactation is associated with less food allergy at 1 year of age
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Background: Allergies have increased in countries with a Western lifestyle during the past decades. There are yet no cures and no effective means of prevention. We have previously found that maternal intake of oily fish during pregnancy and lactation was negatively associated with allergy development in the offspring at 3 years of age, while the opposite was found for margarine. We aim to investigate these associations further in the NICE birth cohort (Nutritional impact on Immunological maturation in Childhood in relation to the Environment).

The NICE study: The overall aim of the study is to evaluate the influence of environmental factors, such as microbes and diet, during pregnancy and the first years of life on infant immune system maturation, immune mediated diseases and neurological development. The recruitment started in January 2015 and takes place at maternity clinics in the Norrbotten County, Sweden, and will end in December 2017. So far, approximately 500 families have been recruited.

Methods: The mothers’ diet during the past month was registered during pregnancy week 34 and at 1 and 4 months postpartum. The web-based and interactive food frequency questionnaire ‘Meal-Q’ was used, including 102-174 food items depending on the number of follow-up questions. Allergy diagnoses have been made at one year of age by one pediatrician, using strict predefined protocols.

Preliminary results: To this date, 309, 264 and 215 food questionnaires have been completed during pregnancy and 1 and 4 months postpartum, respectively. Of the children, 164 children have been diagnosed as either healthy (n = 129, 79%) or allergic (n = 35, 21%): 15 with food allergy and asthma, respectively, 12 with pet allergy and 11 with eczema; of which 8 had more than one allergy. Our results indicate that maternal consumption of butter and saturated fatty acids during lactation may be associated with a decreased risk of food allergy development in the offspring, also after adjustment of confounding, such as maternal food allergy. However, we have not yet processed breastfeeding data. Hence, length of breastfeeding has not been evaluated as a potential confounder. Also, non-breastfeeding mothers have not yet been excluded from the analyses of lactating mother’s diet in relation to offspring allergy.

PO1.05.14
Eczema and allergies in childhood associate with psychological and behavioral problems primarily in girls
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Background: Atopic dermatitis (AD) otherwise known as eczema and other allergies are common conditions in young children. Eczema is the most prevalent chronic medical condition in children ranging between 12 and 20% prevalence in western populations and Asia. More recently, several European studies have described that eczema is often co-morbid with mental health disorders. These findings have been confirmed in a large population based study in the United States. In particular, eczema is associated with an increased risk of ADHD, conduct and behavioral problems. Allergic diseases besides eczema are more commonly linked with internalizing disorders including anxiety and depression. While this association between eczema, allergies and mental health disorders has been established, the role of gender in influencing this association has not been fully addressed.

Methods: Mother-infant dyads from the Maternal Adversity and Neurodevelopment (MAVAN) cohort involving subjects from Montreal and Hamilton, Canada, were assessed in this study. Mothers reported the presence of eczema and allergies in their children from birth to 60 months of age on health questionnaires. Socioemotional development was assessed using the mother-reported Child Behavior Checklist (CBCL) (60 months) and the Strength and Difficulties Questionnaire (SDQ) (60 months). T-tests were used to assess if the presence of allergies or eczema associated with socioemotional outcomes in children at 60 months of age. The data was also analyzed separately by gender.
Results: The presence of eczema from birth to 60 months associated with some socioemotional outcomes at 60 months of age. Children with eczema had more internalizing and pervasive problems and greater emotional reactivity. Mothers of children with eczema reported greater total difficulties, emotional and conduct problems. Presence of allergies until 60 months of age associated with no socioemotional outcomes at 60 months. When the analysis was conducted in girls only, the presence of eczema associated with many more socioemotional outcomes including internal, external and total problems score on the CBCL at 60 months. Girls with eczema also had greater scores on anxiety, depression, pervasive problems, oppositional defiance, emotional reactivity, somatic complaints, aggression, mother reported total difficulties, emotional symptoms and conduct problems. Meanwhile, the presence of eczema until 60 months associated with no socioemotional outcomes in boys. Allergies also associated with several outcomes in girls including the internal and total CBCL score, depressive problems and somatic complaints. In boys, presence of allergies only associated with anxiety problems on the CBCL at 60 months.

Conclusions: We found the association between childhood eczema/allergy presence and the risk for socioemotional problems in children was influenced by the children’s gender. Girls with eczema or allergies during early childhood appear at greater risk of socioemotional problems than boys. Neuroimmune differences between boys and girls with allergies or eczema could explain the gender based differential risk for socioemotional problems.

POI.05.15
Eczema phenotypes across childhood
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Background: Childhood eczema is a major common chronic health problem with a prevalence rate up to 25%. The age of onset and the persistence of eczema during childhood vary widely. To better predict or prevent eczema, it is urgently needed to define more detailed eczema phenotypes and to understand its specific underlying risk factors.

Objective: We will identify eczema phenotypes in childhood, and examine whether exposure to specific environmental factors influence the development of these phenotypes.

Methods: This study among 5,828 children will be performed in a population-based prospective cohort from fetal life onwards. Information on socioeconomic, lifestyle and dietary factors, and parental-reported physician-diagnosed eczema was obtained by questionnaires from birth until the age of 10 years. Latent class analysis will be used to identify eczema phenotypes based on the variation of having eczema at different time points, and weighted regression models for associations of specific environmental factors with eczema phenotypes.

Results: We will present results of the minimum number and characteristics of eczema phenotypes. We will also examine which specific environmental factors are associated with each of these phenotypes.

Conclusion: Main conclusions and clinical relevance will be provided during the congress.

POI.05.16
Correlation of maternal fatty acid status during pregnancy with childhood inflammatory markers: the MEFAB cohort.
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Background: The increasing prevalence of asthma in western countries has been hypothesized to be caused by a shift in the fatty acid (FA) composition of our diet, which would skew our immune system towards a pro-inflammatory state. Therefore, we tested whether the maternal FA status during pregnancy is associated with various inflammatory markers in the offspring at age 7.

Methods: In the MEFAB cohort, plasma phospholipid FAs were measured in pregnant women (n = 174) at 16, 22 and 32 weeks of pregnancy and at the day of delivery. Total leukocyte, monocyte, granulocyte and lymphocyte counts, tissue plasminogen activator (tPA) level and activity and plasminogen activator inhibitor-1 (PAI-1), leptin, C-reactive protein (CRP) and fibrinogen levels were measured in the children’s blood at age 7. Canonical correlation analysis – a multivariate extension of the Pearson correlation – was used to determine the relation between the set of maternal FAs and the set of inflammatory markers.

Results: Preliminary results show a significant correlation between maternal FAs at 16 weeks (r = 0.62, p < 0.001), 22 weeks (r = 0.64, p < 0.001) and 32 weeks (r = 0.63, p < 0.001) of pregnancy and the offspring’s inflammatory markers at age 7. Interestingly, no significant correlations were found at the day of delivery. Various FAs were identified to have large contributions to the significant correlations, but the most consistent was mead acid (20:3ω9).

Conclusions: These preliminary results demonstrate that the maternal FA intake and metabolism during pregnancy could have an impact on the children’s inflammatory markers later in life.

POI.05.17
Influence of early growth on magnetic resonance imaging and spirometry obtained lung function in childhood.
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Background: Preterm birth or low birthweight might lead to lung structure adaptations and lower function, which could subsequently lead to asthma in childhood. We will examine the associations of early growth characteristics with lung function measured by magnetic resonance imaging (MRI) and spirometry at school-age.

Methods: This study among 2,907 children was embedded in the Generation R Study, a population-based prospective cohort study. Gestational age and weight at birth were obtained from midwifery and hospital registries. At the age of 10 years, end-inspiratory spirometry controlled chest MRI was performed using a 3.0T GE W750 MR scanner to measure automatically segmented total lung volumes (TLC-MRI) (Luna software, Polytechnic Milan). Forced expiratory volume in 1 second (FEV$_1$), forced vital capacity (FVC), FEV$_1$/FVC, forced expiratory flow at 25-75% of FVC (FEF$_{25-75}$) and forced expiratory flow at 75% of FVC (FEF$_{75}$) were measured by spirometry. We assessed intra- and interobserver variability of TLC-MRI scored by 2 observers by intra-class correlation coefficient (ICC) and Bland-Altman plots, correlations of TLC-MRI with spirometry measures using Pearson correlation coefficients, and associations of gestational age at birth and birth weight with TLC-MRI using linear regression models.

Results: Intra- and interobserver variability for TLC-MRI measurements was good (ICC: between 0.825 and 1.000, p-values <0.05). TLC-MRI was positively correlated with FEV$_1$, FVC, FEF$_{25-75}$ and FEF$_{75}$ (Pearson r: 0.70, 0.79, 0.23 and 0.16, respectively, p-values <0.01), and negatively correlated with FEV$_1$/FVC (Pearson r: -0.28, p-value <0.01). Gestational age at birth was not associated with any lung function measure. A greater gestational-age adjusted birth weight was associated with increased TLC-MRI (β (95% CI): 39.2 (1.1, 77.3) ml per SDS increase in gestational-age adjusted birth weight) and higher FEV$_1$, FEV$_1$/FVC and FEF$_{75}$ (β (95% CI): 0.03 (0.01, 0.05), 0.01 (0.00, 0.01) and 0.06 (0.03, 0.09), respectively, per 500 gram increase in birthweight).

Conclusions: We observed good intra- and interobserver variability for TLC-MRI, and good correlations of TLC-MRI with spirometry measures. A greater gestational-age adjusted birth weight was associated with a higher TLC-MRI and spirometric lung function measures, which could predispose for better lung development.

PO1.06 – Metabolomics and Circadian rhythm

PO1.06.01

Early life factors, obesity risk and the metabolome of young adults

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Background: Non-communicable diseases such as obesity have become a serious global public health epidemic. Early life factors, for example infant feeding, may have a programming effect on metabolism and obesity in childhood. This study aimed to examine whether there was an association between breast-feeding duration with BMI and waist circumference in offspring at 20 years. Additionally, we aimed to determine potential early programming effects of breast-feeding on the metabolome in young adults.

Methods: Data from the Western Australian Pregnancy Cohort (Raine) Study was analysed using 1024 plasma samples from the 20 year follow-up. A liquid chromatography, tandem mass-spectrometry metabolomics approach was used to measure metabolites. Principal Components Analysis and multiple linear regression models were performed and all models were adjusted for relevant confounders before and around the time of breast-feeding. Inverse probability weighting was used to adjust the 20 year data for the difference in socioeconomic variables between participants and non-participants since commencement of the study.

Results: An inverse association between breast-feeding and BMI or waist circumference at 20 years was lost after adjusting for maternal and paternal pre-pregnancy BMI and maternal smoking during pregnancy. In addition, there was no significant effect of breast-feeding on metabolic concentrations at 20 years. A non-significant trend (uncorrected p-value <0.05) of non-esterified fatty acids and acyl-carnitines associated with shorter breast-feeding duration was also evident.

Conclusions: Although other studies have shown associations between breast-feeding and obesity and metabolite concentrations at younger ages, this was not evident in our study in young adults. Metabolites associated with waist circumference at 20 years were not associated with breast-feeding in early life.

PO1.06.02

Relation of clinical and metabolic characteristics to neonatal adiposity among obese pregnant women.


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Background: Amongst overweight and obese women metabolic dysfunction is evident in early pregnancy, and increased fetal growth precedes the clinical diagnosis of gestational diabetes at 20 weeks’ gestation, followed by excessive fetal adipose tissue accretion. However, in obese women it is currently unknown which early pregnancy maternal exposures, including dietary, metabolic and demographic factors, contribute to the development of fetal adiposity. Our primary aim was to examine the relationship of early (15-18 weeks’ gestation) pregnancy maternal clinical and biochemical variables with neonatal adiposity as assessed by skin fold thicknesses (SFT). As a secondary aim, we assessed pathways between early pregnancy maternal characteristics and neonatal adiposity, and explored the potential mediating role of the maternal late second trimester metabolic profile using casual mediation analysis.

Method: We used data from the UK Pregnanacies Better Eating and Activity Trial (UPBEAT), a randomised controlled trial of 1555 obese pregnant women (mean BMI 36.3 kg/m²) which assessed an antenatal intervention promoting a low glycaemic diet and increased physical activity. Maternal and neonatal adiposity were assessed by skinfold thicknesses (SFT). Maternal baseline socio-demographic, medical and family characteristics were recorded at 15-18 weeks’ gestation. The mother’s biochemical profile was evaluated at 15-18 and 24-29 weeks’ gestation by measurement of targeted candidate biomarkers and metabolomics profile using nuclear mass spectrometry (NMR). Detailed neonatal anthropometry was collected in a subgroup. To examine associations with infant adiposity, multivariable linear regression was undertaken with adjustment for potential confounders. To assess potential pathways between early and late 2nd trimester variables and neonatal adiposity, mediation analysis using parametric regression was undertaken.

Results: Neonatal (n = 502) SSFT (sum of triceps and subscapular skin fold thicknesses) was greater in multiparous vs. nulliparous mothers (β = 1.06 mm, 95%CI 0.58 to 1.53), and was linearly associated with higher maternal birthweight (β = 0.55 mm/kg; 0.001 to 0.01). Neonatal SSFT was also positively associated with maternal 15-18 week triceps SFT (β = 0.04 mm/mm, 0.013 to 0.079), and inversely related to maternal 15-18 week suprailiac SFT (β = -0.035 mm/mm, -0.057 to -0.013). Neonatal SSFT was not related to any biochemical variables measured in early (15-18 weeks) pregnancy but was associated with maternal fasting concentrations of glucose, serum insulin, C-peptide and glycoprotein acetyls at 26-28 weeks’ gestation. Associations of parity (4.5%), early pregnancy triceps (12.5%) and suprailiac SFT (13.9%) with neonatal SSFT were partially mediated by fasting glucose at 26-28 weeks’ gestation.

Conclusions: This extensive study has identified some novel and potentially modifiable maternal characteristics in early pregnancy that are associated with neonatal adiposity. The mediating role of second trimester glycaemia emphasises the need for optimal glucose control in obese women before conventional 28 week screening for gestational diabetes.

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PO1.06.03

Wireless communication devices and sleep problems in adolescents

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Background: Sleep is important for the body to conserve energy, restore its normal processes, promote physical growth, and support mental development, especially during childhood and adolescence. Experimental studies have shown that electroencephalographic (EEG) spectral power is enhanced during and following pulsed-modulated radio frequency field exposure and provided the first indications of a dose-dependent relation between the field intensity and its effect on brain physiology. Some epidemiological studies, in children, adolescents and adults found a relationship between radiofrequency electromagnetic fields (RF-EMF) exposure levels or new wireless communication devices usage and poor sleep affecting daytime functioning. The objective of the study is to assess the association between wireless communication devices usage and sleep problems in adolescents of 17 to 18 years of age.

Methods: We used data from Menorca, a region part of the Spanish INMA –Environment and Childhood- Project, a population-based birth cohort established in 1997 (n = 485). Children were followed from birth to the assessment. Information about mobile and cordless phone use (calls, SMS and others), other devices usage (tablet, laptop and vide console), frequency and type of usage (call, text, consult social networks, watch videos online and play games online) the hour before going to bed was collected with self-reported questionnaires and Mobile Phone Problem Use Scale (MPPUS-10) was used to assess problematic mobile phone use when adolescents were 17 to 18 years of age. Pittsburgh Sleep Quality Index (PSQI) and its subscales (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction due to sleepiness) were used to assess sleep problems. Logistic regression models adjusted by parental and adolescent socioeconomic and lifestyle variables were used to estimate the association between mobile and cordless phone...
Usage, other devices usage, usage before going to bed and problematic mobile phone usage but not with PSQI score and each subscale.

Multivariate models showed that night-sleep duration at 2 years old was negatively associated with night-feeding at 4 months ($\beta$ [95% CI] = -0.16 [-0.30; -0.02]), whereas frequent night-waking was related to night-feeding at 8 months (OR [95% CI] = 2.44 [1.02; 5.83]) and sleep onset difficulties at 2 years old were positively associated with gastrointestinal reflux between birth and 8 months (OR [95% CI] = 1.75 [1.01; 3.07]) and negatively with predominant breastfeeding longer than 4 months (OR [95% CI] = 0.46 [0.22; 0.93]).

Conclusions: Results showed that some night-feeding practices during infancy were related to lower night-sleep quantity or quality while breastfeeding duration and gastrointestinal reflux in infancy were related to sleep onset difficulties at 2 years.

PO1.06.05

Maternal and fetal SCD-1 activity are associated with elevated birth weight and adiposity and influenced by diet in late gestation


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Background: Stearoyl-CoA desaturase (SCD-1) is an enzyme involved in the metabolism of saturated and monounsaturated fatty acids. Elevated levels of SCD-1 activity have been associated with obesity and insulin resistance. Recently, ratios of fatty acids depicting SCD-1 activity in cord blood have been found to strongly correlate with birth weight. SCD-1 transcription and activity are regulated by many factors, amongst others, leptin, insulin, sugars and fat intake. In this analysis, we investigated (1) the effect of SCD-1 activity on fetal and infant anthropometry up to 2 years of age and (2) whether diet in pregnancy has an impact on SCD-1 regulation.

Material and methods: The analysis was conducted on a subpopulation of the ROLO Study (Randomized eOntrolled trial of LOw glycaemic index diet versus no dietary intervention to prevent recurrence of fetal macrosomia, 2007-2011, National Maternity Hospital, Dublin, Ireland). Plasma samples were taken in early pregnancy (at first antenatal visit, approximately 14 weeks gestation) late pregnancy (LP, 28 weeks) and birth (CB, cord blood) and analysed using liquid-chromatography coupled to tandem mass-spectrometry in a targeted metabolomics approach. Dietary data were collected via 3-day food diaries in each trimester of gestation; maternal and child anthropometric were measured from study entry up to 2 years after birth. Ratios of monounsaturated to saturated non esterified fatty acids (NEFA) and lysophosphatidylcholines (lysoPC) were computed as SCD-1 activity markers (desaturation indices, DIs); the relationships between DIs, fetal anthropometry, maternal diet, leptin and insulin were investigated via linear regression models.
Results: DIs in LP and CB were positively associated with weight, weight-to-length ratio, and other anthropometric measurements at birth (most significant associations: LP and CB NEFA 18:1/NEFA 18:0 with birth weight-to-length, uncorrected p < 0.001 and p = 0.0027, respectively). LP and CB NEFA 19:1/NEFA 19:0 indices were positively associated with 6m and 2y adiposity independently from birth measures. Micronutrients and ratios of carbohydrate and sugars to fat intake (especially in the third trimester) positively affected fetal SCD-1 activity. Limited regulatory effect of leptin on SCD-1 activity was found.

Conclusion: Elevated maternal and fetal SCD-1 activity is related to fetal and infant adiposity and might have a programming effect on later obesity onset. Maternal diet in pregnancy might help to downregulate fetal SCD-1 activity.

PO1.06.07

Amino acid profile in early pregnancy in a heterogeneous group of women at high risk of gestational diabetes

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Background: Fasting plasma levels of branched chain (BCAA) and aromatic amino acids (AAA) associate with insulin resistance and further predict development of type 2 diabetes. Insulin resistance is also involved in the pathophysiology of gestational diabetes (GDM). Previous findings concerning association of BCAAs and AAAs with development of GDM are inconsistent. The association of amino acids with insulin resistance is only observed in women with abdominal obesity. The women who develop GDM are not, however, all obese. Our aim was to assess amino acid profiles in early pregnancy in a heterogeneous group of women at high risk for GDM.

Methods: This is an observational study of 215 women from The Finnish gestational diabetes prevention trial (RADIEL). The participants in this study were at high risk for GDM either because of a prepregnancy BMI ≥30 kg/m2 and/or a history of prior GDM, but showed normal glucose tolerance in early pregnancy when assessed with a 2-hour 75 g oral glucose tolerance test (OGTT). The concentrations of BCAAs (isoleucine, leucine, and valine) and AAAs (phenylalanine and tyrosine) were analyzed from fasting serum samples, drawn at on average 13.1 weeks of gestation, by targeted NMR spectroscopy. A second OGTT was performed at on average 26.5 weeks of gestation. For the OGTT the following thresholds were used: fasting plasma glucose ≥ 5.3 mmol/L, one hour glucose ≥ 10.0 mmol/L and two hour glucose ≥ 8.6 mmol/L (American Diabetes Association 2008). One or more pathological value resulted in the diagnosis of GDM. The participants were divided into four groups according to their phenotype: 76 of the women were obese nulliparous (group A), 48 obese multiparous without prior GDM (group B), 68 non-obese with prior GDM (group C), and 23 obese with prior GDM (group D). The incidence of GDM was 11.8% in group A, 12.5% in group B, 36.8% in group C, and 34.8% in group D.

Results: In early pregnancy the concentrations of BCAAs and AAAs, except for valine, differed between groups (p < 0.001). The difference localized to group C in which the levels were all lower. Per every 1-SD increase of phenylalanine concentration the OR for subsequent GDM was 0.69 (95% CI 0.49 to 0.6; p = 0.027) for the whole population, and within group C the respective OR was 0.49 (0.25 to 0.95, p = 0.035) (Figure 1).

Conclusions: In early pregnancy non-obese women at high risk for GDM have a different amino acid profile compared to obese women. This may offer one possible explanation for inconsistent findings concerning the associations of GDM with BCAAs and AAAs.

PO1.06.08

Melatonin prevents the development of hypertension programmed by prenatal dexamethasone plus postnatal high-fat diet in adult offspring of both sexes

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Background: Pre- and post-natal environmental insults can induce developmental programming, leading to hypertension. Renal programming is considered a key mechanism for programmed hypertension. We recently observed that pre-natal dexamethasone (DEX) exposure plus postnatal high-fat (HF) consumption induced hypertension in adult male offspring. Emerging evidence support early intervention with melatonin could be a reprogramming strategy to prevent programmed hypertension. Hence, we intended to examine whether melatonin can reprogram two-hit induced programmed hypertension in both sexes of adult offspring. Also, we sought to identify candidate proteins involved in renal programming and programmed hypertension through a proteomic approach.

Methods: Five groups (n = 8-10/group) of both male and female offspring were studied: control, DEX, HF, DEX + HF, and DEX + HF + M. Dexamethasone (0.1 mg/kg body weight) was intraperitoneally administered to pregnant Sprague Dawley rats from gestational day 16–22. Offspring received high-fat diet (D12331, Research Diets) from weaning to 4 months of age. In the DEX + HF + M group, mother rats received 0.01% melatonin in drinking water during pregnancy and lactation. All rats were sacrificed at 16 weeks of age. Additionally, we identified protein expression in offspring kidneys by proteomic profiling and protein identification using tandem mass tag labeling and LC-MS/MS.

Results: We found HF diet aggravated prenatal DEX-induced programmed hypertension, which was prevented by early melatonin therapy in both sexes of offspring. The protective effects of melatonin therapy are related to regulation of renin-angiotensin system (RAS), melatonin signaling pathway, and proteomic profiling alterations. We observed that expression of renal proteomic profiling was sex differentially regulated by DEX + HF exposure. In male offspring, DEX + HF upregulated renal parvalbumin (PVALB) protein level, which melatonin therapy prevented. Additionally, dimethylaniline monooxygenase 2 (FMO2) and hemoglobin subunit α (HBB1) and -2 (HBB2) were upregulated, whereas prothymosin α (PTMA) was downregulated by DEX + HF exposure in female offspring kidneys. These changes were prevented by maternal melatonin therapy.

Conclusions: In conclusion, prenatal DEX and post-weaning HF diet synergistically induced programmed hypertension, which was related to alterations of RAS, melatonin pathway, and proteomic profiling in offspring kidneys. DEX + HF induced sex-specific alterations of protein expression in offspring kidneys: PVALB in males; while FMO2, HBB1, HBB2, and PTMA in females. By providing potential applications of reprogramming strategy targeting protein and pathway involved in renal programming, our results can form a strong scientific basis for developing therapeutic strategies to prevent programmed hypertension in children exposed to antenatal corticosteroids and postnatal HF intake.

PO1.06.09
Beyond the genome. How the metabolome can help uncover gene function

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Genetic factors modifying the blood metabolome have been investigated through GWAS of common genetic variants. Using Whole genome sequencing we looked at low frequency and rare variants to associate genetic variations with metabolite levels in blood plasma. Analysis was focussed on 644 metabolites across three data sets. It was noted that genetic sequence variations at 101 loci were associated with the levels of 246 metabolites. 13 of the 17 genes influenced by heterozygous rare variants are associated with inborn errors of metabolism and other pediatric conditions. This emphasizes the importance of heterozygous rare variants in determining abnormal metabolic phenotypes in the blood of adults. This approach confirms the importance of rare gene variants in effecting common diseases and links them to metabolic changes that influence the phenotype showing the value of broad metabolic profiling in population studies.

PO1.06.10
Atopic women have lower breast milk levels of acetate and butyrate


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Background: Worldwide, breast milk protects children against respiratory conditions and obesity, an effect attributed to its many bioactive compounds. These benefits are not consistently seen in children of mothers with the allergic (atopic) phenotype. Still in its infancy, studying the breast milk metabolome has proven valuable in identifying variability by maternal phenotype, diet and disease. In addition to sugars and amino acids, the breast milk metabolome includes other low molecular weight, short-chain fatty acids (SCFAs) such as butyrate, acetate and valerate, which are produced by microbiota present in breast milk. With a focus on these less well-studied metabolites, the LactoActive research group undertook an international comparison of breast milk metabolomics.

Methods: This was a comparative study of 109 breast milk samples from 6 international cohort studies: Perth, Australia (n = 29 from 2 cohorts); Chiba, Japan (n = 12); Detroit, USA (n = 18); Oslo,
Norway (n = 40); Cape Town, South Africa (n = 10). With representation across ethnicity, maternal atopic status and infant sex, breast milk samples were collected 1 month after birth. Milk metabolite levels were determined by NMR spectroscopy because of its high reproducibility and coverage of a large range of metabolites. All NMR spectra were processed and analyzed with the Chenomx NMR Suite Professional software package version 8.1.

**Results:** Atopic women had significantly lower levels of the SCFAs, acetate (p < 0.02) and butyrate (p < 0.001), in their breast milk than non atopic women. Variations in milk metabolites were seen between women of the same atopic status living in different countries and they were more evident for atopic women. Country-specific variations among atopic women were more common for acetate (p < 0.001), butyrate (p < 0.001) and the SCFA pathway intermediate, succinate (p < 0.001), followed by valerate (p < 0.003) and creatinine (p < 0.006). Milk levels of acetate and butyrate were lower in Australia/US women compared to those living in Norway or Japan, but were higher for creatinine. Valerate and succinate levels were the highest in the breast milk of Norwegian women. These 5 metabolites did not differ between atopic women in Australia and the US. Among non-atopic women, breast milk concentrations of lactose (lactation performance biomarker) were significantly higher in South African versus Norwegian (p < 0.02) or Australian (p < 0.04) women. Levels of maltose (dietary sugar) and creatine/creatinine was also significantly higher in South African women versus women residing in other countries.

**Conclusion:** Our metabolomics study identified breast milk variation by maternal phenotype and country of residence. Milk levels of acetate and butyrate, SCFAs produced by breast milk microbiota, were significantly lower in atopic than non-atopic women. Atopic women in Australia and the US had the lowest levels of these SCFAs compared to atopic women in other countries. These observed variations in breast milk composition may account for regional differences in prevalence rates of childhood atopic disease.

**PO1.06.11**

**Influence of maternal and socioeconomic factors on human breast milk metabolome among South Africa cohorts**

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**Background:** Human breast milk (HBM) is a complex species-specific biological fluid universally known as the optimal post-natal source of nutrition for infants. It consists not only of essential nutrients but also an array of commensal bacteria and a host of non-nutritive bio-molecules including nucleotides, polyamines, oligosaccharides which are known to support innate immunity and shape the development of adaptive immunity of the infant during the first months of life. HBM metabolomics has revealed diverse metabolites including some whose abundances are highly conserved and they have also been shown to be affected by several factors such as gestation age, maternal well-being (HIV status, stress, obesity, and diet), mode of delivery, chemotherapy and even the sex of the child. We hypothesize that the HBM metabolome varies according to a number of maternal, infant and environmental factors. We therefore aim to characterize the metabolite profiles among South African mothers and to study the role of possible determinants influencing the HBM metabolome (maternal stress and BMI, antibiotic therapy, mode of delivery, smoking).

**Methods:** Breast milk samples were collected from 588 breastfeeding mothers from two poor, rural communities in Drakenstein sub-district, Western Cape, South Africa both with low socioeconomic status but are ethnically distinct. The women were enrolled at their 20-28 week antenatal visits to the clinics and samples collected within 7-10 weeks postpartum. Necessary information were captured in a meta-data. Untargeted 1H-Nuclear Magnetic Resonance Spectroscopy will be performed on the supernatant of the HBM samples as previously described (Sunde-kilde et al. 2016). Briefly, the samples will be skimmed by centrifugation and filtered to remove residual lipids and protein. An internal chemical shift reference will be added to the filtered sample. The proton NMR spectra will be phase and baseline corrected and signals will be identified based on one dimensional and two dimensional data using pure compound spectral databases. The proton NMR spectrum will be reduced into separate variables in the regions. Principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA) will be performed in order to identify differences in the metabolite profiles. The data will be mean-centred and Pareto-scaled prior to analysis. Covariance will be investigated by analysis of OPLS-DA regression coefficients back-transformed to original data and colour coded by the loading weights as described. The multivariate data analysis will be performed using SIMCA-P + 13 (Umetrics AB, Umea, Sweden). Alignment by Icoshift, binning and analysis of OPLS-DA plots will be performed in MATLAB 7.13. Univariate statistical significance will be evaluated by Students t-test using the Statistics Toolbox in MATLAB 7.13 (MathWorks Inc., Natick, MA, USA).

**Result and Conclusion:** Pilot study revealed Human breast milk to contain diverse metabolites dominated by lactose and oligosaccharides. A more robust approach with a larger cohorts will reveal more metabolites and will be used to establish the influence of several maternal, environmental factors influencing the breast milk metabolome.

500 MHz 1H-NMR spectrum of human breast milk.
PO1.06.13
In vitro amino acid restriction programs pancreatic beta-cell to damage when challenged by glucotoxicity without changes in redox balance.

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Background: Early-life malnutrition is a common outcome in developing countries, a phenomenon that leads to obesity and diabetes in adult life. Despite several other alterations, both conditions were reported to alter intracellular redox balance by increasing ROS production and/or antioxidant capacity reduction, leading to glycemic control impairment. We aimed to investigate the effects on redox balance and death of amino acid restriction on INS-1E cells challenged by high glucose exposure.

Methods: INS-1E were treated for 48 hours in RPMI 1640 medium supplied with 5% FCS and 11 mmol/l glucose, with 100% (Control – C) or 25% (Malnutrition – M) of amino acids solution (RPMI 1640 Amino Acid Solution 50x R7131 – Sigma) at 37 celsius degrees in a humidified atmosphere of 95% O2 and 5% CO2. After 48 hours of amino acid restriction (Malnutrition), we treated the cells with glucose (25mM) for 6 hours. Control High Glucose (C + HG) or Malnutrition High Glucose (M + HG). We evaluated insulin secretion (Radioimmunoassay) in C and D groups. After glucose treatment, we evaluated the redox balance by hydrogen peroxide (Amplex Ultra Red), cytosol and mitochondrial superoxide content (DHE and MitoSOX) essays and cleaved Caspase-3 protein content in M + HG.

Results: Insulin secretion was reduced in M INS-1E cells treated with M solution in presence of stimulatory glucose to C: 0.063 ± 0.006 ng/ug*ml-1 and M: 0.038 ± 0.006 ng/ug*ml-1 (p < 0.05). We observed that, amino acid restriction followed by high glucose exposure, increased cleaved caspase-3 protein content in M + HG when compared to C + HG (+3 fold increase, p < 0.05), despite no changes were observed in hydrogen peroxide (C: 218106 ± 23714, M: 160458 ± 24190, C + HG: 156333 ± 21300, M + HG: 158317 ± 19014, Amplex Ultra Red fluorescence) as well as cytosol superoxide release (C: 12.17 ± 1.189, M: 9.25 ± 0.94, C + HG: 14.78 ± 2.97; M + HG: 11.68 ± 1.68, DHE fluorescence (RFU)/mg*ml-1 protein). However, high glucose reduce mitochondrial superoxide release in both groups (C + HG: 4.85 ± 0.86 and M + HG: 4.54 ± 0.84, Relative fluorescence/ mg*ml-1 protein, p < 0.05) when compared to C and M (C: 22.61 ± 12.17 and M: 24.78 ± 9.25, Relative fluorescence/ mg*ml-1 protein).

Conclusions: We concluded that amino acid restriction programs pancreatic beta cells, favoring cell death when exposed to high glucose. However, in this model cell death seems not to be mediate by changes on redox balance (hydrogen peroxide and superoxide release). We suggest that amino acid restriction can program pancreatic beta cell for death by other mechanisms involved with cell viability, but not thought oxidative damage.

PO1.07 – Neurodevelopment – Early life exposures

PO1.07.01
Environmental tobacco smoke exposure during pregnancy and child neurodevelopment
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Background: The developing fetus is especially vulnerable to environmental toxicants including tobacco constituents. The aim of this study was to assess the impact of environmental tobacco smoke (ETS) exposure during pregnancy on child neurodevelopment within the first two years of life.

Methods: The study population consisted of 461 non-smoking pregnant women (saliva cotinine level <10 ng/ml). Maternal passive smoking was assessed based on the cotinine level in saliva analyzed by the use of the high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-ESI + MS/MS) and by questionnaire data. The cotinine cut-off value for passive smoking was established at 1.5 ng/mL (sensitivity 63%, specificity 71%). Psychomotor development was assessed in children at the age of 1 and 2 years using the Bayley Scales of Infant and Toddler Development.

Results: About 30% of the women were exposed to ETS during pregnancy. The multivariate linear regression model indicated that ETS exposure in the 1st and the 2nd trimesters of pregnancy was associated with decreasing child language functions at the age of one (β = -3.0, p = 0.03 and β = -4.1, p = 0.008, respectively) and two years (β = -3.8, p = 0.05 and β = -6.3, p = 0.005, respectively). A negative association was found for cotinine level ≥1.5 ng/ml in the 2nd trimester of pregnancy and child cognition at the age of 2 (β = -4.6, p = 0.05) as well as cotinine levels ≥1.5 ng/ml in all trimesters of pregnancy and child motor abilities at two years of age (β = -3.9, p = 0.06, β = -5.3, p = 0.02, and β = -4.2, p = 0.05, for the 1st, the 2nd and the 3rd trimester of pregnancy, respectively; for the 1st trimester the effect was of borderline statistical significance).

Conclusions: This study confirmed that ETS exposure during pregnancy can have a negative impact on child psychomotor development within the first two years of life and underscores the importance of public health interventions aiming at reducing this exposure.
PO1.07.02

Exposure to environmental chemicals in early life is associated with ADHD and autism spectrum disorders in Norwegian children

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Background: Environmental pollutants are ubiquitous in daily life, and exposure begins in utero. Multiple environmental chemicals are established or suspected neurotoxicants, yet few studies have assessed associations with the risk of attention-deficit hyperactivity disorder (ADHD) or autism spectrum disorders (ASD), two common neurodevelopmental disorders. We investigated measured perinatal and estimated postnatal chemical exposure levels in relation to ADHD and ASD.

Methods: A birth cohort of 2606 Norwegian mother-child pairs was followed until children were a median age of 11 years (HUMIS-NoMIC cohort). ADHD (n = 40) and ASD (n = 15) cases were ascertained using the national patient register (ICD-10 classifications). In a sample of 1199 oversampled by case status, concentrations of 45 environmental chemicals [18 polychlorinated biphenyls (PCBs), 14 organochlorine pesticides, 6 brominated flame retardants, 2 novel flame retardants, 2 poly- and perfluoralkyl substances (PFASs), 2 pyrethroid pesticides, and methylmercury] were quantified in ≥50% of pooled maternal breast milk samples, reflecting both pre- and postnatal exposures. Postnatal concentrations in the first two years of the child’s life were modelled for the lipophilic chemicals using a pharmacokinetic model. To identify associations between exposures and neurodevelopmental outcomes, we used confounder-adjusted elastic net penalized logistic regression models to account for confounding by correlated co-exposures; unpenalized effect estimates for selected exposures were obtained from multivariable regression models.

Results: Eight chemicals were associated with ADHD. Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and β-hexachlorocyclohexane (β-HCH) were associated with an increased risk (range, OR = 1.64-2.49); the largest effect estimate was observed for β-HCH (OR = 2.49; 95% CI: 1.22, 5.09 per 2-SD increase in ln-transformed maternal breast milk levels). Several chemicals showed inverse associations with ADHD. β-HCH was associated with an increased risk of ASD (OR = 4.28, 95% CI 1.82, 10.08); associations were null for other chemicals. Associations with postnatal exposures estimates were generally attenuated.

Conclusions: In a multi-pollutant analysis of 7 classes of chemicals, early-life exposure to several ubiquitous persistent organic pollutants was associated with ADHD, and one with ASD. Further chemical exposome-wide association studies are warranted to replicate these findings.

PO1.07.03

Childhood exposure to tobacco smoke and midlife cognitive performance: The Cardiovascular Risk in Young Finns Study

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Background: Our previous study suggested a longitudinal association between smoking in adolescence/young adulthood and worse midlife learning and memory. Furthermore, previous studies have proposed cross-sectional and short-term negative associations between childhood exposure to tobacco smoke on cognitive performance, intelligence or academic achievements. However, the longitudinal association between childhood/adolescence exposure to tobacco smoke and midlife cognitive performance is unknown.

Methods: From 1980, a population-based cohort of 3,596 children (baseline age 3-18 years) have been followed-up for 31 years in 3-9 year intervals. In 2011, cognitive testing was performed in 2,026 subjects aged 34-49 years using computerized test battery. The subjects were divided into two groups according to their cognitive performance: 1) low cognitive performance (lowest quartile of cognitive performance distribution) and 2) high cognitive performance (highest quartiles of cognitive performance distribution). Regular and current smoking status was queried separately from both parents at baseline and the first follow-up study in 1983. Childhood fasting serum samples were collected in 1980 and cotinine levels were analysed. Parental smoking hygiene was determined using questionnaire data on parental smoking and the child’s serum cotinine levels. The subjects were divided into: 1) no parental smoking (children with non-smoking parents and a serum cotinine level <3.0 ng/mL); 2) hygienic parental smoking (children with at least one smoking parent and a serum cotinine level <3.0 ng/mL); 3) non-hygienic parental smoking (children with at least one smoking parent and a serum cotinine level ≥3.0 and <20 ng/mL).

Results: The subjects exposed to non-hygienic parental smoking in childhood/adolescence had worse midlife memory and learning compared to subjects with non-smoking parents (β = -0.26 SD, SE = 0.12; p = 0.03, adjusted for age, sex, childhood family socioeconomic status and adulthood smoking). The difference in midlife memory and learning between the exposed and non-exposed subjects corresponds to 5 years effect of aging. Childhood/adolescence exposure to non-hygienic parental smoking associated with increased risk of low midlife memory and learning (RR 1.64; 95% CI 1.04-2.57) and a borderline significant association was found for hygienic parental smoking (RR 1.30; 95% CI 0.95-1.80) compared to subjects with non-smoking parents even after taking into account several potential confounders. Additionally, a significant association was found between hygienic parental smoking and increased risk of low midlife short term
and working memory (RR 1.48; 95% CI 1.08-2.03), while the association for non-hygienic parental smoking was borderline significant for that cognitive domain (RR 1.43; 95% CI 0.89-2.29).

Conclusions: Exposure to tobacco smoke in childhood and adolescence may associate with worse learning and memory as well as poorer short term and working memory in midlife. Avoidance of exposure to tobacco smoke is important since childhood in order to promote adulthood cognitive performance.

PO1.07.04
Is there a relationship between maternal gestational weight gain and offspring fundamental motor skills?

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Background: Children’s whose fundamental motor skills (FMS) competence is low are at increased risk of physically inactive lifestyle and thus obesity in later life. More research is required to understand the various determinants of FMS and identify early targets for intervention. There is a growing body of literature illustrating that gestational weight gain (GWG), a surrogate marker for the intrauterine environment, is associated with many aspects of offspring’s health. However, it remains to be determined whether early intrauterine exposure to maternal weight-related factors contributes to development of FMS. Therefore, the purpose of this study was to investigate the association between GWG and locomotor and object control skills among preschool-aged children, and to investigate whether these associations are sex dependent.

Methods: As a part of a larger study, we assessed 3 – 5 year old boys (n = 65) and girls (n = 59) of singleton pregnancies. Children’s FMS, both locomotor and object control skills scores, was measured using the Test of Gross Motor Development—Second Edition (TGMD-2), and reported as raw scores. A maternal health questionnaire was used to collect information on pre-pregnancy body mass index (BMI), GWG, and gestational age at term. Linear mixed effect models were used to investigate the association between the GWG and locomotor skills and objects control skills scores. All models were adjusted for pre-pregnancy BMI, gestational age, age, and socioeconomic status.

Results: The association between the GWG and score on the locomotor skills was dependent on sex (interaction, p = 0.007). When analyses were stratified with sex, GWG was independently associated with poorer locomotor skills score in boys (β = -0.3, 95% CI -0.5 to -0.1, p = 0.003) but not in girls (β = 0.1, 95% CI -0.2 to 0.3, p = 0.545). No significant sex and GWG interaction was found on object control skills (interaction, p = 0.438). Furthermore, GWG was not significantly associated with object control skills score either in boys (p = 0.287) or girls (p = 0.754).

Conclusions: Maternal GWG is an independent predictor of male, but not female, offspring’s locomotor skills. Our findings suggest the sex-dependent developmental programming of locomotor skills.

PO1.07.05
The effect of maternal perceived stress on child development in the Chinese population

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Background: It is well known that mother’s anxiety and depression adversely impact infant and child development. However, it remains unclear whether maternal stress during pregnancy negatively affects child development.

Methods: A total of 624 Chinese pregnant women were recruited in a prospective study in 2012-2014 and completed questionnaire surveys at 6, 12 and 24 months postpartum. Perceived stress during pregnancy was classified as mild (reference) and moderate/intensive. Child development problems at 24 months were assessed by Ages and Stages Questionnaire (ASQ) with five subscales (communication, gross motor, fine motor, problem solving, and personal social activities). Generalized linear models was used to compute the relative risk (RR) of maternal perceived stress in relation to child development problems adjusting for maternal education level, maternal smoking and second hand smoke, pre-pregnant weight, marriage status, perceived pre-pregnant stress, and concurrent diseases during pregnancy including hypertension and diabetes.

Results: Compared with children with mothers reporting mild stress during pregnancy, those with mothers reported moderate/intensive stress had a much higher risk of having difficulties in solving problems (adjusted RR 2.69, 95% CI 1.24-5.71), fine motor problems (adjusted RR 2.04, 95% CI 1.30-3.20), and personal social problems (adjusted RR 1.86, 95% CI 1.03-3.36). However, maternal perceived stress was not significantly associated with communication problems (1.31, 0.67-2.59) or gross motor problems (0.46, 0.15-1.36).

Conclusions: Maternal perceived stress during pregnancy may adversely affect child development, especially in the aspects of problem solving, fine motor, and personal social activities. Prospective studies with larger sample size are warranted to further explore the causality between maternal stress during pregnancy and child development problems.

PO1.07.06
Sleep patterns during pregnancy and child neuropsychological and behavioral development: Mother-child cohort (Rhea Study) in Crete, Greece

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Background: Sleep in women is affected by the hormonal changes and physical discomforts associated with pregnancy. Despite the large body of data investigating the association of children’s sleep habits with behavioral difficulties, there are only a few studies evaluating the impact of sleep habits during pregnancy with child neurodevelopment. Maternal sleep disturbances during pregnancy, including sleep disordered breathing, poor sleep quality and short sleep duration, may impact child neuropsychological and behavioral outcomes. Sleep deprivation may result in increased stimulation of the inflammation pathway conferred from the mother to the fetus, while sleep disorder breathing has been associated with reduced oxygen delivery to the fetus. The present study aims to explore the association of maternal sleep habits during late pregnancy on child neuropsychological and behavioral development in preschool years.

Methods: The study included longitudinal data on 638 mother-child pairs participating at the 4 years of age follow-up of the Rhea mother-child cohort in Crete, Greece. Information on sleep patterns during pregnancy was collected through a computer-assisted interview. Furthermore, a total quality of sleep score was created based on the sum of 3 sleep-related responses: a) sleep duration (>8 hrs = 0, 6-7 hrs = 1, ≤5 hrs = 2), b) snoring (non-snorers (never/rarely) = 0, occasional snorers (sometimes/often) = 1, severe snorers (frequently/always) = 2), and c) excessive daytime sleepiness (Epworth Sleepiness Scale score: ≤ 10 = 0, 11-14 = 1 and ≥15 = 2). This score ranges from 0-6 with higher values indicating worse sleep quality. Children’s neuropsychological and behavioral development was assessed using the McCarthy Scales of Children’s Abilities (MSCA), the Attention Deficit Hyperactivity Disorder Test (ADHDRT) and the Strengths and Difficulties Questionnaire (SDQ). Multivariable linear regression models were used to investigate the associations between maternal sleep patterns and children’s neurodevelopmental outcomes after controlling for a wide range of confounders.

Results: Maternal sleep duration less than 8 hours was associated with reduced scores in the general cognitive scale (β = -2.28, 95% CI: -4.54, -0.02), while mild-severe daytime sleepiness was associated with reduced scores in the memory scale (β = -5.58, 95% CI: -11.1, -0.05) of MSCA. Snoring in late pregnancy was related to higher child hyperactivity scores in SDQ (β = 1.03, 95% CI: 0.14, 1.92). Further adjustment for child sleep patterns (duration and sleep breathing difficulties) did not meaningfully change the observed associations. Worse quality of sleep was associated with reduced scores in the memory scale (β per unit increase of the score = -1.87, 95% CI: -3.29, -0.46), increased conduct problems in SDQ (β per unit increase of the score = 0.17, 95% CI: 0.01, 0.33), and increased behavioral difficulties (β per unit increase of the score = 0.58, 95% CI: 0.12, 1.04).

Conclusions: Maternal sleep patterns during pregnancy may be associated with impaired child neuropsychological and behavioral development during the preschool years. Early detection and intervention is necessary to reduce or eliminate poor sleep habits in pregnancy and improve child neurodevelopment.

PO1.07.07

Maternal blood pressure trajectory during pregnancy and offspring neurodevelopment at 1 year old: a prospective cohort study in China


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Background: Hypertensive disorders in pregnancy is negatively associated with offspring adulthood neurodevelopmental outcomes. However, the knowledge on the association at early life remains little. In addition, the diagnosis of pregnancy-associated hypertensive disorders does not take into account the trajectory of maternal blood pressure trajectory during pregnancy. In this study, we aim to evaluate the association between maternal blood pressure trajectory and offspring neurodevelopment at 1 year old.

Methods: Between February 1st 2012 and April 30th 2015, 4,538 women with singleton delivery and neurodevelopment assessment from the Born in Guangzhou Cohort Study (BIGCS) were included into this study. Diagnosis of hypertensive disorders in pregnancy was extracted from medical records. Gesell instrument was used to assess the neurodevelopment of the offspring at 1 year old. Group-based trajectory (Proc Traj module in SAS) was used to differentiate different trajectories of maternal blood pressure during pregnancy and Analysis of Variance (ANOVA) to analyze the between-group differences in terms of five dimensions (Adaptive, Gross motor, Fine motor, Language and Social ability) of Gesell. Covariates include maternal age, pre-pregnancy BMI, parity, maternal income, maternal educational level and offspring birth weight Z score.

Results: There were three different trajectories to systolic blood pressure (SBP) measurements during pregnancy with 26.60% of women being classified in the low SBP group, 48.70% in the moderate SBP group and 24.70% in the high SBP group. Participants with higher trajectory tend to deliver less neuro-developed offspring than lower ones in terms of score differences from five dimensions of Gesell evaluation. With the highest trajectory being the reference, for Adaptive, the score
differences were 0.96 (95% CI 0.32 - 1.60) and 0.89 (95% CI 0.34 - 1.45) for lowest group and moderate group, respectively; for Gross motor, 1.08 (95% CI 0.27 - 1.90) and 0.90 (95% CI 0.19 - 1.61); for Fine motor, 1.37 (95% CI 0.66 - 2.08) and 1.00 (95% CI 0.38 - 1.62); for Language, 0.64 (95% CI -0.20 - 1.48) and 0.62 (95% CI -0.10 - 1.35); for Social, 1.05 (95% CI 0.24 - 1.87) and 0.43 (95% CI -0.28 - 1.14). Excluding those participants with positive diagnosis of hypertensive disorders in pregnancy did not substantially attenuate the observed association. Findings with regard to diastolic blood pressure (DBP) and mean arterial pressure (MAP) grouping were comparable to those of SBP.

**Conclusion:** Higher blood pressure during pregnancy is associated with offspring neurodevelopment during the first 6.5 years of life.

**PO1.07.08**

**Associations between maternal gestational weight gain and child neurodevelopment during the first 6.5 years of life**

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**Background:** It has been suggested that adverse intrauterine environment may directly damage the developing fetal brain causing offspring cognitive, behavioral and motor development delays. Maternal gestational weight gain (GWG) is one of the key markers of intrauterine nutritional environment and there would be a potential impact on future development of their offspring. We aimed to investigate the relationship between maternal GWG and standardized measures of mental and motor development in children participating in the PREOBE Study up to 6 years of life.

**Method:** GWG were classified into 3 groups (low, adjusted, upper) depending on the compliance to the international recommendations of the American Institute of Medicine (11.5–16.0 kg in normal weight women, 7.0–1.5 kg in overweight women, and 5.0–9.0 kg in obese women), and according to pre-conceptional body mass index (BMI). Children were assessed by Bayley III test at 6 and 18 months, Cumanin test and K-abc test at 3.5 years and BENCI neurobattery at 6 years. ANOVA, MANCOVA and Chi square tests were performed using SPSS version 23.0, and adjusted for confounding factors. All results were corrected by Bonferroni. P ≤ 0.05 was considered as significance level.

**Results:** At 6 months no significant results were shown, but at 18 months, infants born to mothers who achieved the recommended GWG according to their BMI during gestation, had a better development in gross motor skills, respect to those born to mothers who exceed the recommendations (p = 0.009, adjusted by maternal age and gestational diabetes (GD)). Furthermore, at 3.5 years, children born to mothers who comply with GWG recommendations have a higher score in articulatory language (Cumanin test) than children born to mothers who did not comply with the recommendations (low (p = 0.05); furthermore, children born to mothers who did not reach the recommendations, had a lower score in eye-hand coordination (Visomotor Cumanin test) respect to those born to mothers who exceeded the recommended weight gain (p = 0.05); these results were adjusted by maternal age, BMI and familiar situation). Finally, at 6 years, the results shown that children born to mothers who fulfilled the recommended GWG had higher score in verbal memory hits (third trial) than those born to mothers who exceeded this recommendation (p = 0.042, adjusted by maternal age).

**Conclusion:** GWG during pregnancy exert a significant long-term effect on children neurodevelopment. So, an optimal GWG should be encouraged to all pregnant women and especially if they are obese or develop GD.

**PO1.07.09**

**The association between low-to-moderate prenatal alcohol exposure and offspring structural brain morphology: a population-based MRI study**

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**Background:** Numerous reports have demonstrated the teratogenic effect of heavy prenatal alcohol exposure (PAE) on offspring brain structure and function. Microcephaly, alongside structural deformities of the basal ganglia, hippocampus and corpus callosum, are frequently reported to be associated with significant exposure of the foetus to alcohol. The impact of low-to-moderate drinking in pregnancy on neurodevelopment is less well understood, with a critical gap in the existing literature regarding low-level exposure. This is of particular interest given the conflicting results produced by observational studies examining low-to-moderate PAE and offspring cognitive outcomes. In this study we explored whether low-to-moderate alcohol exposure was associated with a reduction in total cortical surface area in late adolescence.

**Methods:** Participants included 451 mother-son pairs from the Avon Longitudinal Study of Parents and Children. Detailed questionnaire data regarding maternal alcohol consumption
was collected prospectively throughout pregnancy. Alcohol drinking in the first trimester was our primary exposure, defined over three categories: abstainers, low alcohol consumption (less than 1 alcoholic drink per week), and moderate alcohol consumption (between 1 and 6 alcoholic drinks per week). Structural magnetic resonance images (MRI) of the brain were collected at a single time point when the offspring were between 18 and 21 years of age (mean 19.55). Structural MRIs were processed using the automated FreeSurfer pipeline to derive total cortical surface area for each participant. A wide range of covariates relating to the prenatal and postnatal environment were examined as potential confounding variables. Of these, maternal smoking during pregnancy, antenatal depression, maternal education, maternal socioeconomic status and parity were selected to be included in our analyses.

Results: Linear regression models produced little evidence against the null hypothesis, including after adjustment for selected confounding variables. In unadjusted analyses, compared to the offspring of abstainers, offspring of low-level drinkers showed a larger (953.30 mm²) total cortical surface area (p = 0.18, 95% confidence interval (CI) -450.00, 2356.51 mm²). A larger total cortical surface area (815.71 mm²) was also observed in the offspring of moderate drinkers (p = 0.42, 95% CI -172.57, 2804.00 mm²). After adjustment for confounding variables, a larger total cortical surface area was also observed in both groups compared to the offspring of abstainers; by 748.47 mm² in the offspring of low-level drinkers (p = 0.33, 95% CI -760.38, 2257.33 mm²), and 1366.86 mm² in the offspring of moderate drinkers (p = 0.19, 95% CI -674.75, 3408.47 mm²).

Conclusions: The current analysis did not find any evidence to suggest that either low or moderate PAE are associated with a difference in total cortical surface area in late adolescence. This preliminary analysis will form part of a larger study which will include subjects from other population cohorts, and the association of low and moderate PAE on regional variations in brain structure will be examined.

POI.07.10
Maternal High Estradiol Exposure Impair Cognition of Offspring
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Background and aims: Accumulating researches suggest that exposure to abnormal environment in the uterus causes chronic diseases in future life. High intrauterine estradiol level is a major characteristic of in vitro fertilization. Here, we explored the potential nervous and mental harm of prenatal high estradiol exposure.

Materials and Methods: Patients who received fresh embryo transfer and of whom estradiol concentration on hCG administration day were >10,000 pmol/l were recruited in the reproductive center, women’s hospital, Zhejiang University from Dec 2006 to Dec 2007. Their children were brought back at the age of 3-7 and their intellectual development was evaluated by the Chinese Version of the Wechsler Intelligence Scale for Children-Revised. Moreover, a high estradiol intrauterine exposure mouse model was established. Behavior test was conducted to evaluate learning, memory, sociability, anxiety and depression of offspring, and gene expression profile of hippocampus was detected by microarray.

Results: A total number of 209 women were recruited in this study and 238 children completed the IQ tests. We performed linear correlation analysis between maternal serum estradiol level on hCG administration day and intellectual development of offspring, and the result showed that logarithm of maternal serum estradiol level on hCG administration day were negatively correlated with Verbal IQ, Performance IQ, and Full IQ. Intrauterine high E2 mouse model showed that intrauterine E2 exposure caused fetal weight decrease, learning and memory ability impairment, but no influence on anxiety and depression. Microarray showed prenatal high estradiol exposure altered the profile of hippocampus gene expression.

Conclusion: In conclusion, our data demonstrated that prenatal high estradiol exposure impair cognition function of offspring.

POI.07.11
White matter integrity showed an abnormal development in child born to mothers with high BMI
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Background: Recent researches have shown that maternal obesity influences an abnormal development of the white matter of the infant brain [1] but, as far as we know, no studies has examine if those effects remains in the long-term. This study aims to test whether maternal BMI is linked with the structural connectivity in the offspring brain at to the age of 6 years.

Methods: 116 children (50.9% boys, age 6.02 ± 0.02) born to mothers (age 31.4 ± 4.2, BMI range:18-40) involved in the PREOBE study [2] underwent a diffusion tensor imaging (DTI) session. DTI images were processed using the functional MRI of the Brain’s software library (FMRIB, FSL) [3]. Fractional anisotropy (FA) maps were computed using the dtifit tool from the FMRIB’s Diffusion Toolbox and probabilistic fiber tractography analyses were performed using the FSL plugin “AutoPtx” [4]. Mean FA values from each tract were extracted and used as dependent variable in the subsequent
analyses. Linear regression analyses were performed in SPSS using the Z score of the maternal BMI as the independent variable. Those regression analyses also included the age and sex of the child, the birth weight and the maternal age as covariates. 

**Results:** Maternal BMI was negatively related with FA values in the medial lemniscus tract ($r = -0.265$, $R^2 = 0.154$, $p = 0.003$). We also found negative tendencies between maternal BMI and FA values in the forceps major ($r = -0.177$, $R^2 = 0.047$, $p = 0.061$), the uncinate fasciculus ($r = -0.173$, $R^2 = 0.086$, $p = 0.061$), and the corticospinal ($r = -0.160$, $R^2 = 0.036$, $p = 0.091$) tracts. These results suggest that higher maternal BMI is related with lower integrity of the white matter microstructure of their offspring.

**Conclusions:** Maternal BMI is linked to long-term effects in some white matter tracts of the offspring brain. The medial lemniscus, the corticospinal and the forceps major tracts are involved in the proprioception, motor and visual functions; three main factors of the child development that showed an abnormal process in those children born to mothers with higher BMI. Damage of the microstructure of the uncinate tract has been previously related with social anxiety and depression symptoms.

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**References**


**PO1.07.12**

Transmission of maternal adverse childhood experiences to infant developmental outcomes: Findings from the All Our Families Cohort, Canada

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**Background:** Exposure to Adverse Childhood Experiences (ACEs) including abuse, neglect, and household dysfunction, has been associated with higher rates of depression in pregnancy, as well fertility difficulties and increased risk of fetal death (Benedict et al, 1999; Leeners et al., 2006; Roberts et al., 2013; Jacobs et al., 2015). A history of childhood maltreatment in mothers is associated with maladaptive infant socioemotional developments and a small body of research has started to examine the mechanisms by which this association is transmitted, including infant birth weight (McDonnell & Valentino, 2016). The current study examines mechanisms by which maternal adverse childhood experiences (ACEs) predict the early development of their offspring, specifically via maternal antepartum health and psychosocial risk in pregnancy.

**Methods:** Participants were 1,994 women (mean age = 30.87 yrs) and their infant who were recruited in pregnancy as part of a prospective longitudinal cohort from 2008 to 2011. Pregnant women completed self-report questionnaires in pregnancy related to psychosocial risk (e.g. poverty, low education, immigrant status, psychological difficulties) and a questionnaire about hostile behaviour when their infant was 4-months of age. A health care professional assessed the mother’s cumulative antepartum health risk (e.g. high maternal weight, diabetes, heart disease, hypertension, chronic renal disease, other medical disorders) in pregnancy and cumulative information about infant health risk at birth was obtained (i.e. low birth weight, congenital anomaly, low gestational age, neonatal intensive care unit admission). Mothers completed child development questionnaires when their infants was 12-months of age.

**Results:** Path analysis (see Figure 1) revealed that the association between maternal ACEs and infant development outcomes at 12 months operated through antepartum risk in pregnancy and infant health risk at birth. Maternal psychosocial risk in pregnancy also predicted infant development outcomes at 12 months via maternal hostile behavior when the infant was 4 months of age. These patterns were not explained by maternal age, child age, child sex, or maternal psychosocial risk in the postpartum period.

**Conclusion:** Both physical health and psychosocial risks in pregnancy may contribute to the transmission of vulnerability from maternal ACEs to child development outcomes in infancy. Maternal behaviour also appears to confer risk from psychosocial difficulties in pregnancy to child development outcomes and infant health risk contributes to the association between maternal physical health in pregnancy and child development outcomes. Maternal health and psychosocial well-being in pregnancy may be key targets for intervention to mitigate the transmission of risk from maternal adversity to their offspring’s development.

**Figure:***

Solid lines indicate sig. paths; dashed lines indicate non-significant paths (*$p < .05$; **$p < .01$). APRS: antepartum health risk score.
PO1.07.13

Maternal pregnancy disorders are associated with neonatal regulatory behavior problems and child developmental milestones: findings from the prospective PREDO Study

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Introduction: Maternal obesity, diabetes and hypertensive disorders have been linked with neurodevelopmental adversities in the offspring. It still remains unknown if these disorders are associated with early signs of offspring neurodevelopmental adversity, namely regulatory behavior problems in infancy. It also remains unknown if regulatory behavior problems mediate between these disorders and child neurodevelopment. The current study sought to determine associations between early pregnancy body mass index (BMI), gestational and chronic hypertension, pre-eclampsia, pre-pregnancy and gestational diabetes, and regulatory behavior problems of the offspring in infancy, and explored if neonatal regulatory behavior problems mediated between these maternal pregnancy disorders and developmental milestones of the offspring in early childhood.

Methods: The participants came from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) Study, which enrolled 4777 pregnant women who gave birth to a singleton live child between 2006 and 2010. This study sample comprised 3136 mother-child dyads. Data on early pregnancy BMI and diabetic and hypertensive pregnancy disorders were extracted from the Finnish Medical Birth Register (MBR). Neonatal regulatory behavior problems were mother-rated using the Neonatal Perception Inventory at the infant's average age of 16.9 days, and developmental milestones using the Ages and Stages Questionnaires at the child's average age of 42.2 months.

Results: Maternal overweight (BMI ≥ 25 kg/m²), obesity (BMI > 30 kg/m²), pre-pregnancy and gestational hypertension, pre-eclampsia, and pre-pregnancy and gestational diabetes, were not associated with neonatal regulatory behavior problems. Yet, they had an additive effect: neonates born to mothers having at least one of these conditions as opposed to none had higher levels of mother-rated regulatory behavior problems (β = 0.23 (0.04, 0.43), p = 0.02). Higher levels of regulatory behavior problems in the neonatal period were associated with lower total developmental milestones score, measuring motor function, verbal competence, problem solving and personal/social skills in childhood (β = -0.12 (-0.22, -0.01), p = 0.04). While children of women having any of the pregnancy disorders as opposed to none had lower total developmental milestones scores in the childhood period (β = -1.14 (-1.74, -0.53), p = 0.002), there was no mediation of these effects by neonatal regulatory behaviours on developmental milestones.

Conclusions: We showed that maternal obesity, diabetes and hypertensive disorders are associated with regulatory behavior problems of the offspring in infancy and lower developmental milestones total score in the childhood period. Even though regulatory behavior problems predicted the lower developmental milestones total score in the childhood period, regulatory behavior problems did not mediate the association of maternal pregnancy disorders and developmental milestones. This suggests that these disorders may affect neonatal regulatory behaviors problems and child developmental milestones via different mechanisms. Future studies need to unravel the mechanisms that underpin these effects.

PO1.07.14

Maternal thyroid dysfunction during pregnancy and behavioural and psychiatric disorders of children: A systematic review

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Background: Maternal thyroid dysfunction during pregnancy may lead to persistent neurodevelopmental disorders in the offspring appearing in later life. This study aimed to review the available evidence concerning the relationship between maternal thyroid status during pregnancy and offspring behavioural and psychiatric disorders.

Methods: Systematic electronic database searches were conducted using Pubmed, Embase, PsyCNET, Scopus, Google Scholar and Cochrane Library. Studies including gestational thyroid dysfunction as the exposure and offspring behavioural and psychiatric disorders as the outcome were included. The PRISMA guideline was followed and, after thorough screening by two independent reviewers, 12 articles remained eligible for inclusion in this study.

Results: Indicators of maternal thyroid dysfunction, including low and high thyroid hormone level and autoimmune thyroiditis, during early pregnancy, were found to be associated with several offspring behavioural and psychiatric disorders such as attention deficit hyperactivity disorder, autism, pervasive developmental problems, externalising behaviour, in addition to epilepsy and seizure. The majority of associations were found with low maternal thyroid hormone level.

Conclusion: Maternal thyroid function during pregnancy, particularly hypothyroidism, is associated with behavioural and psychiatric disorders in children. Further studies with a capacity to adjust for a fuller range of confounding factors and basic research aimed at elucidating the underlying biological mechanisms are needed.

PO1.07.15

Maternal pre-pregnancy obesity and childhood physical and cognitive development of children: a systematic review

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**Background:** Maternal obesity, usually associated with adverse birth outcomes, has been a serious public health concern. Studies examining its effect on the physical and cognitive development of children have only recently emerged and the findings are inconsistent. This review aimed to systematically examine the role of maternal obesity on children’s physical and cognitive development using the available evidence.

**Methods:** The CINAHL, EMBASE, PSYCINFO, PUBMED and SCOPUS databases were searched. Studies addressing children’s (≤12 years) physical and cognitive development as outcome and maternal pre-pregnancy body mass index (BMI) as an exposure were included. Data were extracted and evaluated for quality by two independent reviewers. Meta-analysis was not undertaken because of the heterogeneous measures of cognitive, language and physical development outcomes as well as the use of diverse BMI classifications.

**Results:** A total of 17 articles were eligible for this systematic review; 10 of them were birth cohorts from the USA. Nine of the fourteen studies supported an adverse association between maternal obesity and childhood cognitive development. A few studies also demonstrated a negative association between maternal obesity and gross motor function in children (5 of 10) but not with fine motor function (none out of five studies). Whether the observed negative association between maternal obesity and children’s cognitive and gross motor abilities is casual or due to residual confounding effects is unclear. The current evidence is based on a limited number of studies with heterogeneous measurement scales and obesity definition.

**Conclusions:** From the available evidence, it seems that exposure to maternal pre-pregnancy obesity in the intrauterine environment has a detrimental effect on children’s cognitive development. However, evidence of the association between maternal obesity and physical development of children is too scarce to offer a conclusion. More research work is required to delineate the intrauterine effect of maternal obesity from the residual confounding effects.

**PO1.07.16**

**Structural and functional alteration of developing rat cerebellum by administration of autism-inducing drugs**

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**Background:** Medicines and environmental chemicals make severe developmental neurotoxicity to embryo. Several chemicals are known to play some roles in onset of autism. Autism, a severe neurodevelopmental disorder, becomes increased in young age, and in human patients, cerebral and cerebellar developmental abnormalities are reported. Especially, reduction in size and number of Purkinje cells in cerebellum is revealed in both the postmortem human studies and some drug-administrated adult animals.

In this study, we investigated cerebellar cytological and behavior changes in developmental rat with some drug administrations.

**Methods:** Valproate (VPA), an antiepileptic drug, and Chlorpyrifos (CPF), an organophosphorus agent, are known as the candidates of inducer of autism. Because VPA is also known as a HDAC inhibitor, the effects of other HDAC inhibitors, suberoylanilide hydroxamic acid (SAHA), trichostatin A (TSA) and MS-275, were also investigated. Each drug was administrated to embryonic day 16 p.o. (VPA: 600mg/kg, MS-275; 4mg/kg, and CPF; 4.3mg/kg of mother weight, respectively) or i.p. (suberoylanilide hydroxamic acid, SAHA; 50mg/kg of mother weight).

**Results:** In normal cerebellar development, the soma of Purkinje cells form a single layer and elongate their dendrites with synapses during the first two weeks. In VPA-administrated rat, we have observed the elongation of Purkinje cell dendrites started earlier and reached all over the molecular layer even in P12. It was observed also in SAHA, or CPF administrated rat, while in MS-275 administrated rats, it was not. The behavior of VPA- or CPF-administrated animals was observed as same as control animals in the first week, however, VPA-administrated became differentiated from others in the second week. MS-275-administrated animals showed unique behavioral development. After the facilitation of Purkinje cell development in these drugs in the first week, excess folding in cerebellar lobules, especially in lobule V to VII, was formed in the second week. During the developmental progress, this excess folding was maintained with elimination of some Purkinje cells.

**Conclusions:** Some autism-inducing drugs changed developing cerebellar structures and functions. We suggest that drug-induced autistic model rat would become useful to evaluate the developmental neurotoxicity of a drug.

**PO1.07.17**

**Association between breastfeeding and better preserved cognitive ability in an elderly cohort of Finnish men**

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Background: Being breastfed in infancy has been shown to benefit neurodevelopment. However, whether the benefits persist to old age remains unclear.

Methods: We examined the associations between breastfeeding and its duration on cognitive ability in young adulthood and old age, and on aging-related cognitive change over five decades. 931 men from the Helsinki Birth Cohort Study born in 1934-1944 in Finland took the Finnish Defence Forces Basic Intellectual Ability Test (total and verbal, arithmetic and visuospatial subtest scores) twice, at ages 20.2 and 67.9 years, and had data on breastfeeding (yes vs. no) and its duration (never breastfed, up to 3, 3 to 6 and 6 or more months). We linked data from administrative and population medical registries. Linear and mixed model regressions tested the associations.

Results: At 20.2 years, breastfed men had higher cognitive ability total score and visuospatial subtest score (mean difference [MD] > 3.41 Intelligence Quotient [IQ] points, 95% Confidence Interval [CI] = 0.94, 5.88), and its longer duration predicted higher cognitive ability total and arithmetic and visuospatial subtest scores. At 67.9 years, breastfeeding (MD > 2.56 IQ points, 95% CI = -0.02, 5.14) and its longer duration were associated with higher cognitive ability total and all subtest scores. Verbal subtest scores decreased over five decades in men who were never breastfed or were breastfed for three months or less, and increased in those breastfed for longer than three months.

Conclusions: Neurodevelopmental advantages of breastfeeding and its longer duration persist into old age, and longer duration of breastfeeding may benefit aging-related change, particularly in verbal reasoning ability.

Change in cognitive ability verbal subtest score between 20.2 and 67.9 years according to duration of breastfeeding.

Association between prenatal manganese exposure and long-term neuropsychological development at 4 years old in a population-based birth cohort

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Background: Manganese is an essential micronutrient that plays a critical role in normal growth and development. Nevertheless, overexposure to Mn can also be detrimental to health and accumulation of Mn in the brain may result in neurotoxic effects. Previous studies reveal the complexity of the association given the differences in the child’s age or developmental and nutritional status (1). While in various transversal studies a negative association has been found with cognitive development (2, 3, 4), in cohort studies a positive trend has been observed with cognitive development and a lack of consistency with motor development (5, 6). There is also limited and inconsistent evidence of gender-specific neurological effects; generally greater effects in girls (2, 7), but also found in boys (8).

The goal of the study was to assess the association between Mn levels in hair at birth, derived from prenatal exposure, and longer-term neurodevelopment in a population based birth cohort derived from the INMA Project (Environment and Childhood).

Methods: Study subjects were 249 children, participants in the INMA (Environment and Childhood) birth cohort study. Pregnant women were recruited at the first trimester of pregnancy between 2006-2008 in Gipuzkoa, Spain (http://www.proyectoinma.org). Sociodemographic variables were collected through questionnaires in the 1st and 3rd trimesters of pregnancy. Atomic Absorption Spectrometry-furnace technique was used for Mn determination. The cognitive and psychomotor development was assessed at 4 years of age by using a standardized version of the McCarthy Scales of Children’s Abilities (9). The MSCA comprises 18 subtests that yield standardized test scores for six conventional domains (Verbal, Quantitative, Perceptive, Memory, Motor and General Cognitive). MSCA raw scores were centered to a mean of 100 and a standard deviation (SD) of 15 to homogenize the scales. Multivariate linear regression models were built for each cognitive and psychomotor scale. The sex specific association was also analysed by interaction analysis.

Results: Complete information was available for 249 children for whom we had data on both the Mn hair levels and neurodevelopment. The new-born hair Mn mean levels were 0.41µg/
g (SD = 0.34 μg/g). Overall results show no association between Mn levels and longer-term neurodevelopment. General cognitive score increases 0.93 points [IC95% = -4.67 to 6.53] and motor scale decreases points [IC95% = -6.36 to 4.35] per each Mn 1 μg/g increase but the associations are not statistically significant. A statistically significant interaction was found between sex and manganese for the Quantitative scale. While a positive association was found in boys (β = 6.84; 95% CI = -1.95 to 15.63) a negative association was found in girls. (β = -2.02; 95% CI = -10.06 to 6.02). This sex specific trend was found for all the neuropsychological scales except for Fine motor in boys and Gross motor in girls.

Conclusions: No statistically significant association has been found between prenatal Mn levels and longer-term neuropsychological development. There is a lack of consistency in the association between Mn and the different neuropsychological scales. Results suggest an opposite sex specific trend in the association between Mn and neurodevelopment, positive for boys and negative for girls.

PO1.08 – Nutrition – Metabolic health, socio-economic and behavioural factors

PO1.08.01
Effect of infancy-onset dietary counselling on a comprehensive metabolic profile from childhood to early adulthood

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Background: Dietary choices may delay or prevent atherosclerosis. Effects of dietary saturated fat replacement on circulating concentrations of metabolic biomarkers remain unknown. We studied the effects of repeated, infancy-onset dietary counselling on a detailed metabolic profile.

Methods: The Special Turku Coronary Risk Factor Intervention Project (STRIP) study is a longitudinal, randomized atherosclerosis prevention trial in which repeated dietary counselling aimed at reducing the proportion of saturated fat intake. Nuclear magnetic resonance metabolomics quantified circulating metabolites from serum samples assessed at age 9 (n = 554), 11 (n = 553), 13 (n = 508), 15 (n = 517), 17 (n = 457) and 19 (n = 417).

Results: Intervention reduced dietary intake of saturated fat (mean difference in daily percentage of total energy intake: -2.1 [95% confidence interval: -1.9, -2.3]) and increased intake of polynsaturated fat (0.6[0.5, 0.7]). The intervention led to higher proportions of polynsaturated fat (P < 0.001), with higher proportions of omega-3 (P = 0.02) and omega-6 (P < 0.001) fatty acids. The proportion of saturated fatty acids in serum was lowered for both sexes (P < 0.001). The proportion of monounsaturated fat was lower for intervention boys (P < 0.001). The intervention reduced intermediate-density-lipoprotein and low-density-lipoprotein lipid concentrations (P < 0.01). Very-low-density lipoprotein lipid concentrations and particle size were reduced for the intervention boys. Effects on non-lipid biomarkers were minor.

Conclusions: Repeated dietary counselling from infancy to early adulthood yielded favourable effects on multiple circulating fatty acids and lipoprotein subclass lipids, particularly in boys. These molecular effects substantiate the beneficial role of saturated fat replacement on the metabolic risk profile.

PO1.08.02
No adverse metabolic programming of dietary fructose versus glucose post-weaning by extensive basal and challenged phenotyping in mice

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Background: Nutrition in early post-weaning life can have long-lasting consequences by programming metabolic health into adulthood. Diets of children contain a large amount of simple sugars nowadays, and especially the monosaccharide fructose is suspected to contribute disproportionally to obesity and metabolic disorders. This study aimed to assess whether fructose, in comparison to glucose, in the post-weaning diet programs body weight, adiposity, glucose tolerance, and metabolic flexibility at adult age.

Methods: Three-week-old male (n = 12) and female (n = 14) C57BL/6JrccHsd mice from standardized nests were placed on a control post-weaning low fat intervention diet with 32 energy percent (en%) glucose (GLU) or fructose (FRU) for three weeks. Afterwards, all animals were switched to the same 45en% humanized high fat diet (HFD) for nine weeks. Body weight, food intake, and body composition (lean and fat mass; Echo-MRI) were determined (bi)weekly. Indirect calorimetry (TSE) was used for basal and fasting-refeeding challenged energy expenditure and substrate usage in weeks 5 and 14; after fasting in light phase, mice were refed with GLU diet. A standard oral glucose tolerance test (2 g glucose/kg body weight by gavage) was performed in week 11 with blood glucose levels measured till 120 minutes. At sacrifice, blood and tissues were isolated, and livers were used to determine triglycerides levels using standardized protocols.

Results: Body weights and fat mass did not differ between GLU- and FRU-fed groups. Also after the switch to HFD,
body weights and fat mass remained similar between the two groups. Glucose tolerance, assessed in week 11, and metabolic flexibility, studied with a fasting-refeeding challenge in week 5 for direct nutritional effects and in week 14 for metabolically programmed effects, were not altered by the post-weaning intervention diet. At the end of the study in week 15, serum insulin levels and HOMA-insulin resistance index in FRU-fed females were significantly lower than in GLU-fed females, with similar glucose levels, yet in males no differences were observed. Liver triglycerides levels were not affected by the post-weaning diet in either sex.

Conclusions: In conclusion, there was no adverse metabolic programming of dietary fructose in the post-weaning diet in comparison to glucose on body weight, adiposity, glucose tolerance, and metabolic flexibility in both females and males. However, high fat diet-induced insulin resistance was decreased by post-weaning FRU diet, but only in female mice.

PO1.08.03
Diet quality in early and mid-childhood in relation to growth and body composition
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Background: A poor diet in childhood is associated with several adverse health outcomes in children, such as poor growth or obesity. Obesity in childhood may cause serious health complications in childhood, and it may increase the risk of obesity in adulthood and thereby the risk of chronic diseases. Therefore, it is important to study the role of diet in childhood in the prevention of obesity. Several previous studies that examined these associations often focused on BMI as a measure of obesity. However, BMI only is not a good measure of adiposity, since it does not distinguish between fat mass and lean mass. Therefore, we aimed to explore the associations of overall diet quality of children aged 1 year and 8 years with their growth and detailed measures of body composition up to the age of 10 years. In addition, we aimed to examine the direction of the association between diet quality and these outcomes. Furthermore, we examined whether associations are independent of diet quality at the other time point, and whether associations differ between boys and girls.

Methods: We included 3,991 children participating in the Generation R Study, a population-based, prospective cohort in the Netherlands. At their ages of 1 year and 8 years, dietary intake was assessed using validated food-frequency questionnaires, and diet quality scores were calculated, measuring adherence to age-specific dietary guidelines. Around the ages of 6 and 10 years, height and weight were measured and body composition was assessed using dual-energy X-ray absorptiometry. We calculated body mass index (BMI), fat mass index (FMI), and fat-free mass index (FFMI). All outcomes were expressed in sex- and age-specific standard deviation scores (SDS). Multivariable linear regression analyses were used to analyze associations of diet quality with growth and body composition, and path models were used to analyze bidirectional associations.

Results: After adjustment for lifestyle and sociodemographic factors, children with a higher diet quality at the ages of 1 year and 8 years, had a higher height, weight, and BMI at the age of 10 years. The association of diet quality at 8 years with a higher BMI was fully driven by a higher FFMI (0.07 SDS, 95%CI: 0.05, 0.10), but not FMI. This association was independent of diet quality in early life. In line with this, a higher BMI at age 6 years predicted a higher diet quality score at age 8 years (0.13, 95%: 0.08, 0.17). For diet at the age of 8 years, associations were stronger in girls than in boys.

Conclusion: We observed that a higher diet quality in childhood was associated with a higher height, weight, and FFMI, but not FMI around the age of 10 years. These associations were independent of diet quality in early life. Our findings suggest that a dietary intake according to dietary guidelines, both in early and mid-childhood, may have a beneficial effect on growth, and decreases the risk of obesity.

PO1.08.04
Rates of growth during nutritional rehabilitation, whole-body fat oxidation and fatty liver disease in adult survivors of severe acute malnutrition
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Background: Severe acute malnutrition (SAM) in infancy is associated with later cardiometabolic risk. The clinical phenotype of marasmus is associated with lower birth weight (BW), increased cardiometabolic risk and more liver fat as adults compared to kwashiorkor. Additionally, birth weight is inversely associated with liver fat and this may be mediated by whole-body fat oxidation. Nutritional rehabilitation in SAM promotes catch-up growth (CUG), to attain 90-110% weight-for-height. Catch-up in height usually follows weight repletion. However, a rapid increase in size may worsen cardiometabolic risk factors. We hypothesized that rapid CUG weight gain during hospitalization as well as height gain post-discharge are correlated with more fatty liver in adult survivors of marasmus (MS) and kwashiorkor (KS). We also hypothesized that greater liver fat in MS is associated with lower BW and reduced whole-body fat oxidation.

Methods: We recruited Jamaican adult survivors of SAM (42 MS, 40 KS) and 64 unexposed community controls matched by age, sex and BMI. From the hospital records of the SAM survivors, we abstracted BW and weights and heights measured during hospitalisation for SAM up to 2 years post discharge. A 5-mm slice abdominal CT scan, taken at the T12/ L1 disc space, was used to estimate liver fat. Three regions of interest were placed in the liver and one in the spleen. The liver fat outcome variables (mean liver attenuation and liver spleen...
ratio) were treated as continuous variables. Indirect calorimetry was conducted in 27 MS, 30 KS and 64 controls to estimate whole-body fat oxidation.

**Results:** The participants were 50% men, aged 28.8 ± 8.2 years; BMI was 23.5 ± 5.0 kg/m² (mean ± SDs). BW was lower in MS (2.5 kg vs 3.0 kg; \( P = 0.01 \)) and was not associated with liver fat. KS gained weight at a faster rate during catch-up growth \( (P = 0.05) \). In MS, but not KS, rate of catch-up weight gain was inversely correlated to both mean liver attenuation \( (r = -0.45, P = 0.004) \) and LS ratio \( (r = -0.48, P = 0.005) \) and this association was not altered by BW. Gains in height were not associated with liver fat after adjusting for admission height-for-age. MS and KS had similar resting energy expenditure and whole-body fat oxidation. Adjusting for age, sex and BMI, there was no correlation between birth weight and fat oxidation and no correlation between fat oxidation and LS ratio, or mean liver attenuation \( (P-values > 0.1) \).

**Conclusion:** In MS, faster catch-up weight gain from childhood SAM was associated with greater liver fat even though they gained weight more slowly than KS. Marasmus, the more wasted syndrome, might be more susceptible to risk associated with rapid weight gain which may predispose to higher cardiometabolic risk. Whole-body fat oxidation was not associated with birth weight or liver fat in adult survivors of SAM.

**PO1.08.06**

**Breastfeeding and infant body mass index: associations differ according to method of milk feeding and type of complementary nutrition**

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**Background:** The global obesity epidemic is a major public health challenge, and its origins are rooted in early life. Breastfeeding may protect against childhood obesity, although existing evidence is inconsistent. Epidemiologic studies rarely identify the method of breast milk feeding (direct breastfeeding at the breast versus bottled breast milk) and often do not specify the type of complementary nutrition provided to partially breastfed infants (formula versus solid foods). We aimed to document these nuances of infant feeding in a large national birth cohort, and determine their association with body mass index in the first year of life.

**Methods:** Infants were enrolled in the http://www.canadian-childstudy.ca. The main exposure was infant feeding, reported at 3, 6 and 12 months. Breastfeeding was classified as exclusive, partial, or none. At 3 months, exclusive breastfeeding was sub-

**PO1.08.05**

**Advising consumption of green vegetables, beef and full-fat dairy products has no adverse effects on the lipid profiles in children**

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In children, little is known about lipid profiles and the influence of dietary habits. In the past, we developed a dietary advice for optimizing the immune system, which comprised green vegetables, beef, whole milk and full-fat butter. However, there are concerns about a possible negative influence of the full-fat dairy products of the diet on the lipid profile. We investigated the effect of the developed dietary advice on the lipid profile and BMI/BMI-z-score of children. In this retrospective cohort study, we included children aged 1 to 16 years, of whom a lipid profile was determined in the period between June 2011 and November 2013 in our hospital. Children who adhered to the dietary advice were assigned to the exposed group and the remaining children were assigned to the unexposed group. After following the dietary advice for at least 3 months, there was a statistically significant reduction in the cholesterol/HDL (High-Density Proteins) ratio \( (p < 0.001) \) and non-HDL-cholesterol \( (p = 0.038) \) and a statistically significant increase in the HDL-cholesterol \( (p = 0.006) \) in the exposed group, while there was no difference in the BMI and BMI-z-score. The dietary advice has no adverse effect on the lipid profile, BMI and BMI-z-score in children but has a significant beneficial effect on the cholesterol/HDL ratio, non-HDL-cholesterol and the HDL-cholesterol.
classified according to feeding method (direct breastfeeding only, or including some bottled breast milk). At 6 months, partial breastfeeding was sub-classified according to type of supplementation (without formula; solid foods only, or with formula; with or without solid foods). The main outcome was infant body mass index z-score (BMIZ) at 1 year, calculated according to the World Health Organization reference standard from measurements taken by study staff. Associations were determined by linear regression with adjustment for maternal BMI, ethnicity, education, smoking, infant sex and birth method.

Results: Among 2892 infants assessed at 1 year, the mean BMIZ was +0.18 ±1.06. At 3 months, 61% of infants were exclusively breastfed (28% direct breastfeeding only; 33% with some bottled breast milk), 26% were partially breastfed, and 14% were not breastfed. At 6 months, 18% were exclusively breastfed, 59% were partially breastfed (33% without formula; 26% with formula), and 23% were not breastfed. Nearly half (45%) were breastfed at least 12 months. Compared with exclusive direct breastfeeding, all other feeding styles at 3 months were associated with significantly higher BMIZ by 1 year: adjusted beta estimate (95%CI) +0.14 (0.03, 0.24) for some bottled breast milk; +0.30 (0.03, 0.24) for partial breastfeeding with formula; +0.41 (0.28, 0.55) for no breastfeeding. Similarly at 6 months, partial breastfeeding with formula (+0.28; 0.16, 0.40) and no breastfeeding (+0.43; 0.30, 0.55) were associated with higher infant BMIZ; however, partial breastfeeding without formula was not significantly associated with infant BMIZ (+0.09; -0.03, 0.21). In a sensitivity analysis, results were similar following adjustment for breastfeeding duration.

Conclusions: Our results confirm that formula feeding is associated with higher infant BMIZ in the first year of life, and demonstrate two novel features of this association. First, providing bottled breast milk is not equivalent to direct breastfeeding in this context. Second, providing solid foods (without formula) to breastfed infants before 6 months is not significantly associated with BMIZ at 1 year. These nuances could help explain the inconsistencies observed across previous studies where infant feeding methods are not precisely captured. Ongoing research in the CHILD Study will address causal mechanisms (eg. appetite regulation, psychosocial effects, breastmilk bioactives) and evaluate associations with obesity later in childhood.

**Infant feeding and BMIZ score in the first year of life in the CHILD cohort (n=2892).**

<table>
<thead>
<tr>
<th>Infant Feeding</th>
<th>BMI z-score at 1 year</th>
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<tr>
<td></td>
<td>n</td>
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<tr>
<td>Feeding at 6 months</td>
<td></td>
</tr>
<tr>
<td>Exclusive BF, all direct breastfeeding</td>
<td>763</td>
</tr>
<tr>
<td>Exclusive BF, some bottled breast milk</td>
<td>920</td>
</tr>
<tr>
<td>Partial BF with formula</td>
<td>710</td>
</tr>
<tr>
<td>No BF</td>
<td>376</td>
</tr>
<tr>
<td>Feeding at 6 months</td>
<td></td>
</tr>
<tr>
<td>Exclusive BF</td>
<td>514</td>
</tr>
<tr>
<td>Partial BF without formula (+ solids)</td>
<td>934</td>
</tr>
<tr>
<td>Partial BF with formula (+ solids)</td>
<td>752</td>
</tr>
<tr>
<td>No BF</td>
<td>630</td>
</tr>
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</table>

BMI, body mass index; SD, standard deviation. Adjusted for maternal BMI, ethnicity, smoking, infant sex, and method of birth. Significant associations (p<0.05) are shown in bold. n=2892 infants with BMIZ data at 1 year; feeding data were missing for 113 infants at 3 months and 92 infants at 6 months.

Infant feeding and BMIZ score in the first year of life in the CHILD cohort.

**PO1.08.07**

Anthropometry and body composition in infants of malnourished Bangladeshi women supplemented or not supplemented during pregnancy

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Background: In 2005, 32% of mothers of under-5 children in Bangladesh were underweight (BMI <18.5 kg/m²), whilst 36% of newborns in the country were Low Birth Weight (LBW) in 2003. Between 1995 and 2010, the National Nutrition Programme supplemented pregnant women with BMI < 17 kg/m² (low BMI) in increasing numbers, covering at its peak one quarter of the country. The objectives of the NNP were to increase mean pregnancy weight gain to ≥9 kg in 50% of these mothers and to reduce LBW incidence to 20% by 2010.

In an initial assessment of the NNP, it was found that four months of maternal supplementation were associated with an 118g increase in birth weight. Our study investigated whether supplementation primarily affected infant lean or fat tissue.

Methods: Between April 2010 and September 2011, a total of 90 pregnant women were recruited early in the 2nd trimester in three groups: 31 low BMI women from intervention areas; 29 low BMI women from control areas; 30 normal BMI (18.5-22.9 kg/m²) women, in equal proportions from control and interventions areas. The daily supervised supplement for low BMI women in intervention areas comprised a mixture of roasted lentils, roasted rice, molasses and soya bean oil, providing 600 kcal/day from the 1st trimester to the end of pregnancy. Socioeconomic status, anthropometry and health related information was collected at recruitment. After delivery, anthropometry was done on both mother and offspring (birth and 14-27 days), along with assessment of body composition by bio-impedance analysis (BIA) in mothers and stable isotope (18O-labelled water) in the infants at 14-27 days.

Results: The intervention promoted subcutaneous adiposity in low BMI mothers, but not lean mass estimated by BIA. Contrary to expectations, the main effect of the intervention on the neonate was a significant deficit in length (Δ = -1.6 cm, 95% CI -2.5, -0.7) but no difference in weight or BMI compared to the unsupplemented group. Offspring of supplemented mothers did however grow faster in length between birth and 14-27 days of age. At this follow-up time, infants of supplemented mothers still had shorter length (Δ = -0.89 cm, 95% CI -1.8, 0.02), slightly lower lean mass (Δ = -2.5 mm, 95% CI -3.4, -1.6), and higher skinfolds (triceps: Δ = 2.5 mm, 95% CI 1.7, 3.2; subscapular: Δ = 0.8 mm, 95%CI 0.2, 1.5) compared to those of unsupplemented mothers. The offspring of supplemented malnourished mothers were also shorter than...
those of normal BMI mothers (neonate: -1.2 cm, 95%CI -2.2, -0.3; infant: -1.0 cm, 95%CI -1.2, 0.1), whereas those of un-supplemented malnourished mothers were similar to those of normal BMI mothers (neonate: 0.3 cm, 95%CI -0.7, 1.3; infant: -0.1 cm, 95%CI -1.1, 1.0)

**Conclusions:** The only potential benefit of the intervention was that infants of supplemented malnourished mothers had faster gain in length after birth. They therefore made good some, but not all, of their birth length deficit, and such catch-up might continue subsequently. Overall, the increased energy from supplementation primarily benefited mothers rather than their offspring, while their offspring were also fatter.

**PO1.08.08**

Maternal protein intake during pregnancy impacts child growth up to five years of age: Findings from the ROLO Study

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**Background:** Protein intake in infancy has been shown to increase child growth however research on maternal protein intake in pregnancy is limited. Insulin-like growth factors (IGFs) are thought to play a vital role in early fetal development with low IGF-1 levels being associated with low birth weight. It is hypothesised that maternal protein intake can influence child weight by influencing IGF-1 levels.

**Aim:** Investigate the association of maternal protein intake during pregnancy and IGF-1 on child body composition up to 5 years of age.

**Methodology:** Analysis was carried out on 570 mother-child dyads from the ROLO study (Randomised cOntrol trial of LOw glycaemic index diet). Protein intake (g/day) was recorded using 3-day food diaries in each trimester of pregnancy and protein intake per kg of maternal body weight (g/day/kg) was calculated. IGF-1 was measured in cord blood. Infant height, weight and anthropometry were recorded at birth, 6 months, 2 years and 5 years of age. Mixed modelling, linear regression and mediation analysis was carried out.

**Results:** IGF-1 was not associated with dietary protein intake during pregnancy. Trimester 2 absolute protein (g) was positively associated with birth weight and weight centile ($P <0.001$). Child weight at 5 years was negatively associated with first trimester protein g/day/kg intake, above that seen for the influence of protein on birth weight ($P <0.01$). Weight centile was negatively associated with first trimester protein g/day/kg intake at birth however this relationship reversed with a negative association being identified at 2 and 5 years of age ($P <0.5$). Child length was also negatively associated with trimester 1 protein intake (g/day/kg) up to 2 years of age ($P <0.001$). Less than 1% of these associations were mediated by IGF-1.

**Conclusion:** Maternal protein influenced child weight and length up to 5 years of age. Interestingly, maternal protein intake in early pregnancy appears to exert an in-utero influence on infant body composition with a higher weight initially at birth but slower growth as the child ages. These associations were not mediated by IGF-1. Further research is needed to elucidate the exact mechanisms by which dietary protein modulates fetal growth.

**PO1.08.09**

Maternal early-pregnancy determinants of childhood eating behaviour and dietary patterns at aged 6 years: Children of SCOPE

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**Background:** Observational studies suggest a robust association between maternal BMI (body mass index) and offspring adiposity. Mechanistically, this could reflect persistence of in utero influences of maternal BMI on childhood pathways of energy balance and appetitive behaviours, as suggested in animal models. It is recognised that eating behaviours acquired during childhood may persist into adulthood. However, there is limited information on the effect of maternal BMI on offspring dietary patterns and eating behaviours; a better understanding is required. We examined relationships between maternal BMI, childhood eating behaviour and dietary patterns in the Auckland Children of SCOPE study, a prospective cohort of 1,208 children born to nulliparous mothers in the International SCOPE cohort.

**Methods:** Maternal BMI was measured at 14-16 weeks’ gestation. A Food Frequency Questionnaire (FFQ) and the Child Eating Behaviour Questionnaire (CEBQ) were administered when the offspring were aged 6 years; factor analysis was used to characterise dietary patterns. The relationship between maternal BMI and CEBQ assessments of eating behaviours and dietary patterns were examined using linear regression, adjusting for potential socioeconomic confounders. Effects are expressed as standardised beta coefficients. Pearson correlation was used to examine the association between CEBQ assessments and dietary patterns.

**Results:** Among 1,173 (97.1%) mother-child dyads responders, mean (standard deviation) maternal early-pregnancy BMI was 24.7(4.16)kg/m². 118(10.1%) were obese women (BMI ≥30). After adjustment, there were associations between higher maternal BMI and higher child’s satiety responsiveness ($β = 0.02$ (95%CI 0.01 to 0.03), $p = 0.02$) and desire to drink ($β = 0.02$ (0.01 to 0.03), $p = 0.03$). There was a correlation between desire to drink and consumption of sugar sweetened beverages ($r = 0.09$, $p < 0.01$). Factor analysis identified two distinct dietary patterns at age six (N = 1,108); ‘Healthy-Balanced’ (HB) and ‘Processed & Snacks’ (P&S). HB was characterised by high loadings (>0.25) on foods such as fruit, vegetables, fish and legumes. P&S was characterised by foods...
such as processed meats and sugar sweetened beverages. After adjustment, there was an association between higher maternal BMI and lower childhood HB ($\beta = -0.02$ ($95\%$CI -0.04 to -0.01), $p < 0.01$). Compared to mothers with a normal BMI, maternal obesity was associated with lower child’s HB diet ($\beta = -0.24$ ($95\%$CI -0.44 to -0.04), $p < 0.02$). The mean z-score for the child’s P&S dietary pattern was similar across maternal normal, overweight and obese BMI groups. Desire to drink was associated with lower HB ($r = -0.07$, $p = 0.03$) and higher P&S dietary pattern scores ($r = 0.15$, $p < 0.01$). Likewise, higher satiety responsiveness was associated with lower HB ($r = -0.18$, $p < 0.01$) and higher P&S scores ($r = 0.06$, $p = 0.05$).

**Conclusion:** Although weak associations were observed, our data suggests that among women with a heterogeneous BMI, higher maternal BMI is unlikely to play a major role in determination of offspring adiposity through the mechanism of eating behaviours and habits. Although effects were small, significant findings warrant further investigation of maternal diet to assess the overall impact of maternal influences on food behaviour and dietary patterns during childhood.

**Funding:** The Children of SCOPE Study was funded by Health Research Council of New Zealand, Cure Kids and Gravida. LP and PTS are supported by Tommy’s Charity

**PO1.08.10**

High fat and very low carbohydrate intake during pregnancy does not influence the folate nutritional status in mother and foetuses

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**Background:** Gluconeogenesis commonly occurs during gestation in humans because of hyperemesis gravidarum or gestational diabetes. According to a recent study, a mother’s nutritional status during gestation may affect methylation modifications on the pup’s DNA before and/or after birth. However, the effects of maternal gluconeogenesis enhancement during gestation in terms of their pups’ vitamin B$_{12}$ (VB$_{12}$) and folic acid status are not fully understood.

**Methods:** On day 1 of gestation, rats were separated into two groups and fed either a control or ketogenic diet (KD), i.e. a diet particularly high in fat and low in carbohydrate content, until day 20 of gestation (G20). We then analysed ketone body and glucose levels in maternal and foetal blood, as well as two water-soluble vitamins, VB$_{12}$ and folic acid, in maternal and foetal blood and amniotic fluid.

**Results:** Maternal body weight, foetal weight and litter size did not differ between the two groups at G20. Maternal and foetal ketone body levels in blood increased in the KD group, while VB$_{12}$ and folic acid levels did not change in all samples from the two groups.

**Conclusions:** Maternal gluconeogenesis enhancement by KD feeding does not affect maternal and foetal folic acid and VB$_{12}$ nutritional requirements at G20. The effects of KD on methylation modifications of DNA and pup development after birth require further clarification.

**PO1.08.11**

Study protocol: Why pregnant women eat what they eat. Socio-ecological determinants of antenatal diet and development of an intervention tool

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**Background:** Although the importance of maternal nutrition is evident, pregnant women - especially in lower socioeconomic status (SES) populations - do not meet nutrition guidelines sufficiently. Healthy nutrition promotion in midwifery practice is promising as antenatal diet affects both maternal and child health, pregnant women are open to dietary changes during this critical transition and midwives are their first and most important source of information.

Unfortunately, nutrition communication by Dutch midwives is currently limited and focuses primarily on risks and problems. To provide nutrition advice, insight into the multiple personal, cultural and environmental factors that influence dietary intake (i.e. contextual dietary intake) is needed. Moreover, midwives need knowledge, skills and feasible tools to assess contextual dietary intake and optimize antenatal nutritional status in collaboration with dietitians. This research will contribute to the (further) development of a tool that can be used by midwives and/or dietitians to assess and optimize contextual dietary intake of pregnant women and their families. The overall goal of this project is improvement of nutritional status of low SES pregnant women in the Netherlands.

**Methods:** To map socio-ecological determinants of dietary intake during pregnancy, literature studies will be performed as well as interviews and focus groups with pregnant women and their partners. Midwives will be interviewed to gain insight in their current knowledge, needs and practice. Recruitment will be directed at pregnant women with low SES, through midwives working in low SES areas. Data on dietary intake will be obtained by trained research dietitians using the dietary history method and used to develop a dietary tool. About 100 extra individual consultations and 20 extra Centering Pregnancy group meetings will be organised, video-recorded and qualitatively evaluated to investigate barriers and facilitating factors for using the newly developed tool/method. A realist evaluation perspective will be used to identify key combinations of contextual factors and mechanisms that trigger outcomes of interest. Dietary histories will be transcribed into food codes using the Dutch food composition database and amounts using information on standard Dutch food portion sizes. Total energy and nutrient intakes will be calculated in Complex™ by multiplying intakes by nutrient composition using the same
food composition database. Additionally, biomarker data on folate and vitamin D status will be obtained.

Discussion: This study is scientifically and socially relevant as low SES pregnant women’s contextual dietary intake is studied in depth from an ecological perspective on health and subsequently piloted in real-life practice. Innovatively, midwives, dietitians and pregnant women are engaged in research activities, resulting in context-sensitive usable knowledge that will increase implementation chances. The obtained results will lead to recommendations for multidisciplinary strategies to promote healthy antenatal nutrition in low SES populations.

PO1.08.12

Methionine supply and tissue glutathione in the pregnant rat.

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Background: Glutathione (GSH) is the principal intracellular mediator of antioxidant defence during intrauterine life. The supply of cysteine is rate limiting for GSH synthesis. In addition to dietary sources, cysteine is also a by-product of the methionine cycle, reactions which involve folic acid and choline. As a result methyl metabolism influences the supply of methionine and the production of GSH. It has been suggested that diets deficient in folic acid increase homocysteine and the resulting oxidative stress may affect the developing brain (1).

The aim of this study was to examine the effects of diets deficient in methyl donors (folic acid, choline and methionine) on tissue glutathione concentrations.

Methods: Five groups of Hooded-Lister strain female rats were fed control diet, folate deficient diet (-F), folate deficient low methionine diet (-F LM), folate deficient low choline diet (-F LC) and folate deficient low methionine low choline diet (-F LM LC) described previously (2). After an acclimatisation period, animals were mated and maintained on experimental diets until necroscopy on day 21 of gestation. Total glutathione (GSH) content of the dams liver, together with the brain and liver of the fetuses was measured by the enzyme recycling method (3).

Results: The growth of the animals has been described previously (2). Weight gain in animals fed the -F LM LC diet was approximately 15% less than in the control group. Fetuses of dams fed the -F diet were approximately 18% heavier (4.84 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g) than the controls (4.10 ± 0.07g). Forehead fat was increased by 23% (P = 0.006) in animals fed the SACN diet. This pattern of food intake continued during gestation.

Conclusions: When compared to the control, diets restricted in methionine reduce hepatic GSH concentrations in the maternal liver. This decrease was greater when the diet was additionally deficient in folic acid and choline, conditions which reduce the flow through the methionine cycle (4). The increase in GSH concentrations the folate deficient group is unexplained but may relate to the increased growth of these animals. In contrast to the changes in maternal tissues, GSH concentrations are not changed in the fetal liver where methionine synthesis is maintained (4). GSH the fetal brain of animals fed the LM diets tends to be reduced only slightly.


PO1.08.13

Fetal and maternal corticosterone concentrations in pregnant rats fed a diet reflecting that of the poorest socioeconomic group in Scotland

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Background: Human diets are complex and deficiency or excess of a single nutrient is rarely encountered. For example, pregnant women in deprived populations in Scotland have a poor micronutrient status in addition to a very high intake of saturated fat, refined carbohydrates and salt (1). To investigate the cumulative effects of over provision of energy substrates, combined with multiple micronutrient deficiencies we have developed a rodent diet which models the pattern of nutrient intake of women in the most deprived group of the Scottish population. One consequence of this diet with high levels of both fat, sugar and salt may be an increase in glucocorticoids in the maternal circulation.

Methods: A rodent diet (SIMD) was formulated with a macronutrient composition based on the median intakes of pregnant women in tenth decile of the Scottish index of multiple deprivation (1). The micronutrient composition of this diet, based on the same data, was adjusted using the principle of energy balance. A second diet formula incorporated the recommendations of the Scientific Advisory Committee on Nutrition, i.e. low in saturated fat and sugar with reduced salt and with the micronutrients adjusted to meet the recommended intakes (SACN). Three groups of Hooded-Lister strain female rats were fed either the SIMD, SACN or AIN-93 G diet (reference). Animals were fed the experimental diets for an adaptation period of 3 weeks. Body composition was determined by MRI. After being mated with normal males, the females continued to be fed the experimental diets until they were killed on d21 of gestation. Plasma metabolites were measured by standard methods. Plasma glucocorticoids were measured by ELISA (Bio-Techne)

Results: Food intake during the adaptation period was 10% lower in the animals fed the SIMD diet (P = 0.005) and body fat was increased by 23% (P = 0.006) in animals fed the SACN diet. This pattern of food intake continued during gestation.

Conclusions: Weight gain in animals fed the -F LM LC diet was significantly lower in the animals fed the -F LM LC diet (P = 0.006) and body fat was increased by 23% (P = 0.006) in animals fed the SACN diet. This pattern of food intake continued during gestation.
Maternal body fat at d21 was increased in both experimental diet groups compared to the AIN-93 G however there were no significant differences in litter size and fetal weight. In d21 blood samples circulating triglyceride was 33-82% (P = 0.049) higher in maternal plasma from SIMD and SACN animals. Corticosterone concentrations in fetal plasma were higher than in maternal but there were no differences between the diet groups.

**Conclusions:** Humanised rodent diets high in fat, sugar and salt and low in micronutrients produce marked changes in lipid metabolism and deposition. However the plasma corticosterone levels were not increased at d21 in the maternal or fetal circulation, suggesting that altered glucocorticoid status is not a causative factor in this model.

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**PO1.08.14**

Role of slow-digesting carbohydrates during pregnancy for reducing the risk of developing NAFLD phenotype in obese rats’ offspring (NIGOhealth study)

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**Background:** Maternal obesity and obesogenic dietary intake prior to and through pregnancy program offspring to a broad spectrum of metabolic and physiological alterations later in life such as non-alcoholic fatty liver disease (NAFLD). We examined the effects of two mixtures of carbohydrates (CHO) consumed by pregnant rats, exposed to high fat diet, in order to determine whether the CHO of maternal diet is able to attenuate the offspring’s susceptibility to develop obesity-induced liver disease (NAFLD)

**Methods:** Virgin rats were assigned to one of three experimental groups: control (C) dams fed a standard rodent diet before mating and throughout pregnancy; dams fed an obesogenic diet 6 weeks before mating and then fed a HF diet containing either CHO with high (HF/HC) or low (HF/LC) digestion rate throughout pregnancy. At delivery all the animals were fed with the standard rodent diet for the remainder of the study (13 weeks). Plasma biochemical analysis was performed by using Pentra autoanalyzer. Plasma hormone analysis was performed by using a Multiplex System. Lysates from hepatic tissue were used to analyze molecular mechanism related to NAFLD by western blot. Lipid species were analysed reverse ultra-performance liquid chromatography coupled to mass spectrometry (UPLC-MS) after extraction with chloroform/methanol.

**Results:** Offspring from obese dams that consumed the HF/HC diet presented features consistent with the development of NAFLD. Plasmatic ALT, cholesterol, and triglyceride levels (total, saturated and PUFA) were higher compared with the dams that consumed the HF/LC diet. In the liver, gluconeogenesis and lipogenesis were more activated in the HF/HC group compared to the HF/LC group. Phosphorylation of key metabolites in these routes, such as AKT and AMPK, were lower in the HF/HC group respect to the HF/LC group. Regarding that, the amount of glucose transporter (GLUT2) and acetyl-CoA carboxilase (ACC) were also higher in the HF/HC group than in the HF/LC group. Hepatic metabolome analysis showed that amino acids and saturated triglycerides levels were reduced by the slow digesting CHO in the maternal diet. Membrane lipids, i.e. total phospholipids and phosphatidylcholine and phosphatidylethanolamine species exhibited normal values in this group when compared to the group showing a higher risk of NAFLD (HF/HC group).

**Conclusions:** Nutritional intervention in obese mothers, during gestation period, using a diet with slow digesting CHO is able to reduce the risk of developing a NAFLD phenotype in the offspring. The mechanism of actions responsible for the beneficial effects induced by NIGOHealth CHO system involve the regulation of key enzymes/proteins related to hepatic gluconeogenesis and lipogenesis as well as membrane integrity.

**PO1.08.15**

Maternal protein restriction in young rats alters long chain fatty acid sensing by duodenal entero-endocrine cells, leading to increased-intestinal permeability

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Intrauterine growth retardation due to maternal protein restriction predisposes to gastrointestinal and metabolic disorders in adulthood. We recently showed that maternal protein restriction alters the short term regulation of food intake. Gastrointestinal peptides and particularly cholecystokinin (CCK) play a major role in short-term regulation of FI. Entero-endocrine cells (EEC) in response to duodenal nutrients such as long chain fatty acids (LCFA) secrete peptides such as CCK which relay nutrients actions upon gut and brain functions. In particular, EEC derived peptides can regulate gastrointestinal functions via their paracrine action upon the enteric nervous system (ENS). We therefore hypothesize that in adults, MPR alters GI response to nutrients via pathways involving EEC and the ENS. Low protein rats were obtained by protein restriction of their dams during gestation and lactation [8% (restricted dams, LP) vs 20% (control, C)]. We analyzed, in 2 months-old
In the development of the website, we describe how we have involved end-users and stakeholders in creating a website to promote healthy eating habits. The website has been developed with limited involvement of end-users and other stakeholders. Many behaviour change apps and websites have been designed, however with limited involvement of end-users and other stakeholders. Parents often search for information about their child’s diet on the internet. The website has been developed and tested in Guangzhou. Moves towards what is seen in other more developed societies, so do breastfeeding patterns. Given the long-term health benefits of breastfeeding and the consequences of not, both for the mother and infant, public health intervention is needed to prevent breastfeeding rates in Guangzhou from falling to levels seen previously in high-income countries.

PO1.08.16

Education and income level and their relationship with breastfeeding duration: 8949 mother-infant pairs in the Born In Guangzhou Cohort Study (BIGCS)

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Background: Guangzhou is one of the most rapidly developing urban centres in the world. Economic development and social progress have undoubtedly influenced health behaviours, like breastfeeding, across the socioeconomic gradient for the region. Recently provincial regulations on maternity-leave have changed, extending the former 98 day provision to 178 days. It is likely that the new policy will improve regional breastfeeding rates; however, the currently available data on breastfeeding populations in Guangzhou is poor. More robust studies are needed to evaluate in future how continued economic progress effect breastfeeding rates across different socioeconomic groups, and if the new policy changes have had the beneficial impact expected.

Objective: This study aims to assess sociodemographic disparities, measured by education and average monthly income level, on the risk of breastfeeding cessation before 1-year postpartum in a large prospective cohort study in Guangzhou.

Methods: Data on the education and income level of mothers and fathers in the Born In Guangzhou Cohort Study were extracted for infants born between February 2012-September 2015. Multivariable Cox regression analysis was used to assess the association between the education and income level of both the mother and the father, and the risk of breastfeeding cessation before 1-year.

Results: 8949 mother-infant pairs were analysed. The median breastfeeding duration was 7.0 months (interquartile range: 6.0). At 6-months postpartum 73.0% (95%CI 72.1-73.9) of mothers were still breastfeeding, and by 12-months 19.4% (95%CI 18.6-20.3) remained. After multivariable adjustment, there was a significant inverse linear association between education and the risk of early breastfeeding cessation. With each additional level of maternal education above high school, the risk of early breastfeeding cessation dropped by 10% (HR: 0.90, 95%CI 0.86-0.93). A similar trend was observed for the association with the father’s education level as well. There was no association between the income level of either parent and the risk of breastfeeding cessation before 1 year.

Conclusions: The socioeconomic breastfeeding patterns observed here more closely resemble patterns observed in developed populations than other regions in China. Thus, these findings may indicate that as the socioeconomic distribution in Guangzhou moves towards what is seen in other more developed societies, so do breastfeeding patterns. Given the long-term health benefits of breastfeeding and the consequences of not, both for the mother and infant, public health intervention is needed to prevent breastfeeding rates in Guangzhou from falling to levels seen previously in high-income countries.

PO1.08.17

Co-creation of knowledge: Involving end-users and stakeholders in creating a website to promote healthy eating habits, The food4toddlers study

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Background: With rapidly developing e-health technology, new possibilities in research and public health initiatives emerge. Many behaviour change apps and websites have been designed, however with limited involvement of end-users and other stakeholders. Parents often search for information about toddler’s diet on the internet. The website has been developed to promote healthy dietary habits in toddlers through targeting parental awareness of child food and eating environment. Here we describe how we have involved end-users and stakeholders in the development of the website.
Methods: Users were involved in several steps in the development of food4toddlers. The first step in the development was to contact three public health nurses to get an overview over the field, and three interviews were performed. We further conducted a focus group interview with health care nurses at their workplace and an individual telephone interview to further elaborate on what they perceived as the most customary questions asked by parents regarding diet. One of the nurses worked in a disadvantaged community with low socioeconomic status (SES) and many non-native inhabitants. Our next step was to invite parents with toddlers to attend focus groups to share and discuss what information they lack and would find useful to improve diet and food environment for their children. One focus group interview for end-users were delivered at the university, one in a home setting, and three in settings were parents meet for other reasons (e.g. baby singing class). Two telephone interviews with mothers were done separately. In the interview that was conducted at a home, both parents attended. The other participants were mothers. Approximately 40% of the participants were non-native. Except from the first three interviews, the rest have been taped and seven out of the nine interviews have been transcribed. The content of food4toddlers has been developed based on these interviews, recommendations from health authorities, and updated research in the field.

Results: Effort was made to invite parents to come to the university for interviews, but hardly anyone attended (two). Especially fathers were hard to involve. Parents with low SES attended focus groups interviews outside the university. In this study, the best strategy to include users seemed to be when telephone interview was offered, and when the researcher could meet with parents at other activities. The input from end-users and public health nurses was valuable in identifying elements that should be highlighted more than others.

Conclusions: The involvement of end-users and other stakeholders contributed valuable information in the development of the intervention, and has the potential to make the eHealth intervention more useful and feasible to the target group. It was easier to encounter mothers in a natural setting outside the university, and based on the experience from this study, individual phone interviews may have the potential to engage fathers.

Background: Previous studies have demonstrated that vitamin D affects T cell function and maturation via the vitamin D receptor. However, no studies in children have been performed on this topic. Because most of the T cell memory is formed in the first five years of life, we aimed to determine the association between serum 25-hydroxyvitamin D (25(OH)D) levels and numbers of circulating naive, central memory (Tcm) and effector memory (Tem) T lymphocytes in a large population of healthy children.

Methods: This study was performed among 3,189 children participating in a population-based prospective cohort. We measured 25(OH)D levels and performed detailed immune-phenotyping of naive and memory T lymphocytes at a median age of 6.0 years (95% range 5.7 to 7.9). Multivariable linear regression analyses were performed to determine the association between 25(OH)D and the maturation of T lymphocytes in children adjusted for herpes seropositivity, sociodemographic and lifestyle confounders. Furthermore, multivariable logistic regression analyses were performed to determine associations between 25(OH)D and childhood infections. Data on upper respiratory tract infections (URTIs) were based on questionnaires.

Results: Higher 25(OH)D levels were associated with higher numbers of Tem lymphocytes. Every 10 nmol/L higher 25(OH)D was associated with 2.19% (95% CI 0.53-3.88; \( p = 0.009 \)) higher CD4TemRA, 1.50% (95% CI 0.38-2.63; \( p = 0.008 \)) higher CD4TemRO and 1.82% (95% CI 0.11-3.56; \( p = 0.037 \)) higher CD8TemRA cell numbers. Generally, stronger observations were observed among boys. 25(OH)D levels were not significantly associated with naive, Tcm cell numbers, herpes seropositivity or URTIs.

Conclusion: Our results suggest that vitamin D enhances cellular immunity in young children. Further studies are necessary to examine this association and to relate our findings to the onset and morbidity of infectious and inflammatory diseases.

PO1.09 - Nutrition - Micronutrients

PO1.09.01

The role of vitamin D on circulating memory T cells in children: the Generation R Study.

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Background: Suboptimal vitamin D status is common in young children. Children with celiac disease, an autoimmune enteropathy with intolerance to gluten, are reported to be more frequent vitamin D deficient than their healthy peers. However, since vitamin D is mainly derived from exposure to sunlight instead of dietary intake, it is unclear to what extent the association between vitamin D and celiac disease might be due to malabsorption. Furthermore, most studies have been conducted in selected patient populations where vitamin D
PO1.09.03

Vitamin B12 deficiency in early pregnancy associates with maternal obesity: Findings from two UK cohorts

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Background: Vitamin B12 (B12), the dietary methyl-micronutrient is essential for methionine metabolism which is vital for most metabolic processes. B12 deficiency during pregnancy is associated with obesity, insulin resistance and gestational diabetes in Indian women. Recent evidence shows that B12 deficiency is widely prevalent among pregnant women across many populations. We hypothesise that maternal B12 deficiency in early pregnancy in UK is associated with obesity and cardio-metabolic risk factors.

Methods: Study population were pregnant women from two early pregnancy (16-18weeks) cohorts: (1) Cohort 1 – (Nuneaton; n = 244) and (2) Cohort 2 – (Edinburgh; n = 60). Serum B12, folate, anthropometry and 1-carbon metabolites (SAM, SAH, methionine, homocysteine and MMA) were measured. Lipid profiles were available in cohort 2.

Results: The prevalence of B12 deficiency in early pregnancy was 18% in cohort 1 and 23% in cohort 2. In cohort 1, maternal B12 was associated with BMI (r = -0.225; p = 0.001) and 1-C metabolites such as SAM/SAH (r = 0.173; p = 0.009), homocysteine (r = -0.238; p < 0.0001) and MMA (r = -0.333; p < 0.0001) (Fig 1A). In cohort 2, B12 was associated with BMI (r = -0.577; p < 0.0001) and 1-C metabolites - SAM/SAH (r = 0.268; p = 0.042), homocysteine (r = -0.428; p = 0.001), MMA (r = -0.358; p = 0.005), triglycerides (r = -0.377; p = 0.010) and HDL cholesterol (r = 0.534; p < 0.0001) (Fig 1B). In regression analysis, after adjusting for likely confounders (age, smoking, alcohol, parity, folate, homocysteine, MMA, SAH) in cohort 1, maternal B12 independently associated with BMI (β = -0.297, 95% CI (-0.446,-0.148), p < 0.0001). In cohort 2, B12 associated with BMI (β = -0.439, 95% CI (-0.703,-0.175), p = 0.002) and HDL-cholesterol (β = 0.437, 95% CI (0.027,0.847), p = 0.037), whereas 1-C metabolites – methionine (β = 0.660, 95% CI (-0.897,-0.422), p < 0.0001), SAH (β = 0.377, 95% CI (0.087,0.668), p = 0.013) contributed to triglycerides.

Conclusions: Low B12 status is common in UK women in early pregnancy and is independently associated with maternal obesity and cardio-metabolic risk factors. Thus, B12 supplementation may offer potential to reduce the metabolic risk in pregnant women. As B12, along with folate, are key micronutrients essential for DNA methylation, this may also help the offspring’s future metabolic risk. Studies designed to answer these questions as well as on the effect of low B12 in early pregnancy on incident gestational diabetes are urgently warranted.

Correlation between maternal B12 and cardio-metabolic risk factors in early pregnancy.

PO1.09.04

An inadequate maternal vitamin D status is associated with congenital heart defects in the offspring


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Background: The birth prevalence rate of congenital heart defects (CHD) is 9.1 per 1,000 live births worldwide and accounts for almost one-third of congenital malformation-
related infant deaths. Interactions between genetic and environmental factors, including maternal nutrition and lifestyle, play a significant role in the pathogenesis of most CHD. For example, a deranged maternal lipid profile, a high dietary intake of saturated fats, vitamin A or vitamin E are all associated with CHD in offspring. Although the active form of vitamin D and its receptor have been shown to be involved in cardiogenesis in animal studies, maternal vitamin D levels have not been studied in relation to CHD. Therefore, the aim of this study was to investigate associations between periconceptional maternal vitamin D status and CHD in offspring.

Methods: A case-control study was performed in 345 mothers of a child with CHD and 432 mothers of a child without CHD from four tertiary hospitals in the Netherlands between 2003-2005. Approximately 15 months after pregnancy, i.e., 2 years after conception, mothers filled out questionnaires regarding general characteristics and periconceptional nutrition and lifestyle factors. Maternal blood was obtained to determine serum vitamin D status compared with controls (27% vs. 38%; p = 0.002).

Results: Case mothers less often had an adequate maternal vitamin D status compared with controls (27% vs. 38%; p = 0.002). The use of multivitamin supplements, ethnicity, season and body mass index, ethnicity, smoking and serum total cholesterol concentration. Furthermore, sensitivity analyses regarding the use of multivitamin supplements and seasons were carried out.

Conclusion: A compromised maternal vitamin D status is associated with an approximately two-fold increased risk of CHD in offspring. Adequate maternal vitamin D levels are crucial for optimal transcription during cardiogenesis, a process which has often already started prior to pregnancy recognition. Therefore, improvement of the periconceptional maternal vitamin D status is strongly recommended, particularly for women at high risk for vitamin D deficiency. Future studies should focus on the benefits and safety of strong adherence to a vitamin D rich diet or the use of a vitamin D supplement.

**PO1.09.05**

**Low vitamin B12 induces de novo lipogenesis in human hepatocytes**

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**Background:** There is increasing evidence that lipid metabolism in humans may be regulated by environmental factors including nutrients such as vitamin B12 (B12). B12 deficiency results in disturbance of 1-carbon metabolites (methylmalonyl coenzyme A (MMA), homocysteine and S-adenosyl homocysteine (SAH), S-adenosyl methionine (SAM) and methionine) that collectively favours lipogenesis leading to risk of cardiovascular diseases. In clinical studies, B12 deficiency is associated with higher BMI and dyslipidaemia (high triglycerides and low HDL). *In vitro* experiments in human adipocytes showed that low B12 results in hypomethylation of SREBF1, a master regulator of cholesterol biosynthesis. If similar effects happen in hepatocytes, this may explain the observation of dyslipidaemia in humans. In addition, the role of B12 in hepatic metabolism of lipids in humans is unexplored. Therefore, we investigated whether B12 deficiency affect hepatic de novo lipogenesis.

**Methods:** Human HepG2 cell line was cultured using custom made B12 deficient Eagle’s Minimal Essential Medium (EMEM) and seeded in four different concentrations of B12 media such as 500nM (control), 1000pM, 100pM and 25pM (low) B12. Oil Red O (ORO) staining, gene expression assay using RT-qPCR, total intracellular triglyceride (TG) assay with commercial kit and *de novo* TG biosynthesis using radioactive flux assay were employed to examine the effect of B12 on lipogenesis.

**Results:** HepG2 cells in low B12 (25pM) (Fig 1D) had more lipid droplets that were intensely stained with ORO compared with less stained few oil droplets in control B12 (500nM) (Fig1A) condition. Total intracellular TG levels were higher in low B12 hepatocytes. The gene expressions of nuclear transcription factors sterol regulatory element binding protein (SREBF1) and low density lipoprotein receptor (LDLR) were higher in low B12 conditions compared with control. Similarly, the gene expressions of the enzymes involved in de novo fatty acid synthesis [ATP citrate lyase (ACLY), Acetyl CoA carboxylase (ACC) (Fig 1E), fatty acid synthase (FASN) (Fig 1F) and elongation-of very-long-chain fatty acid (ELOVL6)], cholesterol biosynthesis [3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) (Fig 1G), 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMCS1) (Fig 1J), Isopentenyl-Diphosphate delta Isomerase 1 (IDL1)] and TG biosynthesis [stearoyl CoA desaturase (SCD) (Fig 1G), glycerol-3-phosphate acyltransferase (GPAT), acylglycerol-3-phosphate acyltransferase (AGPAT), phosphatidic acid phosphatase-1 (Lpin1) and diacylglycerol acyl transferase 2 (DGAT2) (Fig 1H)] in low B12 conditions. Lastly, cellular uptake of radio-labelled fatty acid (14C-oleate)
for de novo TG biosynthesis assessed by scintillation was about 80% higher in HepG2 cells cultured in low B12 condition.

**Conclusion:** Our data provide novel evidence that B12 deficiency dysregulates lipid metabolism in hepatocytes. Further studies are required to quantify the effect of this on circulating levels of lipid fractions as well as its epigenetic role on hepatocyte function.

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**PO1.09.07**

**Effect of vitamin B12 deficiency on the lipid lowering effect of metformin in the liver**

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**Background:** Metformin is currently the first drug of choice for treatment of type 2 diabetes (T2D). In addition to improving insulin sensitivity and hyperglycaemia, metformin is also known to reduce lipid levels through activation of AMP activated protein kinase-alpha (AMPK\(\alpha\)). It is known that metformin administration induces deficiency of vitamin B12 (B12) in patients with T2D. Observational studies in humans also show that low B12 is associated with dyslipidemia (higher triglycerides and low HDL). Therefore, we investigated whether B12 deficiency may impair metformin action from achieving the desired lipid lowering effect in the liver.

**Methods:** Hep G2 cell line was cultured using custom made B12 deficient Eagle’s Minimal Essential Medium (EMEM) and seeded in four different concentrations of B12 media such as 500nM (control), 1000pM, 100pM and 25pM (low) B12 until 100% confluence was achieved. The cells were exposed to 24hour treatment with 1mM and 2mM metformin before harvest. Gene expression assays and protein expression were characterized using real time PCR (qRT-PCR) and western blotting, respectively.

**Results:** Low B12 (25pM) in HepG2 cell line decreased levels of AMPK\(\alpha\) (fig 1A) and its downstream target pACC (fig 1B), compared to control. Administration of increasing concentrations of metformin (1mM and 2mM) to low B12 hepatocytes significantly impaired the upregulation of pAMPK\(\alpha\) (fig 1C) and pACC (fig 1D). In addition, we found that down-regulation of nuclear transcriptional factor sterol regulatory element binding protein (SREBF1) and the genes involved in hepatic de novo fatty acid synthesis pathway, [fatty acid synthase (FASN), acetyl coenzyme A carboxylase (ACC) and elongation-of very-long-chain fatty acid (ELOVL6)] and TG biosynthesis [glycerol-3-phosphate acyltransferase (GPAT) and diacylglycerol acyl transferase 2 (DGAT2)] were significantly impaired in low B12 cells treated with metformin.

**Conclusion:** Our study provides novel evidence that Vitamin B12 deficiency (1) lowers levels of pAMPK\(\alpha\) and pACC, and (2) metformin administration in low B12 hepatocytes failed to restore the levels of pAMPK\(\alpha\) and pACC, and the genes involved in lipid metabolism. This supports that the lipid lowering effect of metformin in vitamin B12 deficiency is compromised. The mechanisms involving regulation via AMPK requires further studies.

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**PO1.09.08**

**Prevalence and determinants of vitamin D deficiency in pregnant women and their neonates: a multicentric study in Switzerland**

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**Background:** Vitamin D deficiency during pregnancy is associated with negative health consequences for the mothers and their neonates like gestational diabetes and preeclampsia. From a public health perspective, evaluating the vitamin D status of pregnant women is therefore crucial, but the data was lacking in Switzerland. Our study aimed to measure the prevalence and to identify the determinants of vitamin D deficiency in a sample of 3rd-trimester pregnant women in Switzerland. In addition, we evaluated serum 25-hydroxy-vitaminD (25(OH)D) levels in the cord blood of neonates.
Methods: A three-centre cohort study was conducted between August 2014 and June 2016 in the birth clinics of Zurich (latitude 47.4°, altitude 408 m a.s.l.), Bellinzona (latitude 46.2°, altitude 238 m a.s.l.) and Samedan (latitude 46.5°, altitude 1,721 m a.s.l.). We measured serum 25(OH)D in 305 women in their 3rd trimester of pregnancy and in the cord blood of 278 of their offspring at birth. We used demographic and questionnaire data to explore the determinants of vitamin D deficiency (serum 25(OH)D < 20 ng/mL).

Results: Median concentration of serum 25(OH)D in the 3rd trimester of pregnancy was 18.43 ng/mL (Q1-Q3: 12.2-27.4), which translated into a 53.4% prevalence of vitamin D deficiency. Multivariable logistic regression analysis showed that significant determinants of vitamin D deficiency were the center of study (lower risk in Bellinzona), the country of origin (lower risk for Swiss citizens), the season of delivery (lower risk in the summer and fall) and the intake of vitamin D supplements. In the cord blood of the neonates, median serum 25(OH)D level was 20.0 ng/mL (Q1-Q3: 12.4-30.7). A strong correlation was observed between serum 25(OH)D of the mothers and their neonates (Spearman’s correlation rho = 0.79, p < 0.0001).

Conclusions: Our study indicates that low vitamin D levels are common in pregnant women living in Switzerland and their neonates. As correlation between maternal and umbilical cord blood is high, vitamin D supplementation during pregnancy should receive more attention in clinical practice.

POI.09.10

Early-life stress reduces availability of essential micronutrients; a nutritional intervention strategy to prevent its lasting consequences on cognitive function

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Stressful experiences in the early postnatal period can have long-lasting effects on cognition and the risk to develop psychopathology later in life. Stress during this critical period often affects both the lactating mother and her child. Because prevention of such stress exposure is generally difficult, adequate intervention or support strategies are needed to protect against the permanent detrimental effects of early-life stress (ES) on the offspring. Elucidating the underlying mechanisms will enable the development of targeted strategies for intervention. So far, the role of early nutrition in brain programming has been largely ignored. Since the diet provides the building blocks for brain development and is required for many biochemical processes, we investigated the possible role of nutrition in programming later cognition in the context of ES. We focused on essential one-carbon metabolism associated micronutrients (1-CMAM; i.e. methionine and B-vitamins), important for development and epigenetic modifications. We investigated if ES alters micronutrient availability in milk, plasma and brain and studied the epigenetic, structural and behavioral consequences of ES in an established ES mouse model. Subsequently we tested if early 1-CMAM-supplementation can protect against the ES-induced changes in the offspring. ES was induced in C57Bl/6 mice from postnatal day (P) 2-9, while dams received either control or 1-CMAM supplemented diet. Nutrient content was measured at P9 in offspring’s stomach milk, plasma and brain. Next, we studied effects of 1-CMAM supplementation on ES-induced alterations in maternal behavior and the offspring’s HPA-axis activity, neurogenesis, DNA methylation levels (global and Nr3C1 specific) and DNA methyltransferase expression in the hippocampus. All readouts were measured in male offspring, both at P9 as well as in adulthood. We found that ES reduced methionine levels in offspring’s plasma and brain at P9. Importantly, 1-CMAM
supplementation restored methionine levels in the offspring and ameliorated the ES-induced cognitive impairments in adulthood, abolishing ES induced deficits in object recognition and acquisition in the Morris water maze. The beneficial effects of the 1-CMAM supplementation do not involve changes in maternal care, hippocampal neurogenesis or DNA methylation, but appear to be mediated by preventing the ES-induced HPA-axis hyperactivity. In conclusion, we show that a short nutritional intervention with essential micronutrients in early life can prevent ES-induced lasting effects on hippocampal function. To take these findings from bench to bedside we are currently setting up a human cohort to assess if and how stress affects the nutritional composition of breast milk, and how this relates to history of stress, stress hormones and food intake of the mother. These findings might open new avenues for early nutritional intervention in humans to support infant development in vulnerable individuals, which is non-invasive and easily applicable.

PO1.09.11

**Expressions of Transcobalamin receptor CD320 and transporter TCN2 in low vitamin B12 treated human adipocytes.**

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**Background:** Vitamin B12 (cobalamin) is an essential micronutrient in humans. Cellular uptake of B12 is facilitated by a complex process involving transcobalamin, a plasma protein and a cell surface receptor that specifically binds transcobalamin saturated with cobalamin. Earlier clinical studies and animal models showed that low maternal B12 deficiency is associated with maternal obesity, development of insulin resistance and metabolic syndrome, suggesting the crucial role of B12 inadipose tissue function. Although several studies explored the expression of cellular B12 receptor (CD320) and transporters (TCN2) that may regulate cellular uptake and storage of cobalamin in several tissues like placenta, liver and brain, no study have been conducted on adipocytes so far. Therefore the aim of this study is to investigate the expression of cobalamin receptor and transporter and intracellular B12 levels in human adipocytes.

**Methods:** Human pre-adipocyte cell line (Chubs S7), and human primary pre-adipocytes were grown to confluence (day 0), differentiated in differentiation media for one week and maintained in nutrition media for a further 7 days (day 14). In order to analyse B12 deficiency effects, customized media with different concentrations of B12 (0pM, 25pM, 100pM, 1nM, 10nM, 100nM, 500nM) were used at all stages. On day 14, conditioned media were collected, cells were harvested for RNA analysis and stored at −80°C until use. Intracellular B12 concentration and their corresponding conditioned media were determined by electrochemiluminescent immunoassay using a Roche Cobas immunoassay analyzer (Roche Diagnostics UK, Burgess Hill, UK). Gene expression was performed by RT-PCR.

**Results:** Intracellular levels of B12 in adipocytes cultured in low B12 (25 pM and 100 pM) showed 300-500% higher concentrations of B12 compared to the condition media. However, increasing concentrations of B12 in the condition media to 1nM, 10nM, 100nM and 500nM resulted in progressive reduction incellular uptake of B12 to 9.1%, 3.9%, 1.6% and 1.3%, respectively. However, the intracellular levels are still higher than the normal physiological levels seen in humans. We also observed there was a significant increase in the expression of B12 transporter transcobalamin II (TCN2) and transcobalamin receptor (TChbR) (CD320) in adipocytes under each B12 condition.

**Conclusion:** Our study thus provides novel evidence that when extracellular B12 levels are low (0-100pM), the intracellular B12 levels and the gene expression of receptor and transporter are higher, whereas opposite effects are seen at higher extracellular B12 levels (1-500 nM). This suggests active transport of B12 in adipocytes at low concentrations. In addition, there might be a threshold for the B12 entry at the membrane level in higher concentrations of B12. Our findings support that optimal physiological levels of B12 is required. Further studies are required to assess whether the effects of non-physiological concentrations of B12 (low or high) result in adipocyte dysfunction.

PO1.09.12

**Intracellular uptake and levels of vitamin B12 in hepatocytes**

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**Background:** Vitamin B12 is a key enzyme involved in methylation of DNA and plays a key role for many intracellular reactions. The liver is the principal storage organ for cobalamin containing about 10μg cobalamin per gram protein or 1μg/g wet weight and able to hold 50% (1-1.5mg) of B12 in the body. Hepatocytes make up the bulk of the liver mass expressing specific receptors for B12-bound transporters in circulation that may regulate cellular uptake and storage of B12 in the liver. However, relationship between circulating and intracellular B12 levels and the regulation of hepatic uptake of B12 is not fully understood. In this study we investigated the regulation of intracellular levels of B12 in hepatocytes, we studied the handling of B12 by hepatocytes with varying concentrations of B12.

**Methods:** HepG2 cell line was cultured using custom made B12 deficient Eagles’ Minimal Essential Medium (EMEM) and seeded in ten (10) different concentrations of B12 media such as 500nM, 400nM, 200nM, 100nM, 50nM, 20nM, 10nM, 1nM, 100pM and 25pM B12. Intracellular concentrations of B12 in Hep G2 cells and in their corresponding
conditioned media was determined by electrochemiluminescent immunoassay using a Roche Cobas immunoassay analyzer (Roche Diagnostics UK, Burgess Hill, UK). Gene expression (real-time PCR) of B12 transporter transcobalamin II (TCN2) and transcobalamin receptor (TCbIR) (CD320) were done by RT-PCR.

Results: At lower than normal physiological concentrations of B12 (25pM and 100pM), there was 210-280% higher intracellular levels of B12 compared to the condition media (akin to circulating levels in vivo). At 1000pM (1nM) of B12, the intracellular levels was 42.7% of the conditioned media. Further increasing the concentrations of B12 to 10nM, 20nM, 50nM, 100nM, 200nM, 400nM and 500nM resulted in progressively lower intracellular uptake, with levels of B12 4.7%, 4.3%, 3.1%, 1.6%, 2.3%, 1.3% and 1.8% respectively, compared to the conditioned media. There were no significant differences in the expression of B12 transporter transcobalamin II (TCN2) and transcobalamin receptor (TCbIR) (CD320) in hepatocytes under different B12 conditions.

Conclusion: Our study highlights the tissue specific effect of intracellular B12 when exposed to at varying concentrations. At lower levels (0-100pM), there seem to be active transport of B12 resulting in 2-3-fold higher intracellular levels. However, at higher extracellular B12 levels (1-500nM), the intracellular levels are 2-70 fold lower, highlighting a potential threshold for B12 entry in hepatocytes. In addition, although the fraction that enters hepatocytes is low at higher concentrations, they still result in very high intracellular concentrations. This may hinder the normal physiological functions of hepatocytes. Further studies to assess the tissue-specific effect of B12 on hepatic metabolism.

PO1.09.13

Prenatal iron-deficiency causes sex-dependent mitochondrial dysfunction in the fetal liver and kidney

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Background: Iron deficiency (ID) is the most prevalent nutritional deficiency worldwide, and affects populations across the socioeconomic spectrum. The incidence of ID anemia in pregnant women is of chief concern, with rates estimated to be 50-80% in developing countries, and 30% in Western countries. Our group and others have shown that maternal iron restriction throughout pregnancy causes fetal ID, anemia and hypoxia in fetal liver and kidneys, which may be linked to susceptibility for cardiovascular and metabolic dysfunction later in life. Given the critical role iron and oxygen play in mitochondrial function, we sought to determine whether prenatal ID causes alterations fetal liver and kidney mitochondrial function and reactive oxygen species generation.

Methods: Six-week old female rats were fed either a low iron (3 mg/kg diet) or iron-replete (35 mg/kg diet) for two weeks prior to pregnancy. For the duration of pregnancy, the low iron diet group was further divided into moderate-ID (M-ID, 10 mg/kg diet) and severe-ID (S-ID, 3 mg/kg diet) groups. Pregnant dams and fetuses were euthanized on gestational day 21 and tissues were collected. Dihydroethidium fluorescence staining was used to assess superoxide generation in OCT-embedded cryosections. TUNEL staining was used to assess apoptosis. High-resolution respirometry was used to assess integrated mitochondrial function in tissue homogenates, with respiration expressed as oxygen flux per milligram of tissue homogenate per second. Mitochondrial content was determined with a spectrophotometric citrate synthase activity assay.

Results: Maternal iron restriction resulted in 31% and 54% reductions in maternal hemoglobin (Hb) in the moderate (M-ID) and severe (S-ID) groups on GD21, respectively (both P < 0.001). M- and S-ID both resulted in a 55% decrease in fetal Hb (both P < 0.001) as well as 20% and 35% reductions in body weight (both P < 0.001), respectively. In the liver, ID increased reactive oxygen species generation in male (P = 0.01) but not in female fetuses (P = 0.24). ID also reduced cytochrome c oxidase (complex IV) activity, which correlated with reduced fetal Hb levels in male, but not female fetal liver (Fig. 1a & 1b). In the kidneys, reduced fetal Hb correlated with impaired complex I (P < 0.05), complex II (P < 0.05), and cytochrome c oxidase activity in males, but not in female fetuses (Fig. 1c & 1d). Reductions in kidney mitochondrial content was also found to correlate with lower Hb levels in males (P = 0.02), but not female fetuses (P = 0.21). Moreover, ID caused apoptosis in male (P = 0.01), but not female kidneys (P = 0.86).

Conclusions: These data implicate reduced mitochondrial function and content as a potential mechanism by which prenatal iron deficiency causes sex-dependent programming of long-term cardiovascular and metabolic function.
Complex IV oxygen flux correlated with fetal hemoglobin (Hb) in (a) male liver, (b) female liver, (c) male kidney, and (d) female kidney.

PO1.09.14
Perinatal iron deficiency alters brown fat quantity and thermogenic capacity in adult rats.

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Background: Fetal exposure to an adverse intrauterine environment can lead to altered growth and developmental trajectories, thereby increasing susceptibility to chronic disease in later life. Iron deficiency (ID) is the most common nutritional disorder in the world, and pregnant women are the most susceptible subgroup. We have shown that perinatal ID programs offspring metabolic function, characterized by an increased propensity for fat accumulation in later life; however, the mechanisms underlying this metabolic dysfunction are unknown. Brown adipose tissue (BAT) is highly active metabolic tissue which has the capacity generate large quantities of heat. The capacity of BAT to burn calories as heat makes it an attractive therapeutic target for obesity. We sought to determine whether perinatal ID predisposes offspring to obesity by chronically altering the thermogenic capacity of BAT, and thus whole body metabolism.

Methods: Female Sprague Dawley rats were fed either an iron-restricted (3-10mg/kg iron) or control diet (35mg/kg iron) prior to and throughout gestation. At birth, dams were fed a normal rat chow, and pups were subsequently fed a high-fat/high-sucrose diet at weaning (postnatal day 21). At 4wk of age, one male and female offspring from each litter were subjected to a chronic cold exposure protocol (4˚C, 12h/day, 5wk) to maintain at room temperature (22˚C). Metabolic parameters were analyzed in vivo via open-circuit indirect calorimetry. Maximal thermogenic capacity from BAT was assessed following pharmacological stimulation with the β3 agonist CL316,243.

Results: Maternal iron restriction throughout pregnancy caused anemia and growth restriction in male and female offspring at birth (P < 0.001 for all parameters). All offspring subsequently recovered in the neonatal period, such that Hb levels and body weights were no longer different between groups at postnatal day 21. Cold exposure increased BAT mass, uncoupling protein-1 expression, and thermogenic capacity in all offspring (P < 0.001), albeit these effects were mitigated in the PID offspring. Whereas cold exposure had minimal effects on control offspring body weight and body composition, cold exposure prevented body weight and fat mass gain in male PID offspring (P < 0.001), but not in female PID offspring.

Conclusions: Prenatal ID causes lasting effects on BAT quantity and thermogenic capacity in the offspring, albeit these differences are qualitatively different between male and females. However, changes in BAT physiology did not impair cold-induced fat loss in the offspring, suggesting alternative mechanisms may be implicated in chronic cold-stimulated weight loss.

Funding: This work was supported by the Women and Children’s Health Research Institute and the Canadian Institutes of Health Research.

PO1.09.15
Impact of mandatory iodine fortification on young adults in the Top End of Australia

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Background: Iodine deficiency is an important cause of mental retardation in the developing foetus. Iodine deficiency existed in the south-east of Australia until about the 1970 s but in recent decades Australia was considered to be iodine replete. Documentation of the re-emergence of iodine deficiency in the most populated parts of Australia in the early 2000’s led to the nation-wide mandatory fortification with iodine of salt used in bread making in 2009 by Food Standards Australia New Zealand. No information was available about the status of people living in the central-northern part of the continent. This study measured urinary iodine concentrations in young adults, both Indigenous and non-Indigenous, living in the most northerly part (the “Top End”) of the Northern Territory before and after fortification.

Methods: Spot urine samples were collected from participants of two cohort studies, the Aboriginal Birth Cohort (urban and remote Indigenous) and the Top End Cohort (urban non-Indigenous) as part of planned longitudinal follow-up. This occurred before and after fortification. Median urinary iodine concentration (MUIC) >100 mcg/L (WHO/UNICEF/ICCIDD criteria) in spot urine samples indicates that the population is replete for iodine.

Results: There were 590 urine samples before and 510 after fortification. MUIC (mcg /L) improved for all groups: in men from 47, 78 and 93 to 98, 128 and 132 in remote Indigenous, 58 and 63 to 89, 127 and 94, respectively. Similarly, in women, MUIC increased from 55, 78 and 93 to 98, 128 and 132 in remote Indigenous, urban Indigenous and urban non-Indigenous participants, respectively. Similarly, in women, MUIC increased from 55, 58 and 63 to 89, 127 and 94, respectively. MUIC in urban men, both Indigenous and non-Indigenous, and urban Indigenous women improved to the iodine sufficient range. However, MUIC for remote living Indigenous people and urban non-Indigenous women remained below 100 mcg/L.

Conclusions: Although there was improvement across all the groups after fortification, some groups remain in the mild deficiency range. This is most concerning in this cohort of women of childbearing age as iodine requirements increase in pregnancy and lactation. Our results are generally lower than those reported in this age group in the 2012 national survey.
These results illustrate the usefulness of cohort studies in supporting national surveillance efforts, particularly for small population sub-groups.

**PO1.09.16**

**Vitamin D concentrations in pregnant women and their newborns: relation with gestational birth weight**

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**Background:** Vitamin D (VITD) is a prohormone involved in various systems of the body, including immune, respiratory, endocrine, cardiovascular and bone metabolism. Study evaluating vitamin D concentrations in umbilical cord showed direct relationship between maternal and newborns levels at birth. Premature newborns (PTNB) are more likely to show VITD deficiency than those born at term. This deficiency may be associated with increased risk for sepsis, lung and bone disease. The purpose of the study is to describe, at the time of delivery, maternal and umbilical VITD concentrations in PTNB comparing them with the term newborn (TNB) and to correlate the cord and maternal VITD concentrations.

**Method:** It was a cross-sectional and controlled study that compared PTNB group (n = 37) and TNB (n = 37). At the time of delivery, 10 mL of maternal and umbilical cord blood samples were collected to determine the concentrations of 25 (OH) D, parathyroid hormone, calcium, phosphorus, and alkaline phosphatase.

**Results:** PTNB 25(OH)D concentrations were lower than TNB (23.59 ± 2.42 ng/mL vs 30.49 ± 2.19 ng/mL; p = 0.039); on the other hand, there was no difference in relation to the maternal concentrations. The levels of the other markers of vitamin D metabolism presented a significant difference between the groups, both maternal and newborn, however, without association with 25 (OH) D levels.

**Conclusions:** PTNB have lower VITD concentration in comparison TNB. None of the risk factors studied were associated with lower concentrations of VITD in both of groups.

**PO1.10 – Population health**

**PO1.10.01**

**Generation Victoria: A unique opportunity for better lifelong health and learning**

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**Background:** Addressing the childhood origins of poor health outcomes and low academic attainment will lessen the burdens associated with disease and ageing, increase population productivity and address inequities. Traditional project-driven recruitment, data collection and follow-up do not readily scale up to the numbers and flexibility needed to solve key issues that negatively impact population health and learning. At the same time, existing regional and national routine data are generally under-utilised despite their potential for innovative solutions.

**Methods:** The Gen V project aims to fundamentally shift data collection and utilisation throughout the state of Victoria (population 6 million), Australia, to create an innovative research hub that can drive evidence-based policies. It will: (a) embed an efficient whole-of-state research capability into health, social and education services, augmenting existing data and integrating biospecimens; (b) commence in pregnancy, ensuring DOHaD research derives from total populations; and (c) facilitate researcher-practitioner-policy-community relationships to rapidly address important questions and test feasible solutions.

**Results:** Now in advanced planning, Gen V will comprise three major inter-related components: Gen V 2020, a birth cohort and associated biobank of over 100,000 children, driving enhanced state-wide data linkage. It will bring together and augment the data and biosamples already collected within Victoria’s service system (such as the Maternal and Child Health Service) at key ages. All children born in 2020-21 in the State of Victoria, Australia, and their parents will be invited to take part. A permanent repository of consented information will grow with the children; an anonymised core dataset will be made readily available via licence, with more complex and/or sensitive data also accessible on application. Gen V Big Data, the advanced processing and analytics capability needed to realise the value of new and existing data structures. Gen V will work with diverse centres of computational excellence to stimulate these capabilities. Working with government, services and data custodians to enhance linkage of state-wide data will also make total population data, including from those not participating in Gen V, more readily available. Gen V Solution Hubs, responsive avenues of research underpinned by (1) and (2) to address hypotheses and test new interventions, policies and practices for the major domains of child health and development. We foresee eight Solution Hubs: (1) Discovery research; (2) Population health & learning; (3) Place-based research; (4) Population trials; (5) Health services; (6) Clinical & registry trials; (7) Condition databanks and biobanks; (8) Disaster impacts. The agenda for each will be planned each year by policy-service-consumer-research partnerships. The Hubs will generate their own funding and investment.

**Conclusion:** Now in its preliminary phases, Gen V represents a whole-of-state DOHaD research system that goes beyond a conventional cohort. Gen V is geared to speed up the discovery of practical, testable and translatable solutions to the modern epidemics of childhood and the problems of later life. It will
provide researchers, clinicians, service developers and policymakers with data and a ready testing ground for new prevention and early intervention strategies.

POI.10.02

The ORIGINS Project - a healthy start for a better future

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Background: The inextricable link between the early environment and subsequent NCDs led the WHO to prioritise ‘early-life preventive strategies’ in 2009. Globally, health councils (e.g. NIH, MRC and NHMRC) now have ‘A Healthy Start to Life’ as national priorities. ORIGINS directly addresses the call for integrated interdisciplinary studies to examine these complex interactions; and, the DOHaD mandate to specifically target preventive strategies in early life.

Methods: ORIGINS is a multidisciplinary collaboration between a large hospital campus (JHC) and a children’s research institute (TKI) to establish a new Western Australian birth cohort. A key strength and novelty is that it is fully integrated with clinical and diagnostic services at JHC. A central objective of ORIGINS is to develop a comprehensive research platform consisting of an extensive Databank and Biobank. This will enable investigations into how, when and why NCDs develop through the study of early environments, maternal and paternal physical health and genetics. Recruitment of pregnant women and their partners commenced in November 2016. Over 5 years we aim to recruit 10,000 women and their partners early in pregnancy and collect biological samples, routine data and web-based questionnaires on their physical and mental health, diet, physical activity patterns and a range of factors in their environment, creating a large biobank and databank. Participants also consent to linkage to national government datasets. Initially we will intensively follow up these families until the children are 5 years of age. We will then assess how these early life exposures have influenced their child’s growth, development, and health. Nestled within the main observational cohort will be a series of intervention studies and RCTs to improve modifiable aspects of the early life environment (e.g. nutrition, physical activity, microbial diversity, weight gain, language development).

Results: During 2016, preliminary data was collected from all pregnant women attending their first visit at the antenatal clinics (N = 2,000 +) to better understand the demographics of the community. Four subprojects have commenced: prebiotic supplementation and the effect on allergy risk; strategies for prevention of excessive early weight gain; language development in relation to testosterone levels; and, cardiovascular health of fathers.

Conclusion: The ORIGINS Biobank and Databank will generate many opportunities to explore underlying mechanisms of environmental influences and how these vary with genetic predisposition. It will build substantial future capacity to address critical questions (including genetic, epigenetic, metagenomic and metabolomic studies) in relation to the development of NCDs. The families will be part of a new and exciting research project. They will have the support of a team of healthcare providers who will monitor the development of their child closely. They will have ready access to specialist services such as obstetricians and neurodevelopmental screening, and families will be able to request the results of these assessments, and be given appropriate referral if required. We will also provide more general information about the study progress to the participants through the ORIGINS website, social media, online newsletters and community newspapers. This is anticipated to maintain engagement in the study and retain participants.

POI.10.03

What do pregnant women know about DOHaD: Exploring knowledge translation in the Mothers to Babies (M2B) Study

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Research Question: The Developmental Origins of Health and Disease (DOHaD) hypothesis holds that environmental factors during early development affect long-term and even multi-generational health outcomes. Consistent with this hypothesis, overwhelming evidence indicates that a mother’s metabolic state and nutrition during pregnancy affect her child’s risks for later-life development of obesity-related, non-communicable diseases (NCDs) such as diabetes and heart disease. The uptake of this evidence is growing rapidly among researchers and policymakers. However, it is unclear whether DOHaD messaging is yet reaching the public and, if so, which demographic segments of the public are being reached and whether this messaging influences nutritional knowledge and/or behaviour among pregnant women.

Methods: To begin to investigate these questions, we performed a pilot survey of DOHaD understanding in a socio-demographically diverse sample of 70 pregnant women from Hamilton, Canada. Three components of DOHaD knowledge translation were evaluated using participants’ responses to a 169-item questionnaire. First, we assessed current state of familiarity with core DOHaD-related concepts (hereafter, DOHaD Knowledge or DOHaDK) relative to familiarity with Canada’s general pregnancy health recommendations (hereafter, Pregnancy health Knowledge or PREGK). Second, we assessed whether variation in DOHaDK and/or PREGK were

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associated with variation in socio-demographic factors known to affect NCD risk (age, socioeconomic status, parity, and neighbourhood of residency). Third, we investigated whether variation in self-reported diet quality was associated with DOHaDK and/or PREGK. Two scales were developed to measure DOHaDK and PREGK (5 = low familiarity with current evidence, 25 = perfect understanding of current evidence) and then the means and coefficients of variation (COVs) were compared between the scales. We then developed multivariate linear mixed effects models in which we regressed each scale on socio-demographic characteristics; random effect terms for participants’ neighbourhoods were included to account for geographic clustering in the data. Lastly, a food frequency-based measure of recalled diet quality was regressed on DOHaDK, PREGK, and socio-demographic factors, again clustering the data by neighbourhood.

**Results:** DOHaDK scores were lower (mean = 13.6 out of 25) and more variable (COV = 0.37) than PREGK scores (mean = 20.3, COV = 0.08; p = 0.000). While PREGK scores were not associated with participants’ socio-demographic characteristics, DOHADK scores were positively associated with socioeconomic status and negatively with parity. Diet quality scores were positively associated with DOHaDK but not PREGK, independent of socio-demographic factors.

**Conclusions:** The first two analyses suggest that most participants are receiving and understanding general recommendations about PREGK, but that relatively complex DOHaDK is not yet being well-communicated/understood. DOHaDK is only beginning to reach some segments of the pregnant population (nulliparous women of higher socio-economic status). The positive association between diet quality and DOHaDK may suggest that understanding the longer-term child health implications of nutritional status during pregnancy could improve maternal nutrition in pregnancy. Future research should investigate the relationships between DOHaDK, PREGK, socio-demographic factors, and pregnancy diet quality in a larger sample and in other contexts. If further work supports our findings, policy and interventions targeting early life NCD risks should aim to improve accessibility of DOHaDK, especially in segments of the population whose access to this knowledge base is limited.

**PO1.10.04**

The Welcome Baby Project: follow-up of the first virtual cohort in Brazil


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**Background:** Brazil is a continent-sized country. It has socially underserved areas and its public health system is complex and unable to meet all demands in an effective and consistent manner. According to official estimates, 60% of pregnant women in Brazil attend less than 7 prenatal doctors’ visits. At the same time, it is estimated that over 120 million Brazilians access the internet; 103 millions access social networks and 65% of them are Facebook users.

**Methods:** Based on these data, the Welcome Baby Project took shape and began in October 2014. We selected 642 pregnant women that were in the first trimester of pregnancy. Participation was on a voluntary basis. All pregnant women who were interested, accepted the terms and conditions, and filled out an online form. We followed them in a closed group within Facebook, the social network used, until the children were 2 years old. To operationalize the research 5 questionnaires were answered during pregnancy, and 5 during the first two years of life, with all the data we needed. We provided behavior-changing health information everyday, enabling the future mothers to go through a healthier and more stress-free pregnancy, encouraging them to properly perform prenatal and, after the children were born, we encouraged them to breastfeed as well as to correctly introduce supplementary feeding after 6 months. We also oriented parents to encourage the development of their children in the first two years.

**Results:** We reached women in 21 of Brazil’s 26 states. All educational extracts and family income levels were covered: 7% of the participants had the first grade, 31% completed high school; 41% went to university and 21% had post graduation. Regarding the family income, we had 23% of families that earned less than 2 minimum wages per capita, 64% between 2 and 10 minimum wages and 13% with more than 10 minimum wages. We wrote 535 posts and 123 surveys to promote interactivity. We had 7582 comments and 40385 likes. Our group had a significant improvement (Pearson p < 0.05) in the number of prenatal consultations, compared to Brazilian population. The exclusive breastfeeding rate up to 6 months of age in our group was 44.5%, also well above the Brazilian average, which is 9.3%. The group dropout rate over the full period of pregnancy was 6.16%. Now, at the end of the study, we have 566 women following us.

**Conclusions:** In the twenty-first century digital communication is one of the most important forms to bring together people from different countries and cultures; particularly for people in the most remote places on the planet. We have to imagine and find new ways to disseminate knowledge using various tools at our disposal. Social networks are clearly one of them, and can be used as a tool to promote health to people of all educational and social levels.
Background: The Tohoku Medical Megabank Organization (ToMMo) was established by Tohoku University after the Great East Japan Earthquake to reconstruct the disaster area with introducing an advanced medical system. The mission of ToMMo is to identify health problems in the aftermath of the disaster and to facilitate the solution with developing personalized health care and medicine. One of the projects to achieve its mission is “The Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study (the TMM BirThree Cohort Study)”. The TMM BirThree Cohort Study is a unique, large population based birth cohort study with genome analysis that recruits pregnant women and their fetuses as well as their family members, including relatives. The purpose of this cohort study is to identify health status of people in the aftermath of the disaster and transfer them to the medical facilities for receiving essential medical service, and to analyze the origin or causes of disease based on their genomic information to establish personalized healthcare and medicine in the disaster area.

Methods: Recruitment of the TMM BirThree Cohort Study was started in July, 2013 and finished at the end of March, 2017. The study collects blood or saliva, urine, questionnaires and medical or health records from all participants. Mothers additionally provide questionnaire twice, blood and urine samples during pregnancy. Breast milk from mothers and cord blood from their babies are also collected. Physiological measurements such as eye examination, body composition, blood pressure, and so on are also obtained for participants who are interested in. Brain and femur magnetic resonance imaging (MRI) is also performed on adults. Furthermore, the study plans to collect a set of examination after five years. In addition to the set of baseline examination, we will measure electrocardiography for both adults and children. We will also analyze serum lipid and thyroid-stimulating hormone for children over 10 years old.

Results: By the end of March, 22,504 mothers and 27,871 family members participated in the TMM BirThree Cohort Study. A total of 22,406 babies were born so far. From the perspective of pedigrees, 5,533 trios with newborns and 3,055 quadros with siblings, and 197 hepta families with whole three generations are included in the study. There are 512 big families consists of more than 7 participants including relatives. Those varieties of pedigrees enable us to elucidate the origin or causes of disease and contribute to build more quality-oriented care. We received a questionnaire at 12 months from 6,585 mothers of babies.

Conclusions: The TMM BirThree Cohort Study could achieve to recruit enough number of study participants over the three generations. We needed a strategic plan to keep a sufficient follow-up rate. We will continue to monitor the follow-up rate and consider other plans to collect enough data for the study.

PO1.10.06

Gender specific DOHaD and implications for women’s health

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Background: Studies examining the associations of early life characteristics with women’s health are rare and the hypothesized combined effect of reproductive history and social mobility on health in late life has not been adequately addressed. Our overarching research goal is to explore how the socioeconomic environment in early life and throughout the life course interacts with gender, health, reproductive behaviour and family formation to affect health and social outcomes of men and women across the life course and across generations.

Methods: The UBCoS Multigen is a representative and well-defined cohort of 14,192 males and females born in Uppsala University Hospital from 1915-1929 that has been combined with social and health data on all their descendants, obtained from Swedish routine registers. The multigenerational study comprises over 150,000 individuals, including cohort members, parents, descendants and partners. 98% of the original cohort members were traced to archive and/or register data and the original cohort members appear to be nationally representative in terms of key variables such as infant mortality and lifetime fertility, indicating the potential to generalize to individuals born in Sweden as a whole. In our epidemiological analyses, we aim to integrate research on social determinants of health with the life course model of pregnancy and childbirth as a sensitive period in the life courses of parents and offspring, and we put a strong focus on gender differences in the investigated associations.

Results: (i) In studies of developmental origins of health and disease among the first generation UBCoS, gender-specific associations have been documented for maternal pelvic size and incidence of different types of stroke as well as for umbilical cord length and risk of chronic rheumatic heart disease in later life. (ii) Studies on the relative importance of cumulative processes and sensitive periods in the development of common chronic disease and survival also indicate some potentially important gender differences. While accumulation models appear to provide the best fit for the effect of socioeconomic position across the life course on circulatory disease mortality in UBCoS men, results for UBCoS women indicate a greater importance of sensitive periods in later life. (iii) Most recently, our material has also provided evidence for associations of early life characteristics with specific disease outcomes concerning women’s reproductive health and ageing in the second generation of UBCoS.
Conclusions: Based on the previous findings and identified knowledge gaps, we perceive a need to focus more on the interrelations between reproductive histories and social mobility, and their combined effect on men’s and women’s health in later life in our future research. We wish to explicitly address potential gender-specific mechanisms by giving a central place in our causal modelling to the determinants and effects of reproductive behaviour and family building. Furthermore, we include specific women’s reproductive health and ageing outcomes in studies of developmental origins of health and disease and we hope to stimulate more empirical research into life course determinants of women’s health.

PO1.10.07

The Human Early Life Exposome (HELIX) project: molecular mechanisms

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The exposome is defined as all the exposures from conception to death. Prenatal and early life exposome is thought to exhibit more damaging effects on health than postnatal insults. This is because foetuses have an immature detoxification metabolism and because the prenatal period is characterized by critical epigenetics changes.

The aims of the Human Early Life Exposome (HELIX) project are: i) to characterize the early life exposome, ii) to associate it with child health outcomes, and iii) to relate it to omics imprints and to understand the action molecular mechanisms. The present abstract focuses on the third objective of the project. The HELIX study consists of 1,300 children from 6 European cohorts (BIB in UK, EDEN in France, KANC in Lithuania, INMA in Spain, MOBA in Norway, and RHEA in Greece) which were followed using the same harmonized protocols. The prenatal and postnatal exposome (>200 exposures) including the outdoor exposome (air pollution, build environment, noise), the individual exposome (cotine, metals, POPs, PFAS, phthalates, phenols, and organophosphates) as well as life style factors (diet or physical activity) were measured. Three main health outcomes were assessed: i) growth and cardio-metabolic phenotype, ii) lung function, asthma and allergy, iii) neurodevelopment and behaviour. In addition, molecular signatures at the age of 6-10 years were obtained: blood DNA methylation (450K, Illumina), gene (HTA v2.0, Affymetrix) and miRNA (SurePrint Human miRNA rel 21, Agilent) transcription, serum metabolites (AbsoluteIDQ p180 kit, Biocrates), urine metabolites (1H NMR) and plasma proteins (Luminex). The global effect of the exposome on the omics profiles will be analyzed using the O2PLS (orthogonal two partial least squares) regression. This will give us a measure of the variability of the omics profiles that could be explained by the exposome, which will be compared with the proportion explained by the genome. Linear regressions adjusted for main confounders (cohort, age, sex, and surrogate variables in the case of blood molecular phenotypes) will be applied to identify molecular biomarkers associated with each exposure. Summarized results will be publicly available. Three environmental exposures with high concern in public health will be analyzed in more detail. They are: tobacco smoking, air pollution and persistent organic pollutants (POPs). Exposure to prenatal and postnatal tobacco smoking is a known risk factor for health outcomes in children. It has been reported that prenatal maternal smoking alters cord blood DNA methylation, with some changes being persistent until adolescence. However, the functional consequences of these changes in terms of gene expression remain unknown. In HELIX, we have confirmed the association between prenatal maternal smoking and methylation changes in particular CpGs at the age of 6-10y. Next, we will study the final consequences of these altered methylation patterns on gene expression. Moreover, the effect of prenatal maternal smoking as well as postnatal environmental passive smoking on the urinary and plasma metabolome will be investigated.

HELIX-omics design.
PO1.10.08

Refusal to partake in an electronic health promotion app

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Background: The World Health Organisation predicts that Ireland will be the most obese country in Europe by 2030. Maternal weight retention has been linked to obesity in their offspring. Postpartum weight gain can be a predictor of sustained weight gain in later life. Pregnancy can be an important window where health promotion can affect the development of obesity in at least two generations. However, there is limited evidence supporting the effectiveness of many obesity prevention or reduction interventions among this population. This study proposes that by encouraging weight loss in postpartum women through the use of a health information smartphone application, the cycle of obesity in women and children can be broken.

Methods: Women were recruited from the postnatal wards of the Coombe Women and Infants University Hospital, Dublin over a 24 month period. They were all approached in the immediate postpartum period and invited to participate in a randomised control trial. Participants were randomised into two groups. The intervention group received a customised health intervention smartphone application while the control group only received the current methods of information delivery in use at the hospital. To participate in the study, women were required to complete questionnaires examining their health literacy, diet and physical activity. Repeat visits at 4 and 9 months post partum were offered. At all time points, body composition of mothers and infants were measured using the Tanita and PeaPod devices.

Results: Of 200 eligible mothers approached, 40% declined to participate without stating a reason. The most popular given reason for refusal at 37% was the time commitment required for followup visits. Other reasons for refusal included the use of another similar app (10%) or an expectation to lose weight for followup visits. Other reasons for refusal included the use of another similar app (10%) or an expectation to lose weight for followup visits. Other reasons for refusal included the use of another similar app (10%) or an expectation to lose weight for followup visits.

Conclusion: Most reasons for recruitment failure occurred at initial approach of mothers. The short postnatal stay, coupled with the inherent busy nature of a postnatal ward may have made mothers feel overwhelmed. Mothers also had to leave the ward in order to have their body composition assessed, taking them away from their infant often for the first time. Our findings can be used to help identify effective methods of improving recruitment of participants in this setting.

PO1.10.09

The Canadian DOHaD cohort registry: a far-ReACHing Maelstrom Research initiative toward facilitating collaborative research

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Background: Major financial and time investments in population-based studies worldwide have supported innovative research that has produced advanced understanding of the relation between various environmental and lifestyle exposures and health and disease outcomes. To optimize the value of such scientifically rich databases there is a need to establish cross-study collaborations and develop tools to support data discovery and co-analysis.

Maelstrom Research aims to address some of the challenges of cross-study collaborations by providing the international research community with resources to leverage and support data documentation, integration, harmonization, and co-analysis. Maelstrom Research develops methods and software, conducts methodological research, generates comprehensive catalogues of study metadata, and creates infrastructures supporting data management, harmonization, and co-analysis.

Methods: In 2016, Maelstrom Research launched the Research Advancement through Cohort Cataloguing and Harmonization (ReACH), a CIHR funded Developmental Origins of Health and Disease (DOHaD) research network. The objective of ReACH is to implement a comprehensive web-based catalogue and data harmonization platform to facilitate the use and co-analysis of data and biological samples collected by Canadian pregnancy and birth cohorts. ReACH is built on the close collaboration with 26 longitudinal studies that directly address the DOHaD theme representing 53,300 mother-child dyads and 17,800 fathers totaling 125,000 participants. The ReACH mandate is also to provide support and training to the users of its resources and when foresee, assist investigators in the realization of their research projects involving integration, harmonization, and co-analysis of data from multiple studies.

Results: The ReACH catalogue offers a web-based access to comprehensive descriptions of study as well as a complete list of variables collected. The metadata documented in the catalogue is freely available at www.maelstrom-research.org/mica/net-work/reach. The catalogue is under continual development as the metadata from more studies is added on a regular basis. The catalogue already covers detailed descriptions for almost all the participating studies and the complete information of the data and biological samples collected for several of them. The number of participants recruited by individual studies range from 200 to up to 16,000, the duration of follow-up range between 2 and 22 years with 18 of the studies still ongoing. The studies either followed their participants from pregnancy or have collected pregnancy-related information retrospectively. Once completed, hundreds of thousand variables will be documented in the ReACH catalogue. In addition, a search interface allows investigators to easily identify studies of interest and data items available to answer specific research questions.
Conclusions: Ultimately, ReACH aims to enhance the potential for collaborative and cross-disciplinary research (outputs generated faster and at a lower cost), expand research perspectives (leverage national and international collaborations), improve quality of research practices, and foster the development of innovative evidence-based research on DOHaD. We encourage new studies and networks of studies to join Maelstrom Research efforts and invite investigators to make use of the ReACH resources for their research projects.

PO1.10.10

We learnt and now we are teaching our family: Adolescent DOHaD knowledge translation supporting health development in the Cook Islands

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Background: Adolescent education can contribute to NCD risk reduction in current and future generations. The Commission on Ending Childhood Obesity report states that school-based interventions must link to the core mission of schools and integrate into mainstream curricula. The Liggins Institute’s DOHaD school-partnership programmes do this, focusing on capability development associated with scientific and health literacies. Programmes support adolescents to examine factors that promote poor environmental exposures, and develop evidence-based actions in response to learning. The Cook Islands a Small Island Developing State with 91%/72% adult overweight/obesity collaborated with the Institute to develop contextually adaptable adolescent DOHaD knowledge-translation programmes.

Aim: To assess the potential of school-based DOHaD knowledge translation in Years 9 & 11 to contribute to development relating to education and primary NCD risk reduction in the Cook Islands.

Methods: Community-based participatory partnership involves translational action-research, examining an issue with those affected by the issue, for the purpose of education and action to effect change. An individually matched repeated timeseries design across two years supported qualitative and quantitative data collection, recognizing the importance of individual change analysis within community-based interventions. Evaluation of concepts beyond the programme supported assessment of internal validity. Analysis to 12-months post-intervention occurred for 66% of the cohort (n = 246).

Results: Professional development and learning resources enabled teachers to use DOHaD/NCDs as a context for learning, and public health professionals to learn about DOHaD and support school-based programmes. Experienced teachers with deep community and pedagogical knowledge thrived, whereas early-career teachers found the programme challenging. The context promoted positive adolescent engagement leading to understanding of concepts associated with the NCD crisis, life-course NCD risk, and contributors to nutritional environmental exposures. Understanding was retained at 12-months post-intervention. Application of critical thinking associated with understanding of the intergenerational nature of NCD risk was stronger in 15-year old females (p’ = .002) than in males or 13-year old females. We observed no change in understanding of life-course evidence not examined within the programme. Baseline nutritional behaviour matched existing national adolescent data. At least 50% of students reporting obesity-promoting nutritional behaviours at baseline recorded positive changes in relation to obesity-promoting foods (e.g. doughnuts, a staple snack, + veΔ = 73%; p < .001). However, 2-fruit/3-vegetable consumption remained similar to adults at < 15%. Focus-group evidence confirmed that: behaviour change was in response to learning; 15-year olds became strongly aware of socioecological challenges associated with fruit/vegetable access; many students engaged peers and family in discussion of life-course NCD evidence and nutrition. Teachers elected to retain and develop the programmes, requesting the addition of adolescent health-profiles to support learning and increase evaluative evidence. Community consultation resulted in a decision to seek funding to expand the programme to the remote outer-islands.

Conclusions: Teachers became health promoters through DOHaD/NCD learning programmes integrated into mainstream curricula. Participation positively influenced nutritional attitudes, knowledge of scientific evidence and nudged long-term small, and therefore sustainable, behaviour changes associated with obesity-promoting foods. Development is required within the national NCD strategy to address fruit/vegetable access. That education elected to continue and develop the programme indicates potential for long-term sustainability.

PO1.10.11

Awareness and understanding of DOHaD-related terms and concepts in students during undergraduate health professional programmes in Japan and New Zealand

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Background: The accumulation of evidence in support of the Developmental Origins of Health and Disease (DOHaD) hypothesis has reached the stage where it should be applied in interventions supporting primary noncommunicable disease (NCD) risk reduction. Because such interventions should engage individuals during the periconceptional period, pregnancy, lactation, childhood, and adolescence, they are
Results: Japanese and New Zealand Year 1 undergraduate students showed low levels of awareness of DOHaD-related terms, and understanding of DOHaD concepts. Awareness and understanding increased as students progressed through undergraduate programmes. Although exposure to DOHaD concepts in undergraduate education was associated with a higher level of awareness of the terms DOHaD or First 1000 days, understanding of DOHaD concepts remained relatively low in both countries at completion of the undergraduate courses. Furthermore, the importance of nutrition during pregnancy in relation to offspring health throughout the life cycle was less recognized than was the impact of maternal nutrition during pregnancy on offspring health in the first two years of life and childhood.

Conclusion: The study demonstrated that undergraduate nutrition and nursing programmes in Japan and New Zealand that integrated DOHaD-related content into teaching contributed to increased awareness of DOHaD, but did not develop adequate understanding of DOHaD concepts by course completion. This indicates the need to review undergraduate teaching programmes and develop learning resources that more effectively address the need for students in health-related courses to understand DOHaD concepts, and their potential application in community health settings. Arising from these findings is further research investigating this issue. This will be presented alongside the data described above in the congress.

PO1.10.12
Baseline profile of a birth and three generation cohort study in Japan: The TMM BirThree Cohort Study
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Background: After the Great East Japan Earthquake in March 2011, the Tohoku Medical Megabank Project was launched in the northeast of Japan to make efforts for reconstructing health system and improving people’s health by introducing a better medical system. To identify health problems in the aftermath of the disaster and to facilitate the solution with developing personalized health care and medicine, “the Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study (the TMM BirThree Cohort Study)” was started in July 2013 as a part of the Tohoku Medical Megabank Project. The TMM BirThree Cohort Study is a unique and large population based birth study, which recruited pregnant women (mothers) and their fetuses as well as fetuses’ fathers, siblings, grandparents and relatives. The project finished recruitment of participants in March 2017. We introduce the cohort profile at the baseline period.

Methods: The TMM BirThree Cohort Study recruited mothers at maternity clinics or hospitals in Miyagi Prefecture in Japan. Mothers who visited our own facilities called Community Support Centers were also recruited. Other family members were also invited through mothers and obtained informed consent at maternal clinics or hospitals as well as Community Support Centers. During pregnancy, mothers were asked to fill out a questionnaire twice and provide blood and urine samples. At childbirth, umbilical cord blood was taken, and another questionnaire, blood, urine and breast milk samples were collected. Mothers and fathers were asked to fill out a questionnaire twice and provide blood and urine samples. For the nutrition students in Japan, DOHaD concepts were first introduced in Year 1 via a 90-minute lecture which followed completion of the questionnaire. Throughout the rest of the programme, DOHaD concepts were integrated into lectures covering core concepts of ‘Nutrition in the Life Cycle’. For the nursing students in New Zealand, DOHaD concepts were integrated in the curriculum throughout the programme rather than being treated as a specific topic.

Results: Baseline pro...
Early-life stressors and LifeCycle health

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Early life is an important window of opportunity to improve health across the full lifecycle. European pregnancy and child cohort studies together offer a unique opportunity to identify a wide range of early-life stressors linked with individual biological, developmental and health trajectory variations, and with the onset and evolution of non-communicable diseases. The LifeCycle project will establish the EU Child Cohort Network, which brings together existing, successful pregnancy and child cohorts and biobanks, by developing a governance structure taking account of national and European ethical, legal and societal implications, a shared data management platform and data harmonization strategies. LifeCycle will enrich this EU Child Cohort Network by generating new integrated data on early-life stressors related to socio-economic, migration, urban environment and lifestyle determinants, and will capitalize on these data by performing hypothesis-driven research on early-life stressors influencing cardio-metabolic, respiratory and mental health trajectories during the full lifecycle, and the underlying epigenetic mechanisms. LifeCycle will translate these results into recommendations for targeted strategies and personalized prediction models to improve health trajectories for current and future Europeans generations by optimizing their earliest phase of life.

To strengthen this long-term collaboration, LifeCycle will organize yearly international meetings open to pregnancy and child cohort researchers, introduce a Fellowship Training Programme for the exchange of junior researchers between European pregnancy or child cohorts and develop e-learning modules for researchers performing life-course health studies. Ultimately, LifeCycle will lead to a unique sustainable EU Child Cohort Network, and provide recommendations for targeted prevention strategies by identification of novel markers of early life stressors related to health trajectories throughout the lifecycle.

This project received funding from the European Union’s Horizon 2020 Research and Innovation programme under grant agreement No 733206 (LifeCycle).

PO1.10.14

Sharing Longitudinal, Non-Biological Birth Cohort Data: A Cross-Sectional Analysis of Parent Consent Preferences

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Background: Many funders, institutions and journals now mandate publicly-funded research data sharing for reuse, while data repositories and biobanks proliferate to facilitate reuse. Longitudinal birth cohorts (LBCs) are rich data sources, with their prospective design, large samples, longer-term follow-up, and diverse datasets. The benefits of data sharing are myriad, including further analyses, increased complexity of research opportunities, more collaborations, maximized public contributions, and decreased respondent burdens.

LBC data sharing faces significant ethical challenges including privacy, consent, governance, communication, and child vulnerability. These challenges have been studied for sharing biological data, but such standards may not apply to epidemiological data. Consensus is lacking on how best to garner consent, withdraw, communicate, and respect children’s burgeoning autonomy. Stakeholder engagement is critical for appropriately generating consensus.

Methods: Using a cross-sectional, online survey, this study aimed to understand the consent preferences of LBC parent participants on reusing their, and their child’s, de-identified, non-biological LBC data. The study population included parent participants from two provincial LBCs. Survey design involved literature reviews, a qualitative study, and cognitive interviewing (n = 9). The survey contained background information on repository governance best practices, and questions on consent models, communication frequency and methods, and child involvement in decision-making. Using STATA, data analysis included descriptive frequency distributions, and tests for associations using Chi-squared and Fisher’s exact tests.

Results: Of the 569 parents invited, 346 completed the survey (60.8%). Participants preferred less-active models of consent (no consent asked; opt-out consent) over more-active models (project-specific consent; tiered consent; broad or periodic consent) when asked to share data. Only 55.8% of respondents felt that consent should be sought. Of those requiring permission, the models most frequently preferred were opt-out (47.2%) and project-specific (21.9%). Communication and consent preferences were associated: more-active consent was linked with greater repository update requests, in content (p < 0.03) and frequency (p < 0.01). Child involvement in data-sharing decision-making involves 3 phases: telling child (1-way), talking to child (2-way), and letting child decide. Parents generally agreed (82.0%) that at some point, they would tell their child of their involvement in data...
sharing. There was substantial variability on the age to begin each phase. For decisions on data sharing, 12 years old was the age that parents would tell (21.5%) and talk (22.9%) to their child; but, 18 years (25.6%) was preferred for letting the child decide. The majority of parents (63.8%) wanted to continue to be informed of the child’s decision to share data after yielded decision-making authority.

Conclusions: For non-biological LBC data, LBC parent participants seem to prefer less-active models of consent. LBC parents may be quite supportive of data sharing, and may not view non-biological and biological data similarly, despite many guidelines and policy instruments currently not distinguishing them. Because rigorous governance was discussed within the survey, it may be that parents prioritized governance over consent to protect their and their child’s interests during data sharing. Future research is required to test such associations. Further research is also required to understand how best to mobilize parental agreement that children should be involved.

PO1.10.15
Recruitment of women in early pregnancy in South Africa: the early access conundrum
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Background: South Africa has a high maternal mortality rate at 138 per 100 000 live births in 2015. The infant mortality rate is similarly high at 33 per 1000 live births. Nutrition has been shown to influence birth outcomes and long-term health. Undernourishment in utero can stress the foetus in ways that permanently affect physiological development. Foetal growth retardation and small size at birth due to maternal malnutrition may result in an increased risk of obesity, coronary heart disease, hypertension, stroke, type 2 diabetes, osteoporosis as well as impairments in thymic and spleen size and ultimately immune function in the adult offspring. Therefore understanding the nutritional status of women in South Africa may provide a basis for nutritional interventions which can improve birth outcomes and long-term health. With this intent, the Nutrition during Pregnancy and Early Development (NuPED) study, which aims to assess dietary intake and nutritional status of urban pregnant women in South Africa and to determine associations with birth outcomes, maternal and offspring health, started recruitment of pregnant women in March 2016 and is ongoing. South African statistics show that only 51.7% of women attend antenatal care before 20 weeks’ gestation.

Methods: The study has an observational, longitudinal design. Pregnant women are being recruited from primary healthcare clinics in Johannesburg. Women are informed in the waiting area of the antenatal clinic about the project and those who possibly fit the inclusion criteria are screened individually and invited to take part in the study. Inclusion criteria are less than 18 weeks gestation; aged 18 – 39 years; non-smoking; generally healthy; singleton pregnancy; born in South Africa or neighbouring countries and planning or willing to deliver the baby at the provincial hospital (referral hospital). The intended number of study participants is 250.

Results: A total of 931 women have been screened for inclusion by April 2017. However, only 418 (44.9%) could be invited to take part in the study based on inclusion criteria. Of those invited, only 203 (48.6%) arrived at the study site. After obtaining written informed consent, accessing maternal medical files and performing ultrasound sonography, another 46 participants were excluded on the basis of being >18 weeks’ gestation (n = 28; 61%); missed miscarriage or empty uterus (n = 8; 17%); hypertension (n = 4; 9%); on treatment for hypercholesterolaemia (n = 1; 2%); on treatment for tuberculosis (n = 1; 2%); twin pregnancy (n = 1; 2%); being older than 39 years (n = 1; 2%) relocation (n = 1; 2%) and smoking (n = 1; 2%). Therefore, a total of 157 participants were included after 13 months of recruitment at four primary healthcare facilities in Johannesburg.

Conclusion: Conducting research investigating early pregnancy health status in South Africa poses a challenge mainly due to the women seeking antenatal care late in their pregnancies. Furthermore, late antenatal care access impacts the ability of the South African healthcare system to positively influence maternal and foetal health, with specific reference to mother-to-child-transmission; nutritional supplementation and preventable conditions such as anaemia and hypertension.

PO1.10.16
How could we recruit Grandparents in Genome Birth Cohort Study? Lessons Learnt from the TMM BirThree Cohort Study
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Background: Involving family members especially grandparents in prospective birth cohort studies might be helpful to investigate both genetic and environmental factors for common diseases. We launched a world-leading large birth and three-generation cohort study in 2013. We describe strategies which we used to recruit family members for our prospective birth cohort study, focusing on grandparents in particular.

Methods: Our main strategies are: 1) We standardized informed consent process with reference materials to help
people understand the consent form, based on the interview to some local residents, 2) We created an invitation letter to contact family members, and asked mothers to give the letter to her family members, 3) We recruited family members in clinical settings or our own facilities, and also visited their home or near their home. We implemented many other strategies, too.

**Results:** As of the end of October 2016, the number of invitation letters distributed to family members was 22,995, 18,066 of which were distributed to grandparents. Of these 18,066 letters, 2,827 (15.6%) were returned. As of the end of October 2016, 7,041 grandparents were participating in the study. Maternal grandparents participated in the study more than paternal grandparents. In general, grandparents joined the study anytime during mother’s maternal check-ups or delivery (206.4 ± 172.8 days). The setting in which most grandparents were recruited our own facilities. Both paternal and maternal grandparents significantly participated in the study if the father also participated.

**Conclusions:** We recruited not only pregnant women and fetuses but also fathers and grandparents with many strategies.

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**PO1.10.17**

The impact of the UK 2008-2010 recession on maternal and infant health in the Born in Bradford cohort

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**Background:** The purpose of this study was to assess associations between exposure to the 2008-2010 UK recession, financial stress and maternal and infant health.

**Methods:** Cross-sectional data from the Born in Bradford (BiB) cohort study, which recruited pregnant women from 2007-2010 in a deprived and ethnically diverse city in the North of England, is used to study low birth weight in term babies, preterm birth, smoking during pregnancy and maternal psychological distress in relation to exposure to recession as indicated by a date of recruitment since the first of August 2008.

**Results:** 10 035 mother-infant pairs were analysed. Pregnant women exposed to recession reported higher levels of psychological distress (adjusted β 0.05, 95% CI -0.00 to 0.10). Exposure to recession was not associated with low birth weight or preterm birth, but reporting a worse financial situation was associated with preterm birth (OR 1.32, 95% CI 1.06; 1.66). Exposed women were more likely to smoke during pregnancy (adjusted OR 1.22, 95% CI 1.03;1.43).

**Conclusions:** Exposure to the 2008-2010 UK recession is associated with financial stress, continuing smoking during pregnancy and potentially with maternal psychological distress. A direct impact on birth outcomes could not be demonstrated.

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**PO1.10.18**

Lifelines: a unique biobank providing data to study the development of diseases

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Since its start in 2006, the Lifelines Cohort Study and Biobank follows more than 167,000 inhabitants of the northern parts of the Netherlands (including children and elderslies) over a 30-year period. Every five years, participants visit their local Lifelines site to provide blood, urine, hair, and stool samples, undergo various physical measurements (ECG, blood pressure, etc.), and to fill in extensive questionnaires about their physical and mental health, food intake, exercise habits, quality of life, socio-economic status, physical environment and much more. The whole genome is known for a subset of 13,000 participants, with many more in process. Lifelines currently collects an extensive set of samples and data from pregnant participants and, at several moments after birth, their babies (Lifelines-NEXT). Our participants represent a normally aging population. Most participants are healthy, but an ever increasing number develops one or more (chronic) illnesses – as can be expected in an aging cohort. Our dynamic and rapidly expanding dataset provides a unique opportunity for scientists to perform cross-sectional, longitudinal, or retrospective research into (epi-)genetic, physiological or environmental factors involved in – or even predicting - the development of various diseases and disorders. Interested scientists can apply for access to our data and samples with a suitable research proposal. Moreover, researchers can request the additional collection of more specific biological samples, physical measurements or questionnaire data from our participants, making use of our flexible and efficient infrastructure and extensive background information. Information on all research-related topics can be found on www.lifelines.nl/researcher, and questions/comments can be discussed directly with the Lifelines representative at DOHaD2017 or addressed to research@lifelines.nl.
Potential for postnatal nutrition interventions

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More than a quarter of a century ago, the term “fetal programming of adult disease” was coined reflecting the concept that nutritional and environmental cues modulate long term health and disease risks particularly during the period of fetal growth and development. However, ample evidence from experimental and epidemiological studies, and first human intervention studies have documented the occurrence of developmental programming not only in the fetal but also in the embryonic and early childhood periods. Consequently, the term “fetal programming” has been replaced by the concept of early developmental plasticity ranging from pre-conception through pregnancy to infancy and the toddler age. Numerous observational studies and meta-analyses point to possible programming effects of early life nutrition. For example, associated with a moderate but consistent risk reduction for overweight and obesity in later childhood and adulthood. We followed the hypothesis that the protective effects of breastfeeding is mediated at least in part by the lower protein content than provided with conventional bottle milks, resulting in more moderate infant weight gain and body fat deposition (“Early Protein Hypothesis”). We tested this hypothesis in a large double blind randomised clinical trial funded by the European Commission and enrolled 1678 term born infants in five EU countries (Belgium, Germany, Italy, Poland, Spain). Infants were randomised to receive for the first year of life conventional bottle milk, or isoenergetic intervention formulae with reduced protein supply did not affect length growth but normalised body weight and Body-Mass-Index (BMI) at the age of 2 years, as compared to a reference group of breastfed children and the child growth standards of the World Health Organisation. The effect on BMI lasted until early school age. At age 6 years the adjusted relative obesity risk of children previously fed conventional high protein formula was 2.60 fold higher (95% Confidence Interval: 1.33-5.10) than with a reduced protein formula in infancy. Exploration of potential underlying mechanisms showed lower protein supply to reduced secretion of IGF-1 and insulin. Plasma concentration of IGF-1 at age 6 months is positively associated with weight gain up to the age of 2 years. Dietary effects on the IGF-1 axis outweighed by far the effects of genetics and gender. There was also a significant effect on kidney growth that appeared to be mediated by IGF-1. Results of metabolomic and amino acid analyses suggest that not only the quantity of protein supply, but also the quality of protein provided in infancy is important for modulating infant growth, which provides further opportunities for effective early life prevention of later obesity and for health lasting health promotion by optimized feeding in early childhood.

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PL2.01.02

Nutrition and the first thousand days: maternal and prenatal interventions

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Despite considerable reductions since 1990, 156 million or 23.2% of children under five were still affected by linear growth stunting in 2015, and 43% of children worldwide are at risk of not reaching their developmental potential due to poverty and stunting. This developmental deficit is estimated to result in about a 25% annual reduction in income-earning potential in adulthood, illustrating the consequences of poor development on human capital. Asia and Africa bear the greatest burden of malnutrition; in 2015, 56% and 37% of stunted children lived in Asia and Africa, respectively. Stunting also disproportionally affects children living in the poorest population quintiles and those in rural and remote communities. The urgent need to address malnutrition is reflected in the second Sustainable Development Goal, which sets global targets for eliminating hunger, improving nutritional status, and supporting food security. There is a close link between maternal and infant nutrition as expectant mothers and children under five years are especially vulnerable to malnutrition and micronutrient deficits given their increased nutritional needs. Maternal undernutrition increases the risk of fetal growth restriction and preterm birth, and thereby perpetuates an intergenerational cycle of malnutrition and poverty, especially among adolescents and child brides. Pregnancy and the first 1000 days of life, from conception to age two years, is considered a sensitive window of opportunity for nutritional interventions to promote optimal growth and development –
the benefits of which extend into adulthood. A range of nutrition interventions can benefit growth in infancy of which improving maternal and fetal nutrition through balanced energy protein intake and preconception nutrition improvement are important. Micronutrient deficiencies are prevalent in both underweight and obese populations and are linked to adverse pregnancy outcomes. Iron supplementation can protect against low birth weight (RR 0.83, 95% CI 0.73-0.94 - malaria endemic areas); however, approximately 40% of women between 15 and 49 years still have anemia worldwide. Recent evidence also suggests a possible benefit in at-risk populations in replacing iron-folate supplementation with multiple micronutrient supplementation in pregnancy, further reducing the risk of small for gestational age birth (RR 0.91, 95% CI 0.84-0.97). While postnatal micronutrient supplementation and fortification studies in childhood have not shown consistent effects on growth (other than zinc on height [SMD 0.09, 95% CI 0.06-0.13]), zinc deficiency [RR 0.49, 95% CI 0.45-0.53]), recent data on multiple micronutrient supplementation via micronutrient powders (reduced risk of iron deficiency anemia: RR 0.43, 95% CI 0.35-0.52) and small-quantity lipid-based nutrient supplements is promising, particularly for the prevention of stunting at one year of age and possibly wasting. Several strategies are in use globally to address micronutrient deficiencies in children with a focus on survival, but relatively few have addressed growth. These include supplementation as well as food fortification. This presentation will also summarize the available global evidence of best practices and strategies and discuss next steps in relation to the Sustainable Development Goals.

**PL2.01.04**

**Maternal nutrition and metabolic outcomes in the offspring**

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The Growing Up in Singapore Towards healthy Outcomes (GUSTO) study recruited pregnant women aged 18 years and above, attending their first trimester antenatal dating ultrasound scan clinic at Singapore’s two major public maternity units, namely National University Hospital (NUH) and KK Women’s and Children’s Hospital (KKH) between June 2009 and September 2010. The participants approached were Singapore citizens or permanent residents who were of Chinese, Malay or Indian ethnicity with homogeneous parental ethnic background. Of the 1247 women (response rate 61.3%) recruited, 1162 conceived naturally and 85 conceived through in vitro fertilisation (IVF). At baseline, 55.9% were Chinese, 26.1% Malay and 18.0% Indian. Mean maternal age at recruitment was 30.6 years (range: 18–46 years). A total of 1176 babies were born. The first baby was born on 30 November 2009 and the last baby was born on 1 May 2011. During infancy, the babies were examined at home at 3 weeks, 3 months and 3-monthly thereafter until 15 months of age. The children were then seen at the study clinic at 18 months onwards at 6-monthly intervals. The oldest child will be 8 years old in November 2017. The current attrition rate is about 15%, with most participants having withdrawn before or soon after delivery. The purpose of the GUSTO study is to define the developmental pathways and mechanisms of the origins of metabolic disease, and neurodevelopmental disorders that have major public health and economic importance in Asia and globally. With in-depth and frequent phenotyping during pregnancy and childhood, we captured data on demography, socio-economic status, lifestyle, medical history, dietary patterns, cardio-metabolic and neuropsychiatric status. Multiple biospecimens including umbilical cord, cord blood and placenta at delivery, serial buccal swabs, breastmilk, hair, fecal samples, urine and blood were collected from the mother and child. This talk will report some of our findings around maternal nutrition during pregnancy and the metabolic outcomes in the offspring as reflected by weight and adiposity at birth and the subsequent growth patterns and adiposity of the children.

**CS2.01- DOHaD Annual General Meeting**

**CS2.01.01**

**DOHaD Annual General Meeting**

M. Hanson, D. Sloboda

The International DOHaD Society will hold an Annual General Meeting on Tuesday October 17th at 10.15 am. All Society members are recommended to attend the AGM, where matters of Society business will be presented and discussed. It is here that important decisions regarding the Society business activities are discussed and voted on.

**PA2.01.01 – Placental programming**

**Placental adaptation and offspring outcomes**

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The diversity of placental structures across species demonstrates that placental adaptation promotes offspring survival across generations. Within individual pregnancies, placental adaptation may also occur to optimise fetal survival in response to sensing of the maternal environment. These adaptations in placental function may have consequences for health across the life-course. Of particular interest is how the placenta responds to maternal over nutrition, something that is now common but which is unlikely to have been a primary driver of placental evolution. This talk will address how adaptation in placental structure, transport metabolism and signaling can improve offspring survival and how this may influence postnatal health.
PA2.01.03

Placental nutrient transfer adaptations

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The placenta is interposed between the maternal and fetal circulations and, thus, the essential organ to supply maternal nutrients to the growing fetus. In order to allow the fetus to develop in a rather stable environment, one might expect adaptations of placental nutrient transfer to situations of maternal under- (fetal growth restriction) and oversupply (maternal obesity, diabetes mellitus) of nutrients. In obesity and diabetes the placenta can store some excess glucose and fatty acids as glycogen and lipid droplets, respectively. However, the capacity of these stores is too small to constitute a relevant buffer, and their breakdown into constituents does not (glucose) or is unlikely (fatty acids) to contribute to fetal supply. Changes in the levels and activity of transporters for glucose and fatty acids might be another means of mounting adaptive responses. In fact these changes have been found. However, they do not seem to have a consequence for maternal-fetal transfer of glucose and fatty acids, for which the maternal-fetal concentration gradient may be the most important determinant. In addition, in absence of a glucose transfer change in fetal growth restriction per unit tissue mass, total placental mass is a further determinant, but it does not adapt to fetal nutrient needs. The only example established so far for an adaptive placental response relevant for ‘nutrient’ transfer is hypervascularization. This occurs when fetal demand for oxygen is high, because of metabolic reasons (fetal hyperinsulinemia in overnutrition). Collectively, and with the limitation that it may be different in animal pregnancies, the placenta does not appear to adapt its capacity and activity for the transfer of the key nutrients glucose and fatty acids to fetal needs, at least not at the end of human pregnancy.

PA2.01.05

Maternal 2-hour glucose levels are associated with placenta DNA methylation of genes with potential functional expression adaptations

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Background: Maternal hyperglycemia during pregnancy is associated with fetal growth and adverse perinatal and developmental outcomes. Placental adaptation to maternal hyperglycemia has been hypothesized to be part of the pathophysiology explaining these associations. Although exact molecular mechanisms remain unknown, DNA methylation may be involved.

Methods: We conducted an epigenome-wide association study of prenatal maternal glucose response and DNA methylation of the placenta at birth among 448 mother-infant pairs in a prospective birth cohort. Women without pre-existing diabetes were recruited during the 1st trimester of pregnancy and followed until delivery. All women performed a standard 2-hour 75-g oral glucose tolerance test at 24-28 weeks of gestation. At delivery, we collected placenta samples and measured DNA methylation at >850,000 CpG sites using the Illumina Infinium MethylationEPIC BeadChip. We employed standard quality control procedures, array normalization methods and adjusted for technical batch effects as well as potential confounders, including adjustment for cell type heterogeneity. We analyzed 791,131 autosomal CpGs after excluding low quality, cross-reactive and SNP associated probes and performed CpG-by-CpG analyses using robust linear regression models controlling for the false discovery rate at 5%. Additionally, among genes significantly associated with 2-hour glucose levels we quantified gene expression in placenta samples using real-time quantitative PCR from a random sample of 104 mother-infant pairs.

Results: Maternal 2-hour glucose levels were strongly associated with lower DNA methylation of 4 CpGs (P < 1×10^-6) within the transcription start site and body of the Phosphodiesterase 4B gene (PDE4B), (Figure). The % difference in methylation ranged from 1.2% to 0.6% per one mMol/L increase in 2-hour glucose. Furthermore, we observed that DNA methylation at all four loci was significantly associated with greater PDE4B expression (rspearman: 0.26 to 0.35, P < 0.01). Additionally, three other CpG sites were differentially methylated relative to maternal 2-hour glucose levels found in the body of the Low Density Lipoprotein Receptor gene (LDLR), in a CpG island of the TNF Receptor Superfamily Member 1B gene (TNFRSF1B) and in the body of the Bloom Syndrome RecQ Like Helicase gene (BLM). LDLR methylation at the CpG site was associated with greater LDLR expression (rspearman: 0.22, P = 0.03) while CpG methylation at the TNFRSF1B site was associated with lower TNFRSF1B expression (rspearman: -0.25, P = 0.01). There was no association between BLM methylation and gene expression at the site.

Conclusions: Maternal post-load glucose levels are associated with placental DNA methylation at birth of some genomic loci, particularly within the PDE4B gene. PDE4B hydrolyzes the second messenger cAMP, a key regulator of many physiological processes including inflammatory pathways. PDE4B is also suggested to participate in placental pathophysiology of preterm birth in animal models. Our study provides evidence that maternal glucose response during pregnancy is associated with DNA methylation of genes within the placenta which are partially under epigenetic control for gene expression.
Methods: We further analyzed the relationship between genomic risk and association of schizophrenia with genomic risk. Intrauterine and perinatal environment in modulating the disorder like schizophrenia. Here we analyze the role of environmental context in which genes enhance risk for complex mental illness. Complications, ELCs) on case-control status, in three independent samples of healthy subjects and patients with schizophrenia. From USA (n = 1019) and Japan (n = 919). We further analyzed the relationship between genomic risk and ELCs in two samples of only cases from Germany (n = 919). This increases vascular resistance and hampers placental perfusion. A promising drug to counteract this phenomenon is the phosphodiesterase (PDE) inhibitor sildenafil. Sildenafil enhances vasodilation mediated by the NO-cGMP pathway. In PE animal models, sildenafil improved fetal

Conclusions: Our data suggest that the most significant schizophrenia GWAS variants contribute to risk at least partly by converging on a developmental trajectory sensitive to ELCs and altered placental gene expression. The sex-associated effects on placental transcription suggest that the male preponderance of schizophrenia may arise from gene-environment interactions that influence placental biology. These results highlight placental health as a new public health frontier for primary prevention, particularly in high-risk males.
outcome (increased birth weight, litter size and fetal survival) and additionally diminished maternal symptoms. Preliminary clinical studies in PE patients tend to confirm these findings. In the present study, applying dual perfusion of a single placental lobule (cotyledon) obtained from placentae of gestational age-matched healthy and PE pregnant women, we addressed the question whether sildenafil enhances placental perfusion in humans.

Methods: Healthy and PE placentae (n = 5/group, 31.5 ± 2.1 vs. 33.8 ± 4.8 years, 39.3 ± 0.5 vs. 39.3 ± 1.0 gestational weeks) were perfused, pre-constricted with 3nM to 1μM serotonin, and exposed to the NO donor sodium nitroprusside (SNP, 3nM to 1μM ) in the absence or presence of 500 ng/mL sildenafil.

Results: Our preliminary data show that, compared to healthy placentae, serotonin induced comparable pre-constriction in PE placentae, while SNP responsiveness was lower, as evidenced by a “4-fold reduction in potency. Sildenafil partially restored the reduced SNP responsiveness in PE placentae, but also enhanced SNP responsiveness in healthy placentae.

Conclusion: Our preliminary data confirm that NO-mediated vasodilation is deteriorated in the fetoplacental circulation during PE. Enhancement of NO vasodilation by sildenafil can reverse this phenomenon, thus supporting the use of this drug in PE.

PA2.01.08

Igf2 deletion from the murine placental endocrine layer alters maternal sensitivity to glucose and insulin, and reduces fetal growth

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Background: Abnormal intrauterine growth and its associated programming effects are major financial burdens on health care systems worldwide. Infants born of compromised pregnancies are at increased risk of developing adult-onset metabolic diseases, including diabetes and obesity, which are associated with poor health and premature death. Despite this, our understanding of the regulation of fetal growth is incomplete. The placenta, the site of maternal-fetal exchange, is a key endocrine organ and regulator of fetal growth. Past studies demonstrated that placental-derived hormones have metabolic effects and may thereby impact the maternal nutrient availability for fetal growth. However, the precise role of placental endocrine function in modulating maternal metabolism to support fetal growth and its importance for the future health outcomes of the offspring is unknown. Insulin-like growth factor 2 (Igf2), is a paternally expressed imprinted gene, which drives placental endocrine cell formation. Therefore, the aim of this study was to determine the effect of selective Igf2 deletion from the endocrine layer of the placenta on maternal metabolism and fetal growth in mice.

Methods: TpbpaCre females were crossed with Igf2-floxed males to produce whole litters with specific Igf2 deletion in the placental endocrine layer (leaving the placental transport zone, fetus and mother un-manipulated). On day 16 of pregnancy (term ~ 20 days), dams were subjected to glucose or insulin tolerance tests before being sacrificed for tissue collection. Fetuses and placentae were then weighed and analysed by litter means for greater stringency. Dams from the reverse cross (ie Igf2-floxed females crossed with TpbpaCre males) and non-pregnant mice were used as controls. Procedures were performed according to the UK Home Office Animals (Scientific Procedures) Act 1986.

Results: Compared with non-pregnant mice, control reverse cross dams were significantly glucose intolerant and insulin resistant on day 16 of pregnancy, as reflected by a slower clearance of glucose from the maternal circulation or a smaller fall in maternal circulating glucose following a glucose or insulin challenge respectively (Figure A & B). In contrast, dams with placental endocrine Igf2 deletion failed to adapt and remained sensitive to glucose and insulin, similar to that seen in non-pregnant mice. Importantly, this failure to metabolically adapt was associated with significantly smaller litter sizes (Figure C), a 12% reduction in fetal weight (Figure D), lower placental efficiency as indicated by fetal-placental weight ratios (Figure E), and no change in placental weight (Figure F). Including litter size as a covariate did not change the effect of genotype on parameters significantly affected by litter size.

Conclusions: Therefore, Igf2 expression in the placental endocrine layer is critical in adapting maternal sensitivity to glucose and insulin during pregnancy, with consequences for litter size, fetal growth and placental efficiency. Experiments are currently ongoing to examine whether changes in maternal metabolism relate to altered placental endocrine function and fetal nutrient supply, and to determine the long-term impact of compromised placental endocrine function on offspring metabolic health.

Acknowledgements: This work was supported by funding from the Agency for Science, Technology and Research and the Royal Society.

Figure: Effect of placental endocrine Igf2 deletion on maternal glucose and insulin tolerance, litter size, fetal weight, fetal-placental weight ratio and placental weights on day 16 of pregnancy in mice. Number of dams were 20 per genotype for glucose and insulin tolerance tests. AUC and AINC refer to the area under or above the curve respectively. Number of fetuses and placentae weighed were 240 per genotype. All statistical analyses were performed on litter means. Data are individual values with mean ± SEM shown and analysed by either one way ANOVA with Tukey’s post-test or Student’s t-test (**P<0.01, ***P<0.001).
PA2.02 – Early environment

PA2.02.01

Biodiversity and microbes: Ecological solutions to the human health crisis
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The balance and composition of human microbes are a product of our societal ecosystems and how we live – including both our stressors and our positive emotions and experiences alike. There are clear links between environmental change, “dysbiosis” of the human microbiome, and the pandemic of modern lifestyle diseases. Most of these inflammatory conditions (ranging from allergy, obesity, diabetes heart disease and even mental ill health) are mediated by effects on the immune system, which is altered by dysbiosis. The factors driving personal dysbiosis are ultimately the same factors that are driving planetary dysbiosis (which literally means “life in distress”) on every level, from the first moments of life. Galloping consumerism, excessive consumption of ultra-process food, and an indoor device culture are driving us away progressively from nature and each other - all adding to stress, anxiety, sleep disturbance, alcohol and drug dependence, isolation and depression. All these factors interact with our microbiome and our immune health, promoting dysbiosis and inflammation. Paradoxically in a culture “where there is never enough” we are losing much of what is important for health and happiness. Environmental erosion and “nature deficit” are progressively eroding positive emotions such as empathy, compassion and optimism, which in turn undermine immune resilience. In essence, a spiral of self-destructive interactions manifest at the individual level in our health and across societies in broken systems, environmental degradation and social inequality. The solutions depend on understanding these interconnections - seeing ourselves as part of these ecosystems, and taking lessons from the natural world. Microbial solutions already reveal the value of restoring ecosystems for both human health and for breaking down man-made waste, plastics, and pollutants. However, any such solutions will only be meaningful and sustainable if societal values promote ecosystems that thrive on mutually advantageous relationships, rather than mutually destructive ones. As well as the immediate benefits - for personal health, food choices, nature relatedness, microbiomes, optimism, immune health, sense of purpose and connection to community – a sense of symbiotic mutualism has flow-on benefits to the whole of society. Ultimately, a normative shift towards more mutualistic values is the only way we will to overcome the erosion of our social fabric, the natural environment and our health.

PA2.02.03

The Role of Human Milk in Early Nutrition Programming
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Human milk (HM) from the infant’s own mother (excludes donor human milk) has been linked in multiple cohort studies to a reduction in the risk of childhood- and adult- onset morbidities including infections and noncommunicable chronic diseases such as asthma, obesity, hypertension and diabetes. Furthermore, recent studies reveal a dose-response relationship between amount of HM received by the infant and improved neurodevelopmental outcome into childhood. In infants born preterm, relatively short durations of HM feedings during the neonatal intensive care unit (NICU) hospitalization predict a reduction in post-NICU discharge infections and rehospitalizations through to 20 months corrected age and in a reduction of neurodevelopmental problems through to age 7. The results from these observational cohort studies, which are typically the default research design in HM research due to the inability to randomly assign feeding type, have been supported by recent mechanistic findings. In particular, technologies such as non-culture methodologies for characterizing the HM- and infant gut- microbiomes and the use of magnetic resonance imaging of the brain have provided a window into mechanisms as to how HM feedings may explain these observed cohort findings. This presentation will focus on HM stem cells, the highly personalized HM microbiome, the concept of HM as neuroprotective in premature infants and other nutritional and bioactive HM components that potentially affect and program long-term health. Many of these nutritional and bioactive components are highly concentrated in HM during the first postpartum month and in higher concentrations in prematurely delivered mothers. This early concentration of HM growth factors, cytokines, metabolically active adipokines and select components such as myo-inositol, suggest a role for nutritional programming with HM that is not replicable with formulas or donor HM. Finally, the profiles of HM-borne inflammatory cytokines and dysbiotic bacteria in lactating overweight and obese women will be summarized to exemplify the potential of HM to influence transgenerational health in offspring.

PA2.02.05

Tobacco control policies and perinatal and child health: a systematic review and meta-analysis

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Tobacco smoke exposure during pregnancy and childhood is responsible for considerable morbidity and mortality among newborns and children. We aimed to determine whether
implementation of World Health Organization (WHO)-recommended tobacco control policies benefits perinatal and child health. We extensively searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and 17 other online databases through October 2016 for randomised and clinical controlled trials, controlled before-after studies, and interrupted time series (ITS) studies that studied the impact of WHO-recommended tobacco control policies on health outcomes among children aged 0-12 years. Primary outcomes were: perinatal mortality, preterm birth, and hospital attendance for asthma exacerbations and respiratory tract infections (RTIs). We assessed risk of bias using Cochrane Effective Practice and Organisation of Care (EPOC) criteria. Where possible and appropriate, we combined data from studies in random-effects meta-analysis. We identified 36 eligible ITS studies that assessed (combinations of) the following tobacco control policies: smoke-free legislation (n = 29), tobacco price/taxation (n = 10), and smoking cessation services (n = 3). Following implementation of smoke-free legislation, rates of preterm birth decreased by -3.4% [95% CI -6.8 to -0.1] (8 studies, 22,209,054 individuals) and rates of hospital attendance due to asthma exacerbation and lower RTIs decreased by -9.5% [95% CI -15.4 to -3.7] (5 studies, 356,091 events) and -18.5% [95% CI -32.8 to -4.2] (3 studies, 887,414 events), respectively. Effect estimates were largest for the most comprehensive smoke-free laws. No significant impact on perinatal mortality was seen (1 study, -6.0% [95% CI -12.9 to 2.0]). Although a number of studies also suggested benefit of increasing tobacco taxation and expanding smoking cessation services, meta-analysis of these data was not possible. Smoke-free legislation is associated with substantial child health benefits, particularly if comprehensively applied. Few studies have assessed the impact of other tobacco control policies, some with positive findings. It is important to increase the uptake of comprehensive tobacco control policies worldwide to protect the health of both children and adults, and to simultaneously evaluate the effectiveness of these policy initiatives. Longfonds. Erasmus Medical Centre. Chief Scientist Office’s of the Scottish Government.

PA2.02.06

Socioeconomic position in childhood and adulthood and ideal cardiovascular health: A 32-year longitudinal study

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Background: Recently, there has been a growing interest in factors that promote health and protect from adverse cardiac health outcomes. A socioeconomic gradient has been widely recognized in the cardiovascular diseases, but little is known about the role of early childhood socioeconomic position (SEP) for positive cardiovascular health later in life. Even less is known about the pathways linking early SEP with positive health outcomes in adulthood and whether the effects of early disadvantaged SEP on later health can be mitigated by achieving better SEP in adulthood compared to childhood SEP (i.e., upward mobility). We are examining the associations between childhood SEP, adulthood SEP, and ideal cardiovascular health in adulthood using longitudinal data spanning over 32 years.

Methods: The participants were 697 Finnish children and adolescents from longitudinal prospective The Young Finns Study, which is following people from childhood into middle age. Childhood SEP was reported by the parents of the participants at the baseline of the study (participant’s mean age 10 in 1980). Adulthood SEP was examined from the participants after 27 years (participant’s mean age 37 in 2007). Both childhood and adulthood SEP was based on four components: education, income, occupational status, and occupational stability. The cumulative SEP score was a sum score of these components defined according to the favorable levels: academic/college degree = 1 point, income in the highest quartile = 1 point, upper white collar occupation = 1 point, and high occupational stability = 1 point, ranging from 0 (lowest SEP) to 4 (highest SEP). Social mobility was examined as a difference between childhood and adulthood SEP (stable SEP, downward mobility, and upward mobility). Ideal cardiovascular health was measured after 32 years (participant’s mean age 42 in 2012) according to the American Heart Association’s guide lines. All analyses were adjusted for age, sex, childhood cardiovascular risk factors, and chronic health conditions in childhood and adulthood.

Results: Higher childhood SEP was related to higher ideal cardiovascular health index in adulthood (β = 0.13, p < .001) independently of all potential confounders or mediators. Mediation analysis showed that adult SEP explained 33% of the association between childhood SEP and ideal cardiovascular health index. Upwardly mobile participants scored higher on ideal cardiovascular health in adulthood compared with participants staying in lower SEP (M = 4.05 vs. 3.56, p < .001), but childhood SEP remained a significant predictor of cardiovascular health in the model (β = .22, p < .001).

Conclusions: This study shows that childhood SEP is a predictor of cardiovascular health, which partly operates through adulthood SEP. Although upward social mobility mitigates some of the effects of early SEP disadvantage on later cardiovascular health, childhood SEP remains an important predictor of future health. Encouraging offspring from deprived families to obtain better SEP is recommendable, but early socioeconomic environment seems to leave a permanent mark on health, pointing to a need for early life prevention.

PA2.02.07

Hygiene and health: Results from Pune Maternal Nutrition Study

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10th World Congress
Background: Poor hygiene remains one of the urgent issues in the low and middle income countries (LMICs). Lack of safe water and poor sanitation increase childhood mortality and morbidity, and impair physical and neurocognitive growth and development. Most public health programs have incorporated improved hygiene as an important goal. In support of the Government of India’s flagship sanitation initiative ‘Swachh Bharat Abhiyan’, RB (Rose Bengal) in partnership with the U.S. Agency for International Development (USAID) and EY (Ernst and Young) launched the Hygiene Index program. The importance of hygiene in reducing morbidity and mortality of infectious disease is well known, but its effect on NCDs remains relatively uninvestigated. In Pune Maternal Nutrition Study (PMNS), we have serially documented socio-economic indicators over last 20 years (1993–2014). We now report on change in hygiene parameters and their association with common risk factors for NCDs.

Methods: PMNS is a pre-conceptional birth cohort in 6 villages near Pune, India. We collected serial socio-economic and biometrical data over last 20 years starting 1993. Mothers were studied before and during pregnancy, and families have been followed up every 6 years after birth of the child (1993-96, 2001, 2007, and 2014). We used a socio-economic tool developed in the National Family Health Survey, called the Standard of Living Index (SLI) which included following hygiene parameters: safe water source, toilet facility, separate kitchen, crowding index and use of refrigerator. Each facility was recorded as yes or no and given a score of 1 or 0. The score was added to calculate a ‘hygiene index’, higher index suggests better hygiene. We used median of the index at baseline as a reference. We followed ~700 families in this study.

Results: The SLI and the hygiene index progressively increased over last 20 years. The proportion of families categorised as ‘better hygiene’ (above the median at baseline) increased: 36% in 2001 to 53% in 2007 and 92% in 2014. This was attributable to establishment of tap water supply from the newly constructed dam, establishment of toilets, and reduction in the crowding index. The increased hygiene score was associated with larger body size, lower levels of inflammatory markers, but higher adiposity, and higher levels of NCD risk factors. These results need to be validated. Our findings raise a concern about the unknown risks of apparently healthy aspects of lifestyle in relation to the risk of NCDs.

Conclusion: We have developed an index to investigate hygiene status. Progressive improvement in hygiene in the rural Indian population was associated with larger body size, lower levels of inflammatory markers, but higher adiposity, and higher levels of NCD risk factors. These results need to be validated. Our findings raise a concern about the unknown risks of apparently healthy aspects of lifestyle in relation to the risk of NCDs.
more susceptible than girls to prenatal exposure to lead. Further investigation in other cohorts is required.

**PA2.02.09**

**Prenatal air pollution exposure predicts newborn telomere length at birth**

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**Background:** Telomere length may provide a cellular memory of exposures to oxidative stress and inflammation, and telomere length at birth has been related to life expectancy. Exposure to particulate matter (PM) air pollution has been implicated in age-related diseases and life expectancy. In *in utero* life is a critical window in programming of developing diseases later in life. A connection between prenatal air pollution exposure and telomere length at birth will gain new insights in the environmental influence on molecular longevity. In this study we assessed the association of prenatal exposure to PM with newborn telomere length as reflected by cord blood and placental telomere length.

**Methods:** In the prospective birth cohort study ENVIRONAGE (ENVIRONmental influence ON AGEing in early life) in Belgium, 730 mother-newborn pairs were recruited between February 2010 and December 2014, all with a singleton full-term birth (≥37 weeks of gestation). Relative telomere length was measured in cord blood (n=698) and placental tissue (n=660) at birth using a real-time PCR method. Maternal residential PM$_{2.5}$ (particles with an aerodynamic diameter ≤2.5 μm) exposure during pregnancy was estimated using a high resolution spatial temporal interpolation method. With distributed lag models (DLMs) we associated both cord blood and placental telomere length with average weekly exposures to PM$_{2.5}$ over the entire pregnancy, to identify critical sensitive periods over pregnancy.

**Results:** Average (5-95th percentile) weekly mean PM$_{2.5}$ exposure was 13.4 μg/m$^3$ (4.3-32.7 μg/m$^3$). A 5 μg/m$^3$ increment in PM$_{2.5}$ exposure during the entire pregnancy was associated with 7.2% shorter (95% CI: -1.2 to -1.8%) cord blood leukocyte telomeres and 13.3% shorter (95% CI: -19.3 to -6.9%) placental telomere length. The prenatal exposure between weeks 13 and 26 was most strongly associated with newborn telomere length at birth. These associations were controlled for date of delivery, gestational age, maternal pre-pregnancy BMI, maternal age, newborn sex, newborn ethnicity, season of delivery, parity, maternal smoking status, maternal education and ambient temperature.

**Conclusions:** Mothers who were exposed to higher levels of PM$_{2.5}$ during pregnancy gave birth to newborns with shorter telomere length. The observed telomere loss in newborns by prenatal air pollution exposure indicates less buffer for postnatal influences of factors decreasing telomere length and this may increase the risk for chronic diseases in adulthood. Improvements in air quality may promote molecular longevity from birth onwards.

**PA2.03 - Mental health outcomes**

**PA2.03.03**

**Perinatal Pathways to Psychopathology**

J. Meaney

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Maternal mental health over the peripartum period profoundly influences the risk for later psychopathology in the offspring. Recent findings underscore the importance of the prenatal maternal emotional well-being for offspring mental health. This presentation will summarize findings from longitudinal, birth cohort studies using largely using neuroimaging approaches to document the impact of maternal emotional health for the development of the offspring. Of particular relevance are studies in which the imaging or epigenetic measures were obtained at (or near) birth, thus clarifying the influence of prenatal maternal mood. The results of the neuroimaging studies suggest that the structure and connectivity corticolimbic regions implicated in mood disorders is strongly associated with the quality of prenatal maternal mood, and that such effects are observed across the continuum of maternal symptoms of both depression and anxiety. Finally, the presentation will discuss genotypic moderation of the effects of maternal mood on offspring neurodevelopment.

**PA2.03.05**

**Early life stress, neurodevelopment and glucocorticoid receptor genes: domestic violence increases risk for learning problems in homozygous FKBP5 haplotype carriers.**

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**Background:** Associations among early life stress (ELS), self-regulation difficulties and risk for developing psychopathology are well established. Prospective longitudinal studies have clearly linked ELS with emotion and behavior regulation
problems leading to psychopathology in adulthood.1,2 Similarly, the association between the regulation of the stress response and cognitive control abilities associated with prefrontal cortex (PFC) is also well established. At moderate levels, stress-related neurochemicals, including glucocorticoids and catecholamines, potentiate neural activity in PFC and enhance executive functions (EF). As stress-related neurochemicals rise beyond a moderate level, however, neural activity in PFC is depressed and EF abilities are impaired.3 Here we ask whether genes associated with the activity of the glucocorticoid receptor and thereby regulation of the HPA axis play a role in associations between ELS and cognitive development outcomes. Specifically, we examined the FK506-binding protein 5 gene (FKBP5) to determine whether children with the haplotype associated with demethylation of a glucocorticoid response element leading to transcriptional disinhibition of the gene4 and who experienced domestic violence in the infant and toddler period were more likely to experience comparatively lower EF at school entry and increased learning problems by grade 2, as indicated by reading ability.

**Method:** Participants (N = 914) were drawn from a prospective longitudinal population-based sample of children and families followed from birth in low-income, nonurban communities in the USA. Data were collected in participants’ homes at annual intervals beginning at child age 7mos. At 36mos, saliva for DNA extraction was collected using Oragene kits. At age 60mos, children were administered an EF task battery and in Grade 2 were administered a standardized measure of reading achievement. ELS was operationalized as intimate partner violence (verbal, physical) as reported by the child’s primary caregiver on the Conflict Tactics Scale at child ages 7, 15, and 24mos (mean composite). Child age, race, gender, cumulative demographic risk (7-24mos), and household chaos (7-24mos) were included as covariates. Four SNPs of the FKBP locus (rs9296158, rs3800373, rs1360780, rs9470080) in linkage disequilibrium were targeted to create a CATT haplotype (carriers versus non-carriers). Principal components (PCAs) of 48 SNPs providing information on family relatedness and ancestry were included in analyses to account for population stratification.

**Results:** OLS regression predicting EF at school entry and reading ability in grade 2 in separate equations from FKBP5 haplotype, ELS, and the haplotype by ELS interaction, plus covariates, indicated that EF at school entry in carriers of the haplotype in homes characterized by higher levels of domestic violence was reduced by approximately ES = .33 relative to non-carriers. Reading ability was reduced by approximately ES = .48 in carriers relative to non-carriers of the haplotype in homes characterized by ELS. (Figure)

**Conclusions:** Results indicate that FKBP5, a gene highly relevant to the regulation of the HPA axis, interacts with ELS to predict cognitive development in childhood. Given previously reported associations of this interaction with anxiety and depression in adulthood, results suggest that an early manifestation of this risk may be seen in measures of cognitive ability in childhood.

Grade 2 reading as a function of FKBP5 haplotype and domestic violence

**PA2.03.06**

**Relationships between depression and anxiety symptoms scores and blood pressure in young adults**

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**Background:** Depression and anxiety have been associated with an increased risk of cardiovascular disease, but their relationship to blood pressure (BP) is less clear. Age related comorbidity and lifestyle factors may confound these relationships. We previously reported an inverse association between anxiety and depression scores and systolic BP in 14 year old boys in the Western Australian Pregnancy Cohort (Raine) Study. The cohort is one of the longest running prospective studies on child health and development. The present study aimed to examine the association between depression and anxiety symptoms and BP in Raine study participants at 20 years, an age when they have established adult behaviours, but with little or no co-morbidity.

**Methods:** Data on 1014 participants aged 20 years from the Raine Study were analyzed for cross-sectional associations between clinic BP and Depression, Anxiety, Stress Scale (DASS) questionnaire scores or a reported history of depression, accounting for relevant confounders.

**Results:** Males had a significantly higher systolic BP and a greater percentage were pre-hypertensive or hypertensive compared with females. BMI was not different between the genders, but males were more likely to be overweight. Depression, anxiety and stress scores were lower in males, and the proportion with self-reported depression was significantly higher among females compared to males (19.9 vs. 11.4%).

**Figure:**
Approximately 16% of all participants reported having at some time had a diagnosis of depression. In these individuals, the DASS-Depression score was 8.34 units (P < 0.001) higher than in those without a history of depression. Multivariable adjusted analyses showed DASS-depression and DASS-anxiety scores were inversely associated with offspring systolic BP (coefficient = -0.10; P = 0.012 and coefficient = -0.13; P = 0.018, respectively), independent of gender, BMI, female hormonal contraceptive use, alcohol consumption, birth weight and maternal hypertension in pregnancy. Systolic BP was 1.6mmHg lower for 2SD (16 units) increase in depression score. There was an inverse association between self-reported history of depression and systolic BP (coefficient = -1.91; P = 0.023), with an interaction between self-reported depression and BMI (coefficient = -0.43; P = 0.002). The interaction indicated that the higher the BMI, the more inverse the relationship between the self-reported depression and SBP. The association between self-reported depression and systolic BP was independent of a range of lifestyle confounders. None of the participants used antidepressants at age 20.

Conclusion: Our findings show that systolic BP in young adults is inversely associated with depression and anxiety scores, independent of a range of lifestyle confounders. Despite a positive association between BMI and BP, adiposity enhanced the inverse association between self-reported history of depression and systolic BP. Although we have no ready explanation for a causal relationship between depressive or anxiety tendencies and lower BP, the results are consistent with our previous findings in this cohort during childhood. Our findings contrast with the predisposition of depressed individuals to cardiovascular disease in later life when decades of unhealthy lifestyle changes may dominate. It will be of particular interest to follow the evolution of these effects as the Raine Study cohort ages.

PA2.03.07

Influence of environment on child growth: the non-organic failure to thrive in the context of an affective deficiency syndrome

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Background: The mechanisms that lead to a growth delay in children living in a context of deficient parent affectivity, but receiving an adequate nutrition intake, remain to be clarified. This is the reason why the affective deficiency syndrome (ADS) and its maximum expression, the non-organic failure to thrive (NOFT), represent complex situations that are beyond common nutritional problems. Early affectivity deprivation seems to alter the regulation of the hypothalamic-pituitary-adrenocortical axis, potentially increasing susceptibility to stressors throughout the life.

The aim of this study was to analyse the involvement of specific neuroendocrine markers in the pathophysiology of patients suffering from ADS/NOFT.

Methods: 72 children (4-14 years) were recruited from the specialised health-care department at San Cecilio University Hospital (Granada, Spain). The problem group consisted of 36 children who were cared for in the same boarding institution for a history of significant neglect (parents addicted to drugs, alcoholic parents, parents in prison, parent psychiatric illness, lack of financial resources), without a known history of psychological or physical abuse. None of these participants had ever been diagnosed with neurologic, endocrine or immunologic disorders. None of them had a known history of perinatal pathology, intrauterine growth retardation or suspicion of foetal alcohol syndrome. The problem group was divided into two subgroups: 1) the ADS group, formed by 15 children who lived in a childcare institution and presented normal somatometry; and 2) the NOFT group, composed of 21 children presenting the fundamental characteristic of first-order somatometry (weight and height) lower than the third percentile for Spanish population, with no justifiable organic explanation. The age- and sex-matched control group (CG) consisted of 36 participants. In every case, serum levels of melatonin (aMT), serotonin (5-HT), β-endorphins and adrenocorticotropic hormone (ACTH) were measured. The affective deficiency was scored by State-Trait Anxiety Inventory for Children (STAIC) and Child Depression Scale (CDS). Following the Helsinki criteria, written informed consent was obtained from the adolescent children and/or from tutors of the institution. Statistical analysis included the one-way analysis of variance (ANOVA) with Bonferroni and Dunnett’s T3 post-hoc comparisons for normal variables (ACTH and aMT). Non-parametric methods such as Kruskal Wallis one-way ANOVA were used to compare 5-HT and β-endorphin levels.

Results: The production of ACTH was significantly higher in the CG (p < 0.001) compared with both NOFT and ADS groups. The same occurred in the case of aMT. β-endorphin levels were significantly lower in the NOFT group (p < 0.001) with respect to CG and ADS, while no differences were found between CG and ADS groups. 5-HT concentrations were significantly higher in the CG in relation to ADS and NOFT. Significant differences in 5-HT concentrations were found as well between ADS and NOFT (p < 0.001) (Figure).

Conclusions: Our results suggest that adverse family circumstances in the life of a child may trigger a psychological and affective process with long-term consequences on growth and development. This process overtakes the influence of nutritional factors and seems to be mediated by neuroendocrine markers.
Background: Associations between prenatal selective serotonin reuptake inhibitor (SSRI) exposure and autism have been reported. Yet, developmental outcomes in young children prenatally exposed to these anti-depressants are less understood. Here, we examined whether maternal antidepressant use during pregnancy is associated with children’s development accounting for indication for treatment.

Methods: In the Upstate KIDS Study, a population-based birth cohort in Upstate New York (2008-2010), women reported any prescribed medication use during pregnancy at 12 months postpartum (n = 2524 singleton pregnancies and 611 twin pairs). We used the Slone Drug Dictionary to code the free text and define the prescription of antidepressants according to the Pharmacologic–Therapeutic Classification codes for drug classes. Women reported on their lifetime diagnosis of mood disorders including depression at four months postpartum. Additionally, depression requiring in-/outpatient hospital care during pregnancy was derived from New York State claim data using the International Code for Diseases. Mothers completed the Ages & Stages Questionnaire® (ASQ) for their children at ages 4-6, 8, 12, 18, 24, 30, and 36 months. ASQ is a validated parental-rating instrument which provides an assessment of child development in five domains of fine motor, gross motor, communication, personal-social, and problem solving skills. Exposure was categorized in three groups: a) having no depressive symptoms and no antidepressant use (reference group), b) a history of depression –prior to or during pregnancy–, but no antidepressant use c) antidepressant use during pregnancy. Generalized linear mixed models with random effects were used to test the association of exposure to maternal depression and antidepressant use and a child’s failing on any of the ASQ domains and domain specific failure. Models were adjusted for maternal age, education, race, smoking in pregnancy, infertility treatment, and body mass index, and child sex, plurality, and parity.

Results: In total, 136 (3.9%) women reported antidepressant use during pregnancy including SSRIs (n = 121), serotoninnorepinephrine reuptake inhibitors (n = 8) and norepinephrine–dopamine reuptake inhibitors (n = 15). 342 (11%) women reported having a lifetime history of depression and 54 (1.7%) had a diagnosis of depression requiring in/out-patient hospital care during pregnancy. Prenatal exposure to maternal self-report depression without medication use was not related to child development (adjusted Odds Ratio (aOR) for failing any ASQ domain: 1.24, 95%CI: 0.91-1.69). Compared to the unexposed group, children who were prenatally exposed to antidepressants had higher odds of failing any ASQ domain (aOR = 1.61, 95%CI: 1.00-2.61). When we reran the analyses adjusting for depression requiring hospital care during pregnancy, we had similar results. Children with prenatal antidepressant exposure had higher odds of failing any ASQ compared to children of women with depression/no pregnancy medication (OR = 1.62, 95%CI: 0.93-2.81). Post-hoc analyses on failing specific domains revealed that this association was mainly present in domains of gross motor, communication, and personal-social skills. No interactions with child sex or plurality were observed.

Conclusion: Our findings suggest that early development in children might be affected by prenatal exposure to certain antidepressants. Further work is needed to determine the relative benefits and harms to offspring of discontinuing antidepressant treatment during pregnancy.
positive aspects of the community, rather than deficits, we sought out adult Indigenous fathers who were considered role models and involved fathers. We conducted in-depth semi-structured interviews with six fathers that were recorded and transcribed. Four of the fathers also participated in photovoice and a second round of interviews. All data were analyzed using qualitative content analysis.

Results: The fathers felt they had to support their partners in any way possible and surmount challenges resulting from colonial impacts by reclaiming their roles as men and acknowledging the pregnancy as a positive change in their life. Providing this support was achievable through their own dedicated support system stemming from family, faith, and culture, and a stable upbringing with a positive male role model. The participants called for more programs and services to involve and include fathers during pregnancy to a greater extent than is currently done. The fathers also hoped for perinatal programming that incorporates traditional culture and Elder support, is responsive and flexible to family needs in their approach, promotes cultural understanding among healthcare providers and staff, and adopts a philosophy that acknowledges this as part of a far-reaching plan supporting reconciliation.

Conclusion: Efforts to improve perinatal care for Indigenous women, and ultimately the health and development of offspring, need to allow for more inclusion of and support for Indigenous fathers.

PA2.05 - Early life adversity and late life interventions

PA2.05.01 Later-life interventions to reverse/compensate for effects of early life adversity


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Symposium - Network on Reversibility of Early Life Adversity Effects on Later Life Health

The Reversibility Network, is a research network on later-life interventions to reverse effects of early life adversity (ELA), focusing on identifying opportunities for later-life reversibility/remediation of phenotypes associated with ELA. Established with funding from the US National Institute on Aging and the UK Economic and Social Research Council/Biotechnology and Biological Sciences Research Council, the network brings together senior and junior scientists to foster and facilitate the interdisciplinary research needed to stimulate rapid advances in this field. Overall goals are to (a) promote needed increases in scientific knowledge regarding the array of processes and pathways through which different ELAs (e.g., low socioeconomic status [SES]; stressful experiences, including social isolation, poor parent-child relationships [e.g. child neglect/abuse] or other violence; poor maternal diet, body composition and lifestyle) may similarly or differentially impact later life health and well-being, and (b) leverage evidence from this body of research to promote development and evaluation of novel later-life interventions to reverse/reduce risk processes related to ELAs.

Objectives of the symposium:
The symposium will include invited talks from established scholars together with open discussion with delegates to: - disseminate thinking about the topic and its importance to the broad DOHaD audience from core team/others involved in sub-group themes. - work towards a publication(s) that distils network thinking and evidence to date - grow the field of interest in ‘ reversibility’ by attracting/identifying relevant work that can be tied-in or initiated.

PA2.06 - Environment and DOHaD

PA2.06.01 Expression of micronuclei-related genes in cord blood in association with in utero particulate matter exposure: P53 as a central hub


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Background: Increased micronuclei (MN) frequency, a valid biomarker for genotoxicity, has been associated with particulate matter (PM) exposure-related DNA damage in cord blood. The P53 gene encodes the tumour suppressor protein P53 and has an important role in many stress responses, including MN formation. We hypothesized that expression of genes involved in the MN formation network and P53 protein levels are altered in association with gestational PM_{2.5} exposure in newborns.

Methods: Gene expression of P53, DNMT1, PCNA, BAX, and P21 was measured by quantitative real-time polymerase chain reaction and P53 protein expression by ELISA in cord blood
Retrieved from 170 newborns enrolled in the Belgian birth cohort ENVIRONAGE.

**Results:** We observed a negative association between expression levels of the MN formation-related genes and PM$_{2.5}$ exposure during pregnancy (relative decrease of -52.0%, 95% CI: -68.7% to -26.2%, $p = 0.0009$ for each 5 μg/m$^3$ increment in PM$_{2.5}$ exposure). The association with PM$_{2.5}$ exposure was most pronounced with expression of P53, BAX, and PCNA. On the other hand, P53 protein levels were positively associated with entire pregnancy PM$_{2.5}$ exposure (relative increase of 56.0%, 95% CI: 23.5% to 97.1%, $p = 0.0003$ for a 5 μg/m$^3$ increment in PM$_{2.5}$), as with mothers who reported to have smoked during pregnancy (+46.8%, 95% CI: 7.4% to 100.7%, $p = 0.02$ compared to non-smokers).

**Conclusions:** Based on our transcriptomic analysis, our results are indicative of alterations in expression of MN-related genes in response to PM$_{2.5}$ exposure during pregnancy. Our findings lend support to the development of a reliable reporter gene assay to screen chemically exposed human populations.

**PA2.06.02**

Perinatal exposure to dioxins and body mass index at seven years: A pooled analysis of three European cohorts

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**Background:** Dioxins and dioxin-like compounds are endocrine disrupting chemicals (EDCs). Experimental studies suggest perinatal exposure to EDCs results in later obesity. However, the few epidemiological investigations on dioxins are inconclusive. We investigated perinatal exposure to dioxins and dioxin-like compounds, infant growth and body mass index (BMI) in childhood.

**Methods:** We pooled data from 3 European birth cohorts (Belgian, Norwegian, Slovak) with exposure assessment in cord blood or breast milk. Two cohorts had dioxin-like toxicity assessed using dioxin-responsive chemical-activated luciferase expression (DR-CALUX) bioassay and one cohort had measured concentrations of dioxins, furans and dioxin-like polychlorinated biphenols with CALUX relative potency values applied. Growth was cohort- and sex-specific change in weight-for-age z-score between birth and 24 months (N = 367). BMI was calculated at around 7 years (median 7.17, interquartile range [IQR] 7.00-7.37 years, N = 251), and overweight defined according to international standards for children equivalent to adult BMI ≥ 25 kg/m$^2$ (Cole and Lobstein 2012). We fitted multivariate models using generalized estimating equations, and tested effect modification by sex, breastfeeding and cohort. Results per 10 pg CALUX TEQ/g lipid increase in exposure.

**Results:** Dioxin exposure was highest in the Belgian and lowest in the Norwegian cohort; median (IQR) of the pooled sample 13 (12.0) pg CALUX TEQ/g lipid. Perinatal exposure to dioxins and dioxin-like compounds appeared associated with increased growth between 0-24 months (adjusted estimate for raw BMI z-score: β = 0.07, 95% CI: -0.01, 0.14). At 7 years, dioxin exposure was associated with a statistically significant increase in BMI in girls (adjusted estimate for BMI units $p$-interaction $= 0.044$). Furthermore, girls had a 54% (-6%, 151%) increased risk of overweight at 7 years ($p$-interaction $= 0.023$).

**Conclusion:** Perinatal exposure to dioxin and dioxin-like compounds was associated with increased early infant growth, and increased BMI in school age girls. Studies in larger sample sizes are required to confirm these sex-specific effects.

**PA2.06.03**

Exposure to diesel exhaust particles during the course of gestation increases risk of neurocognitive impairment of male offspring

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**Background:** Diesel exhaust (DE) is a complex mixture of diesel exhaust particles (DEPs) and gaseous-phase compounds. The soluble organic fraction of particulate materials in DE contains more than 1000 compounds including a variety of polycyclic aromatic hydrocarbons and heavy metals. We previously showed that maternal exposure to DE could affect monoaminergic systems in various brain regions of male offspring in mice. Prenatal exposure to DE also affected the morphology of perivascular macrophages and the surrounding tissue in the hippocampus, where accumulation of ultrafine DEPs was observed. This finding suggests that DEPs accumulation may directly affect the hippocampus in murine adult male offspring. However, there was no clear evidence that these effects were caused by DEPs, gaseous compounds, or both. Here, we explored the effects of in utero exposure to DEPs on learning and memory in male offspring.

**Methods:** DEP solutions were administered subcutaneously to pregnant ICR mice at a dose of 0 or 200 μg/kg body weight on gestation days 6, 9, 12, 15, and 18. We examined learning and memory in adult male offspring using the Morris water maze test (MWM) and passive avoidance test (PA). Immediately after the behavioral tests, hippocampi were isolated. Hippocampal N-methyl-D-aspartate receptor (NR) expression was measured by quantitative RT-PCR analysis. In addition, the fixed tissue was also provided into immunohistochemistry to quantify NR expression levels.
Results and conclusions: DEP exposure had no significant effects on litter size. The body weight of male offspring was also not affected by maternal DEP exposure during the adolescent to adult period (postnatal day 1: Control, 2.2 ± 0.3 g; DEP, 2.3 ± 0.3 g; 10 weeks: Control, 40.4 ± 1.0 g; DEP, 40.7 ± 0.7 g). No deaths or malformations were observed in both control and DEP-exposed mice. To examine hippocampus-dependent spatial learning and memory, we performed the MWM. In the hidden platform test, from day 1 to 9, all mice showed a gradual reduction in the time taken to find the escape platform as training proceeded. The improvement in the escape latency of each group following training was reflected in a main effect of day \( [F (8, 269) = 19.20, p < 0.001] \). However, the control mice found the platform faster than the DEP-exposed mice \( [F (1, 269) = 5.06, p < 0.05] \). A post hoc analysis showed significant differences between control and DEP-exposed mice. In the probe test, DEP-exposed mice showed significant deficits in reference memory compared to control mice. In contrast, performance of the DEP-exposed mice was not significantly different from that of control mice in the PA. In addition, DEP-exposed mice exhibited decreased hippocampal NR2A expression. The present results indicate that maternal DEP exposure disrupts learning and memory in male offspring, which is associated with reduced hippocampal NR2A expression.

The distribution of NR2A expressions.

PA2.06.04

Environmental programming of respiratory allergy: utility of a child’s spit epigenome.

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Epigenetic DNA methylation changes can be part of the underlying molecular mechanisms leading to complex diseases. Early life exposures like parental lifestyle and exposure to chemicals can alter DNA methylation patterns, and thereby predispose the child to develop respiratory allergy (RA) later in life. Longitudinal birth cohorts are instrumental to study disease development, but DNA biomarker research is hampered because blood sampling is kept to a minimum for practical and ethical reasons. Saliva is a non-invasive and convenient source of DNA that can be used for biomarker research. In this study, we aimed at discovery and confirmation of differential methylation regions (DMR) in saliva of children with RA when comparing to controls. Saliva samples collected in the two independent longitudinal birth cohorts (Flanders Environment and Health Surveys FLEHS1 & FLEHS2) were analysed using Illumina Methylation 450K BeadChips. A statistical analysis pipeline was developed in R to identify genome-wide differential methylation. We identified 27 DMRs in saliva from 11y old allergic children (self-reported/doctor’s diagnosed RA, Phadiatop IgE ≥ 0.35 kU/L; N = 26) vs. controls (no self-reported/diagnosed RA, Phadiatop IgE < 0.35 kU/L; N = 20) in the FLEHS1 cohort. A set of 8 DMRs was selected for further validation by iPLEX MassArray analysis. First, iPLEX analysis was performed in the same 46 FLEHS1 samples that were previously analysed on the 450K methylation arrays, to allow technical validation. iPLEX results correlated significantly with the 450 K methylation array data \( (P < 0.0001) \), though iPLEX analysis confirmed 5 of the 8 identified DMRs in the FLEHS1 study. Aiming for biological confirmation, we studied these DMRs in an independent birth cohort FLEHS2. Due to a lack of blood samples to measure IgE levels in the FLEHS2 cohort, cases and controls were identified as: 1) cases = doctor’s diagnosed/self-reported RA symptoms ever \( (N = 19) \); and 2) controls = no self-reported/diagnosed RA \( (N = 20) \). When studying the 8 DMRs by means of iPLEX analysis in the FLEHS2 cohort, only a DMR in the GLI2 gene showed a statistically significant difference in methylation between RA cases and controls. GLI2 has a regulating role in IL4 signalling and can modulate T-helper differentiation and allergic disease, and might thus be an interesting DNA methylation marker to study for further biomarker development. Interestingly, the RA-related hypermethylation in GLI2 correlated significantly with life time exposures towards air pollution markers PM\(_{10}\), NO\(_2\) and O\(_3\). Using the statistical framework developed by Valeri and VanderWeele (Psy chol Methods, 2013), GLI2 hypermethylation was observed to partially mediate the effects of PM\(_{10}\), NO\(_2\) and O\(_3\) on RA. This project is providing novel insights in the molecular mechanisms that may predispose children to RA development. We are among the first to show the utility of saliva to identify DNA methylation marks in children that are relevant for RA.
PA2.06.05
Maternal alcohol consumption during pregnancy and offspring epigenome-wide DNA methylation: Findings from the Pregnancy and Childhood Epigenetics (PACE) Consortium

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Background: There is evidence to suggest that moderate alcohol consumption during pregnancy is associated with adverse outcomes in the offspring, but the precise biological mechanisms underlying such associations are currently unknown. Epigenetic modifications have been suggested to play a mediating role.

Methods: To investigate genome-wide DNA methylation in the cord blood of newborns differentially exposed to alcohol in utero, we meta-analysed epigenome wide association study (EWAS) summary statistics from six population-based cohort studies (n mother-child pairs = 3,075) within the Pregnancy and Childhood Epigenetics (PACE) Consortium. We were primarily interested in the effects of sustained consumption throughout pregnancy, which represents a prolonged prenatal exposure to alcohol, but we also explored binge-drinking and timing-specific exposures.

Results: No single CpG-sites were associated with any of our alcohol exposure measures after correction for multiple testing. In an region-based analysis, we identified 19 regions differentially methylated in the offspring of mothers who drank throughout pregnancy compared to the offspring of mothers who gave up drinking at the start of pregnancy. However, we did not validate this result using another regional analysis method.

Conclusion: In this multi-cohort study we found no evidence that (mostly light-to-moderate) maternal alcohol consumption during pregnancy is associated with offspring cord blood DNA methylation. However, it is possible that a combination of a larger sample size, higher doses, different timings of exposure and a more global assessment of genomic DNA methylation might show evidence of effect.

PA2.06.06
Amplification of risk of intrauterine fetal growth restriction due to maternal smoking by illicit drugs and alcohol abuse.

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Background: Maternal smoking is associated with intrauterine fetal growth restriction. However, there is a dearth of information on the effect of smoking in combination with other modifiable risk factors in programming growth.

Methods: Clinical and sociodemographic data were collected at the first antenatal appointment for all women attending a large maternity hospital between 2011 and 2015. Birth outcome data were collected following delivery from the hospital’s computerised system and used to analyse the effect of a number of self-reported adverse health behaviours during pregnancy on infant birthweight. Birthweight was subcategorised, for secondary multivariate analysis, to term birthweight <10th centile for the study population. Multiple pregnancies, preterm births and infants weighing <500g at birth were excluded from analysis.

Results: Of 40, 658 women, the mean age was 31.3 ± 5.5 years, BMI 25.5 ± 5.1 kg/m2 and 39.2% were nulliparas. Birthweight averaged 3502.8 ± 465.9 g. Women who smoked >11 cigarettes per day, independent of alcohol consumption or drug use, had birthweights on average 328 g (95% CI -365.8 to -290.5, P < 0.001) lower than women who did not smoke, consume alcohol or use drugs in early pregnancy. Weekly alcohol consumption, alcohol binges and drug use when analysed independent of other adverse behaviours had no effect on mean birthweight (all >0.05). However, when smoking >11 cigarettes daily was combined with weekly alcohol, illicit drugs use and alcohol binges in pregnancy, birthweight was lower by 528 g (95% CI (-649.2 to -406.1, P < 0.001), 527 g (95% CI -680.5 to -374.0, P < 0.001) and 755 g (95% CI -941.6 to -567.7, P < 0.001) respectively compared to women who did not engage in any of these adverse health behaviours. Multivariate logistic regression analysis found that women who smoked and had at least one alcohol binge in pregnancy were the most likely to have a baby less than the 10th centile (OR 8.9, 5.5-14.9, P < 0.001) (Figure 1).

Conclusions: Our findings confirm previous studies showing that maternal smoking restricts fetal growth but it also shows that the risk of restriction is further amplified by alcohol binging and illicit drug abuse. Drinking alcohol or abusing illicit drugs in pregnancy did not restrict fetal growth in non-smokers. If the programming of fetal growth is to be optimised by smoking cessation, it may also be necessary to address illicit drug and alcohol addiction.
PA2.06.07

The use of carbon monoxide screening in identifying potential maternal smoking.

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Background: Maternal smoking is a modifiable risk factor in programming restricted intrauterine fetal growth. Identification and quantification is usually based on self-reporting which may not be accurately disclosed by women when they present for antenatal care. In this prospective observational study, we examine the use of carbon monoxide (CO) screening in women presenting for antenatal care in a large maternity hospital.

Methods: Pregnant women were recruited at their convenience during their first antenatal visit after they completed a standardised questionnaire which was computerised by a trained midwife. The questionnaire included details on lifestyle behaviour, socio demographic and clinical details. Women <18 years or women unable to understand English were excluded. Eligible women were offered to take part in the study and informed of the studies procedures including a breath test which would measure their recent exposure to CO from all potential sources of CO including smoking status and passive smoking.

Results: Of the 150 women, the mean age was 30.4 (SD 5.2) years, 36.0% were nulliparas and 18.7% (n=3) reported in the questionnaire had a strong, positive correlation between the time since last cigarette was smoked and expired air CO breath (ρ=0.62, n=150, P<0.001) (Figure 1). There was also a negative correlation between gestational exposure to nicotine in the questionnaire and placental TRPC6 expression. In 213 mother-newborn pairs of the ENVIRO-NAGE birth cohort, the expression of TRPC6 was measured in placenta and important for foetal development. Transient receptor potential (TRP) channels encompass a family of Ca2+ transporter channels of which canonical channel TRPC6 is expressed in placenta and important for foetal neurodevelopment. We studied the association between gestational exposure to fine particle air pollution and placental TRPC6 expression.

PA2.06.08

Placental TRPC6 expression and gestational trimester-specific fine particle air pollution exposure in the ENVIRONAGE birth cohort

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Background: Ion channels are indispensable for embryonic development. Transient receptor potential (TRP) channels encompass a family of Ca2+ transporter channels of which canonical channel TRPC6 is expressed in placenta and important for foetal neurodevelopment. We studied the association between gestational exposure to fine particle air pollution and placental TRPC6 expression.

Methods: In 213 mother-newborn pairs of the ENVIRONAGE birth cohort, the expression of TRPC6 was measured using quantitative real-time polymerase chain reaction. We estimated trimester-specific exposures to fine particle air pollution with a diameter equal to or less than 2.5 μm (PM2.5) for each mother’s home address using a high resolution
spatiotemporal model. Trimester-specific exposures and placental TRPC6 expression were regressed while accounting for maternal age, newborn’s sex, maternal BMI, ethnicity, month of birth, maternal smoking and maternal diploma as an indicator for socio-economic status.

Results: A 5 µg/m³ increment in PM2.5 during the last trimester of pregnancy was associated with a 11.1% increase [95% confidence interval (CI): 2.3, 20.0%; p = 0.014] in placental TRPC6 expression at birth. The corresponding estimate for the whole pregnancy exposure window was 16.8% [95% CI: 1.4, 32.3%; p = 0.033], while PM2.5 exposures during the first and second trimester had no significant effect.

Conclusions: Recent findings in mice showed that the placenta has important functions in the development of the foetal brain. The observed placental change in TRPC6 expression opens new avenues for this birth cohort study. Future investigations on the TRPC6 protein level aim to confirm this finding. The association between neurocognitive development in 4-year old children of our birth cohort and current results will also be examined.

PA2.06.09
The association of birth weight and infant growth with changes in renal dysfunction in newborns
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Background: There is evidence that low birth weight (LBW) is associated with low nephron number and susceptible to developing renal dysfunction. Yet, the effects of infant growth on subsequent developmental renal outcomes in later life remain unclear at population level. The aim of this study was to study the effect growth during the early life course of weight gain in the first year of life on the changes in estimated glomerular filtration rate (eGFR) among newborns.

Methods: This study is based on electronic medical records between 2001 and 2015 from the largest medical organization in Taiwan. Body weight growth in the first year of life was retrieved by a 3-month interval for newborns with LBW (n = 816) (<2500 gm) and normal birth weight (NBW) (n = 6,617) were examined (n = 7,743). Changes in eGFR using Schwartz formula were assessed over 11 years follow-up. Linear mixed model was employed to examine the effect of birth weight and infant weight growth on changes in eGFR over time.

Results: The mean baseline eGFR in LBW newborns was 114.3 ml/min per 1.73 m² (±29.83) and declined 0.04 ml/min per 1.73 m² (±1.03) per year on average. Among children with NBW, baseline eGFR was 116.9 (±31.45), and increased 1.61 (±0.49) yearly during childhood. A higher proportion of LBW children (2.7%) had eGFR reduction over 30% than NBW (1.95%) children. Infant weight with 1 gm gain was associated with increased eGFR 0.005 (±1.44) per ml/min/1.73 m² and any congenital disease worsen renal function (-2.02 ± 1.75 per ml/min/1.73 m²).

Conclusions: LBW have lower baseline renal function, which is considered a risk factor for CKD development. Body weight growth during the first year of life was significantly associated with improved eGRF. Further study is needed to identify optimal growth pathway during the early life course in order to design and implement effective intervention to prevent CKD progression.

PA2.07 - LifeCycle and ECHO Networks

PA2.07.01
Environmental influences on child health outcomes (ECHO) – NIH project
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National Institutes of Health

One year ago the US National Institutes of Health launched the Environmental influences on Child Health Outcomes (ECHO) program. This 7-year nationwide research program supports observational and intervention studies to address crucial questions about effects of a broad range of early environmental exposures on child health and development. ECHO prioritizes five pediatric health outcome areas. The first four represent common disorders: pre, peri, and early postnatal outcomes, upper and lower airway conditions, obesity and its cardiometabolic consequences, and the several domains of neurodevelopment. Recognizing the importance of understanding early determinants of well-being in childhood, ECHO also incorporates an innovative fifth outcome, positive health. ECHO is a multi-dimensional program. It comprises 62 grant awards; 110 principal investigators and over 1200 investigators in total; academic and related institutions in 44 states, DC and Puerto Rico; different structures across its components; and multiple stakeholders including diverse sets of children and families across the United States. ECHO offers unparalleled opportunities for innovation in how to conduct—and evaluate—trans-disciplinary team science in the 21st century. Together, the 84 ECHO observational cohorts, with an anticipated combined sample size exceeding 50,000 children from diverse populations across the United States, will leverage rich existing and new data from primary and secondary sources and biosamples. Using these data, ECHO investigators will examine how myriad aspects of one’s environment—including societal, medical, psychosocial, behavioral, and biological—from conception to age 5 years may affect health outcomes throughout childhood and adolescence.

On equal footing to the ECHO Cohorts is the IDEa States Pediatric Clinical Trials Network, a component of ECHO that aims to enhance access to clinical trials among rural and medically underserved children. The network comprises clinical sites in 17 states with historically low rates of NIH funding. Within its first year, the Network is realizing two
complementary goals: 1.) building capacity across the sites through professional development and infrastructure support, and 2.) developing protocols for one or more intervention trials that address prevention or treatment of at least one ECHO priority pediatric health outcome area. Scientific challenges attend to both observation and intervention. In these twin components of ECHO, an essential objective is to maintain focus on “solution-oriented” research questions, that is, questions that drive programs, policies, and practices. ECHO’s guiding principles are teamwork, impact, responsibility, and value. The program operates under the premise that building mutual trust over time through continuous engagement of investigators and other stakeholders will yield a whole that is greater than the sum of its parts. The long-term success of ECHO depends on addressing crucial observational and intervention research questions that smaller-scale cohorts or clinical trials cannot, and whose answers inform strategies to improve health outcomes of youth. In so doing, ECHO is poised to enhance the health of children for generations to come.

PA2.07.05
Newborn DNA-methylation, childhood lung function, and the risks of asthma and COPD across the life course
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Background: Asthma and chronic obstructive pulmonary disease (COPD) are major global health problems. Childhood lung function predicts the risks of asthma and COPD in later life. An accumulating body of evidence suggests that asthma and COPD have at least part of their origins in fetal life. Previous studies reported associations of adverse fetal exposures, such as maternal smoking and suboptimal diet, with increased risks of respiratory diseases throughout the life course. These associations may be explained by epigenetic changes, including DNA-methylation. Fetal development is characterized by high rates of DNA-methylation changes and rapid organ development. We hypothesized that fetal differential DNA-methylation reflected in cord blood DNA of newborns affect gene expression and subsequent respiratory tract development, and predispose individuals for obstructive airway diseases in later life. Therefore, we aimed to identify if differentially methylated regions (DMRs) in neonatal cord blood DNA are associated with childhood lung function and the risks of asthma and chronic obstructive pulmonary disease (COPD) across the life course.

Methods and Findings: We meta-analyzed epigenome-wide data of 1,688 children from five cohorts to identify cord blood DMRs (Illumina HumanMethyl450 Beadchip) and their annotated genes, in relation to Forced Expiratory Volume in 1 second (FEV1), FEV1/FVC (Forced Vital Capacity), and Forced Expiratory Flow at 75% of FVC (FEF75) at ages 7 to 13 years. Identified top DMRs were subsequently explored for their associations with childhood asthma, lung function in adolescence and adulthood, and COPD in adulthood, and explored for association with gene expression and involvement in biological processes. We identified 22, 15 and 22 DMRs associated with FEV1, FEV1/FVC and FEF75, respectively. Eighteen (31%) of all identified DMRs were also associated with childhood asthma, 11 (19%) and 9 (15%) with adolescent and adult lung function, respectively, and 9 (15%) with COPD. Differential gene expression was observed for 32 (54%) DMRs in childhood and 18 (31%) DMRs in adulthood, and genes related to 28 DMRs were expressed in adult lung tissue. Multiple genes related to the identified DMRs have previously been associated with respiratory development and morbidity, and many identified DMRs were located within known regulatory elements for gene expression. A limitation of the study is that blood DNA-methylation does not necessarily reflect lung epithelial DNA-methylation. However, asthma and COPD have systemic manifestations, characterized by increased inflammatory blood markers. Also, although the analyses were adjusted for estimated cell counts, we cannot rule out residual confounding due to alterations in cell type distribution.

Conclusion: We identified 59 DMRs in newborn cord blood that were associated with childhood lung function. Multiple of these DMRs were additionally related with childhood asthma, adolescent and adult lung function, adult COPD, and differential gene expression. These findings suggest that the epigenetic changes at birth might affect respiratory health and disease across the full life course.

PA2.07.06
Gestational weight gain charts for different body mass index groups for women in Europe, North America and Oceania
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Background: Gestational weight gain differs according to pre-pregnancy body mass index and is related to the risks of adverse maternal and child health outcomes. Currently, appropriate gestational weight gain reference charts for women in different body mass index groups are not available. We aimed to construct gestational weight gain reference charts for women in different body mass index groups. We used individual participant data from 219,158 pregnant women (9,124 (4.2%), 149,628 (68.3%), 42,559 (19.4%), 13,137 (6.0%), and 1,101 (0.5%) underweight, normal weight, overweight, and grade 1, 2 and 3 obese women. Methods: We used individual participant data from 219,158 pregnant women (9,124 (4.2%), 149,628 (68.3%), 42,559 (19.4%), 13,137 (6.0%), and 1,101 (0.5%) underweight, normal weight, overweight, and grade 1, 2 and 3 obese women, respectively) from 34 contemporary European,
American and Oceania pregnancy cohort studies. Gestational weight gain charts for underweight, normal weight, overweight, and grade 1, 2 and 3 obese women were derived by the Box-Cox \( \tau \) method using the generalized additive model for location, scale and shape.

**Results:** Gestational weight gain strongly differed per maternal pre-pregnancy body mass index group. The median (inter-quartile range) gestational weight gain at 40 weeks was 13.8 kg (11.2-16.8) for underweight women, 13.8 kg (11.1-16.9) for normal weight women, 12.9 kg (9.5-16.7) for overweight women, and 10.6 kg (6.8-14.6), 8.9 kg (4.7-13.4) and 5.7 kg (1.3-10.1) for grade 1, 2 and 3 obese women, respectively. The slope of weight gain flattened as pre-pregnancy body mass index increased. The rate of weight gain was lower in the first half than in the second half of pregnancy. No differences in the patterns of weight gain were observed between cohorts or countries.

**Conclusions:** Gestational weight gain patterns are strongly related to pre-pregnancy body mass index. The derived charts can be used to improve pregnancy care practices in Western countries and for etiological research.

**PA2.07.07**

**Maternal smoking during pregnancy and birth weight in European cohorts: The HEALS project**

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**Background:** Several studies have indicated that tobacco smoking changes the intrauterine environment that largely affects fetal growth. Low birth weight due to maternal smoking has been found to increase with maternal diseases like diabetes, maternal weight gain and other associated complications. Additional plausible confounders such as, socio-economic status, ethnic groups, sex of the child, alcohol consumption etc. are also found to have a synergistic effect on birth-weight. The aim of this study was to assess the potential impact of maternal smoking during pregnancy on birth-weight, taking into account clinical information and other related factors.

**Methods:** The study included 17383 individuals from different pre-existing cohorts (EPITeen, Generation 21, REPRO-PL, CCM, PHIME and EDEN) across multi-centers of six European countries, namely Portugal, Poland, Italy, Croatia, Slovenia and France respectively. A stratified logistic regression analysis was performed to determine the association between birth-weight and maternal smoking habits. In addition to maternal diseases during pregnancy, the effect of maternal smoking on birth weight was simultaneously controlled for sex of child, maternal weight at the end of pregnancy, maternal drinking habits, ethnic group, work position and educational level of mother, and socio-economic crowding index. Due to the presence of missing values, maximum-likelihood method has been used for multiple imputation in the data.

**Results:** 15.79% of the pregnant mothers were regular smokers, 8.15% of newborns weighed less than 2.5 kg at birth. 7.05% of infants were born with low birth-weight (LBW) in case of non-smoking mothers, whereas 12.44% of LBW infants were documented for mothers who smoked during pregnancy. The number of infants with LBW was found to rise with the increasing number of cigarettes smoked by the mothers during pregnancy. 8.02%, 8.92% and 9.25% of LBW was observed when mothers smoked up to 5, 11 and greater than 11 cigarettes per day respectively. Maternal weight was also found to affect birth weight prominently (\( \text{OR} = 1.06; 95\% \text{ CI} = 1.02, 1.11 \)), along with other factors like infectious diseases during pregnancy. After adjusting for confounders, maternal smoking during pregnancy had a significant association with LBW (\( \text{OR} = 1.95; 95\% \text{ CI} = 1.58, 2.22 \)). Similar findings were observed when sub-samples of the data were considered on the basis of geographic origins.

**Conclusions:** Using large data from pre-existing cohorts of different European countries, our study confirms a prominent birth weight reduction with maternal smoking. This finding supports the biological explanation of placental deformation due to smoking that leads to reduced birth weight and other neonatal complications.

**PA2.07.08**

**Air pollution exposure during fetal life, brain morphology, and cognitive function in school-age children**

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**Background:** Air pollution exposure during fetal life has been related to impaired child neurodevelopment but it is unclear if brain structural alterations underlie this association. Therefore, we aimed to assess whether air pollution exposure during fetal life alter brain morphology and whether these alterations mediate the association between air pollution exposure during fetal life and cognitive function in school-age children.

**Methods:** A prospective population-based birth cohort was set up in Rotterdam, The Netherlands (2002-2006). From the
8,879 mother-child pairs enrolled during pregnancy, 1,070 children aged 6-10 years participated in the MRI sub-study (77% of those invited). Levels of air pollution during the entire fetal period at home addresses were calculated using land-use regression models. Structural neuroimaging including cortical thickness and brain volumes, and cognitive function assessments at 6-10 years were performed. Models were adjusted for several child and parental socioeconomic and life-style characteristics.

Results: A total of 783 children were included in the analysis where multiple imputation and inverted probability weighting were applied to deal with attrition and missing data. Children exposed to higher particulate matter levels during fetal life had thinner cortex in several brain regions of both hemispheres (e.g. cerebral cortex of the precuneus region in the right hemisphere was 0.048 mm thinner (95% Confidence Interval 0.038 to 0.061) for each 5μg/m3 increase in fine particles during fetal life). The reduced cerebral cortex in precuneus and rostral middle frontal regions partially mediated the association between exposure to fine particles during fetal life and impaired inhibitory control. No associations were found between air pollution exposure and global brain volume measures.

Conclusions: Exposure to fine particles during fetal life was related to child brain structural alterations of the cerebral cortex and these alterations partially mediated the association between exposure to fine particles during fetal life and impaired inhibitory control. Such cognitive impairment at early ages could have significant long-term consequences in particular due to the ubiquity of the exposure.

LM2.01 - Trainee lunch workshop

LM2.01.01

How to make sure your research has great impact

M. Hanson

University of Southampton, United Kingdom

Maximizing research impact is an important focus of researchers and funders alike. How can you make sure your research has a strong societal impact? How can you optimize this impact and how can you best communicate this? In this workshop, Professor Mark Hanson will discuss his views on this, based on his extensive experience. Professor Hanson is Professor of Cardiovascular Science at the University of Southampton, UK and President of the DOHaD Society. He is the founding director of LifeLab, a collaborative initiative between the University of Southampton, University Hospital Southampton NHS Trust and local schools, which aims to promote health and science literacy in school students. LifeLab was shortlisted for the BBSRC Innovators Award in 2012 and a Times Higher Education Award in 2015. In addition, Professor Hanson has a leading role in many public health and policy initiatives, including co-chairing the Science and Evidence Working Group for the WHO Director-General’s Commission on Ending Childhood Obesity and being a consultant to WHO. He is also involved in the wider public understanding of science through public lectures and popular science books.

LM2.02 - Slam session: Fetal and childhood outcomes

LM2.02.01

Dietary acrylamide intake during pregnancy and postnatal growth and obesity: results from the Norwegian mother and child cohort study (MoBa)

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Background: Acrylamide exposure during pregnancy has been negatively associated with foetal growth in previous epidemiological studies; long-term associations with the child’s postnatal growth are unknown. Our aim was to study the association between dietary acrylamide exposure during pregnancy and child’s postnatal growth up to 8 years in a large cohort study in Norway.

Methods: In MoBa, acrylamide intake during pregnancy was assessed by combining maternal food intake with concentration of acrylamide in food. Mothers reported their child’s weight and length/height 11 times between 6 weeks and 8 years. Weight and height growth were modelled separately using the Jeness-Bayley’s growth model and then BMI. Overweight and obese children were identified using the International Obesity Task Force cut-offs. Logistic regression models were used to analyse the relationship between acrylamide intake in quartiles and being overweight/obese at 3, 5 and 8 years. Linear mixed-effect models were used to explore the association with longitudinal weight data from 1 month to 8 years. All the models were adjusted for maternal age, parity, education, prepregnancy BMI, gestational weight gain, gestational age, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

Results: In 51,952 mother-child pairs, median of maternal acrylamide intake was 24.7μg/day (interquartile range: 18.4, 33.2). Prenatal acrylamide exposure was associated at each age considered with an increased risk of being overweight/obese in a dose response manner. At 3 years, the adjusted odds ratio (aOR) of being overweight/obese for the 2nd, 3rd and 4th quartile of acrylamide intake were 1.10 (95% Confidence Interval (CI): 1.02–1.20), 1.12 (95%CI: 1.04–1.22) and 1.21 (95%CI: 1.11–1.31). These results were similar at 5 years. At 8 years, the results remained within the same magnitude, while non-significant. Maternal acrylamide at the highest level of intake was associated with increased risk for obesity at 3 years 1.35 (95%CI = 1.06–1.73), but not at the other ages. In addition, acrylamide intake during pregnancy was significantly
associated with higher weight growth in childhood. Children exposed to the 4th quartile of acrylamide exposure had 16.5g (95% CI: 25.3–30.5), 22.2g (95% CI: 7.7–36.8), 33.7g (95% CI: 16.8–50.6), 56.0g (95% CI: 32.2–81.0), 125.3g (95% CI: 72.7–178.5), 194.1g (95% CI: 110.3–277.8) and 453g (95% CI: 297.6–610) higher weight at 3, 6 and 12 months, 2, 5 and 8 years, respectively, compared to their the 1st quartile of acrylamide exposure.

Conclusions: Dietary acrylamide intake during pregnancy was associated with an increased risk of being overweight/obese and having a higher weight gain during early childhood and preschool age. Our study need to be replicated as it is the first one to link acrylamide exposure and postnatal growth.

LM2.02.02

Targeted metabolite profiling in cord blood from offspring of obese mothers reveals alterations in phospholipid and amino acid metabolism

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Background: Maternal obesity alters the metabolic milieu in utero, which may permanently impact regulation and function of the offspring’s metabolism and affect health outcomes. However, epigenetic mechanisms underlying potential dysregulations in fetal development remain to be elucidated. The aim was to investigate whether pregnancy risks including maternal obesity and gestational diabetes (GDM) are reflected by a dysregulation of metabolic pathways in offspring that may play a role in supporting methylation reactions. Therefore, we analyzed profiles of phospholipids and amino acids in cord blood of obese mothers with and without GDM.

Methods: The Programming of Enhanced Adiposity Risk in Childhood-Early Screening (PEACHES) study consists of 1,683 dyads of obese and normal-weight mothers and their offspring to investigate the long-term effect of pre-pregnancy maternal obesity on the development of overweight and associated metabolic diseases in offspring. GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Groups criteria. At delivery, cord blood was collected, centrifuged, and stored at -80°C. Based on complete information on pre-/perinatal data such as gestational age, gender, perinatal infections and availability of sample volume, a sub-cohort of 400 mothers was used for analysis including 144 obese GDM-positive mothers and 144 obese GDM-negative mothers versus 112 normal-weight GDM-negative mothers (controls). 49 amino acids and 109 phospholipids were quantified in cord blood serum samples by liquid chromatography tandem mass spectrometry. Statistical analyses were performed in software R using Wilcoxon’ robust one-way ANOVA for median and related post hoc tests based on bootstrapping with trimmed data. Subsequently, we performed pair-wise comparison of these metabolites in obese GDM-positive and GDM-negative mothers relative to controls, with adjustment for multiple testing and potential confounders (gestational weight gain and smoking, offspring gender) to study the impact of maternal obesity and GDM on metabolites in multiple linear regression models.

Results: Alterations in cord blood metabolites were detected after intrauterine exposure of the offspring to maternal obesity with or without GDM. Quantification of metabolites in offspring from obese GDM-negative mothers resulted in decreased cord blood concentrations of various amino acids including glycine, serine, and methionine along with a decrease in concentrations of 39 saturated and unsaturated long-chain phosphatidylcholines (PC) and sphingomyelins with residue lengths of 14 to 44 carbon atoms when compared to controls. Additionally, increases in two unsaturated long-chain lysophosphatidylcholines were detected, potentially pointing to an alteration of the reaction by phospholipase A2, an enzyme linked to inflammation in obesity. Exposure to obese pregnancies complicated by GDM resulted in similar metabolite alterations as in GDM-negative obesity but generally enhanced effects on the decrease in phospholipid concentrations in offspring at birth. Compared to controls, adjusted regression models showed strongest reductions (p < 0.0001) in concentrations of glycine, PCaeC40:6, and PCaaC42:0 in offspring of obese GDM-positive versus GDM-negative mothers.

Conclusion: Exposure of offspring to an adipogenic intraterine milieu led to alterations in cord blood concentrations of phospholipids and amino acids relevant to the methionine cycle. Whether a decrease in pathways that support the supply of methyl groups might potentially disturb methylation reactions in offspring, needs further investigations.

LM2.02.03

Body composition during infancy and childhood and cardiometabolic health throughout the lifespan: a systematic review

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Background: Worldwide, childhood obesity has increased rapidly over the past decades. Excess body fat has been linked to increased risk of cardiovascular diseases, but associations between adiposity in childhood and cardiometabolic health remain unclear. Body mass index (BMI) is often used to study adiposity and parameters for cardiovascular diseases, however, BMI is a suboptimal marker for adiposity status and is a poor predictor for cardiometabolic status in childhood. Emerging evidence suggest that more detailed measures of body composition better predict associations between adiposity status and cardiometabolic health. Therefore, we aimed to systematically review evidence on the associations between measures of body composition.
composition during the first 12 years of life and cardiometabolic health throughout the lifespan. Additionally, we aimed to study whether these associations differ by sex and ethnicity, since measures of body composition may vary in these subgroups.

**Methods:** We searched Medline, OvidSP, Embase, Web-of-science, Cochrane, PubMed Publisher and Google Scholar for interventional and observational studies in healthy children up to the age of 12 years. Studies were included when they reported associations between measures of body composition (e.g. fat mass index, fat-free mass index, visceral fat or subcutaneous fat) and one or more cardiometabolic factors (e.g. blood pressure, measures of insulin sensitivity or cholesterol levels) or cardiometabolic diseases (Type II Diabetes Mellitus, coronary heart disease or stroke). Reference screening, data extraction, and quality scoring were performed by two independently working researchers.

**Results:** The quality varied across the available studies and was in general low. In our search, most studies were cross-sectional and did not control for many potential confounders. A few studies suggested that a higher fat mass percentage and abdominal fat mass were positively associated with blood pressure, total- and LDL-cholesterol and insulin levels, but negatively with HDL-cholesterol levels. Not only measures of body fat, but lean mass has also been suggested to be associated with systolic blood pressure even after adjusting for fat mass. Evidence suggests that the associations between body composition outcomes and cardiometabolic health factors are modified by sex but not by ethnicity.

**Conclusions:** Our findings suggest that general and abdominal fat measures are associated with cardiovascular risk factors in childhood and adolescence. These findings highlight the importance of identifying modifiable lifestyle risk factors including physical activity and nutrition that may lead to adverse body composition outcomes in children. Long-term implications of adverse body composition outcomes in childhood remain unclear due to the paucity of long follow-up studies with detailed measures of body composition. Future research should address this, preferably with longitudinal examinations of changes in body composition in representative samples of infants and children while taking into account differences in sexes and ethnicity.

**LM2.02.04**

**Diet quality in early life in relation to allergic sensitization and atopic diseases in childhood**


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**Background:** The prevalence of childhood atopic diseases, including allergies, has increased in the past decades, which substantially affects the quality of life of those affected. Genetic background and environmental risk factors, including geographic area and lifestyle factors are associated with the development of allergies. Early-life nutrition is an important modifiable lifestyle factor that influences the development of the child’s immune system, and may therefore influence the risk of atopic diseases in children. There has been great interest in early-life dietary exposure, with studies focusing on breastfeeding, timing of solid food introduction, food allergen avoidance, or intake of specific nutrients, both during pregnancy or in infancy. However, these nutrients may interact as individuals do not consume one specific nutrient at a time, but a variety of nutrients combined in foods and meals. Studying overall dietary patterns takes these interactions into account. Therefore, we aimed to examine the associations between predefined dietary patterns during pregnancy and in infancy with allergic sensitization, allergy, eczema, and asthma in mid-childhood.

**Methods:** We included 4,683 mother-child pairs from the Generation R Study, an ongoing population-based prospective cohort from fetal life onward in Rotterdam, the Netherlands. Dietary intake was assessed during pregnancy and in infancy around the age of 1 year using validated food-frequency questionnaires. For both time points, diet quality scores were calculated, reflecting overall adherence to dietary guidelines. Allergic sensitization measurements in childhood were conducted at our research center around the age of 10 years. Sensitization to inhalant allergens (i.e., house dust mite, grass, birch, cat, and dog) and food allergens (i.e., peanut, cashew nut, hazelnut, and peach) were measured with skin prick tests using the scanned area method. In addition, questionnaires were used to obtain information on physician diagnosed inhalant and food allergies, eczema, and asthma.

**Results:** No associations were observed between diet quality at the age of 1 year and allergic sensitization (OR = 1.00, 95%CI: 0.93, 1.07), allergies (OR = 0.94, 95%CI: 0.86, 1.03), eczema (OR = 1.00, 95%CI: 0.93, 1.07), or asthma (OR = 0.97, 95% CI: 0.87, 1.07) in childhood. Similarly, we observed no associations between diet quality during pregnancy and these atopic outcomes in children aged 10 years (ORs ranging between 0.95 and 1.03). Findings did not differ between boys and girls.

**Conclusions:** Our findings suggest that overall diet quality in early life is not associated with the risk of allergic sensitization or atopic diseases in later childhood. Specific nutrients rather than overall dietary patterns may be more relevant for atopic outcomes in children.

**LM2.02.05**

**Associations of maternal physical activity and sedentary behavior with offspring growth in infancy**

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**Background:** Previous studies have reported sex-specific associations of maternal leisure time physical activity during
pregnancy with offspring birth size. Maternal leisure time physical activity and leisure time sedentary behavior during pregnancy may influence offspring programming of postnatal growth. However, associations of maternal leisure time physical activity and sedentary behavior during pregnancy with offspring postnatal growth have not been studied. Further, the role of offspring sex in these associations is not known.

Methods: This study was conducted among participants of the Danish National Birth Cohort. Study participants (N = 29,593) reported moderate/vigorous leisure time physical activity (hours/week) and time spent watching television or videos (hours/day) during a study interview in early pregnancy (16 weeks gestation, on average). Offspring weight and length at 12 months of age, measured during routine early childhood care, was reported by participants during a postpartum interview at 18 months, on average. Exposures were early pregnancy leisure time physical activity or sedentary behavior. Linear regression models adjusted for offspring length, demographic characteristics, and pregnancy activity or sedentary behavior. Exposures were early pregnancy leisure time physical activity was associated with lower offspring weight at 12 months overall (P = 0.002). Early pregnancy sedentary behavior was associated with -0.01kg lower weight at 12 months (95% CI: -0.02, -0.002). Among male offspring, each additional hour of early pregnancy leisure time physical activity was associated with -0.01kg lower weight at 12 months (95% CI: -0.02, -0.002). Physical activity was not associated with weight at 12 months in female offspring (mean difference = 0.002kg; 95% CI: -0.008, 0.001). Leisure time sedentary behavior was associated with lower offspring weight at 12 months overall (P for trend = 0.003). Early pregnancy sedentary behavior ≥5 hours per day was associated with 0.08kg lower weight at 12 months (95% CI: -0.01, 0.002). Associations of leisure time sedentary behavior with weight at 12 months were similar in male and female offspring (P for interaction = 0.56).

Conclusions: Maternal early pregnancy leisure time physical activity may be associated with lower weight at 12 months in male, but not female offspring. Maternal early pregnancy leisure time sedentary behavior may be associated with lower weight at 12 months in male and female offspring. Our results provide support for potential programming of infant growth by maternal early pregnancy leisure time physical activity and sedentary behavior.

LM2.02.06

History of hypertensive disorders of pregnancy as a risk factor for type 2 diabetes and cardiometabolic deterioration in middle age


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Background: Women with a history of hypertensive disorders of pregnancy (HDP) have twice the risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease post-pregnancy and also develop hypertension at a younger age. Though women with gestational diabetes mellitus (GDM) currently are recommended to be regularly screened for T2DM, the need for similar recommendations in women with a history of HDP is unknown. Therefore, we aimed to investigate the association between history of HDP and incident type 2 diabetes mellitus and cardiometabolic deterioration in middle aged women, taking their baseline cardiometabolic health into account.

Methods: We included parous women born 1940-1952 who attended population-based structured clinical visits in primary care (The Västerbotten Intervention Program) at ages 50 and again at age 60 years in Sweden. Data on reproductive history, including HDP, were collected from regional and national registries on deliveries. Utilizing binomial (for hypertension) or logistic [for T2DM, obesity (body mass index ≥30kg/m²), hypercholesterolemia (total serum cholesterol ≥7.5 mmol/l), or high weight gain (>90th percentile in sample)] regression we investigated the risk of developing each outcome between visits. We adjusted for family history of CVD and T2DM and measures of cardiometabolic health at baseline clinically relevant for each outcome, including the result of a 2 hour 75g oral glucose tolerance test (OGTT), mean arterial blood pressure, and smoking.

Results: In total, 399 (6%) participants developed T2DM between age 50 and 60 years. History of HDP was associated with increased risk of the diagnosis (odds ratio (OR) 2.60, 95% confidence interval 1.82-3.70) even after adjusting for measures of cardiometabolic health at age 50 years (OR 2.11, 95% confidence interval (CI) 1.40-3.18). Between age 50 and 60 years, 1,478 (28.6%) participants also developed hypertension. History of HDP was associated with increased risk of hypertension (relative risk (RR) 1.58, 95% CI 1.32-1.91) but this risk was attenuated when adjusted for baseline measures (RR 1.13, 95% CI 0.98-1.30). When adjusting for baseline cardiometabolic health, history of HDP was also not associated with development of hypercholesterolemia (OR 0.83, 95% CI 0.48-1.43), high weight gain (OR 1.02, 95% CI 0.68-1.55), or obesity (OR 0.77, 95% CI 0.48-1.24).

Conclusions: Women with a history of HDP have increased risk of developing T2DM in middle age, suggesting that women who experience HDP may benefit from more intense primary prevention efforts and screening for T2DM in midlife.
Sex-specific Transgenerational Effects of Bisphenol A on Metabolic Health

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Background: Exposure to an endocrine disruptor, Bisphenol A (BPA), is ubiquitous, and associated with health abnormalities in immediate as well as subsequent generations. However, transgenerational effects of endocrine disruptors on metabolic health that would have major public health ramifications are not widely studied. We recently demonstrated using C57BL/6 mice that maternal (F0) BPA exposure via maternal transmission has multigenerational sex- and dose-specific effects on pancreatic islets. The first (F1) and second generation (F2) female offspring were unaffected. In affected male offspring, lower dose exposure (10 μg/kg/day; LowerB) was associated with reduced β-cell mass, whereas higher dose (10 mg/kg/day; UpperB) was associated with impaired mitochondrial function relative to controls (7% corn oil diet; Control) across two generations. Both doses were associated with impaired β-cell function and increased pancreatic inflammation across two generations. We extended our analysis to the third generation (F3) to determine the transgenerational effects of BPA on pancreatic islets in our model.

Methods: Physiological parameters including weekly body weights, glucose tolerance, and body composition by DEXA scans were assessed in F3 male and female offspring (n = 10-12 litters/group). Islets were isolated from 5 months old F3 male offspring (n = 4-8 litters/group) to determine glucose stimulated and mitochondrial driven insulin secretion in response to α-ketoisocaproate using perifusion ramps. Pancreatic sections from 5 months old F3 male offspring (n = 6 litters/group) were immunostained for insulin, glucagon and somatostatin to determine β-cell, α-cell and δ-cell mass, respectively, as well as for CD3 and F4/80 to identify the presence of T-lymphocytes and macrophages, respectively. Cell death was determined in islet lysates of postnatal day 14 F3 male offspring (n = 5-6 litters/group) using a caspase 3 activity fluorometric assay. Each BPA group was compared with Control by student’s t test, and p < 0.05 was considered significant.

Results: Similar to F1 and F2 generations, we saw no differences in body weight in F3 LowerB and UpperB female offspring from birth to adulthood, and F3 female offspring had similar glucose tolerance as Controls in adulthood. In contrast, as with F1 and F2 males, F3 LowerB and UpperB male offspring had increased body weight, but only moderately increased fat mass relative to Controls in adulthood. Interestingly, both F3 LowerB and UpperB male offspring had comparable glucose tolerance and mitochondrial driven insulin secretion as Controls. However, F3 LowerB, but not UpperB, males had increased glucose stimulated insulin secretion, which is perhaps compensatory to reduced β-cell mass observed in LowerB group. Reduction in β-cell mass was associated with a trend towards increased caspase activity in F3 LowerB males. Finally, like F1 and F2 males, both F3 LowerB and UpperB had increased CD3 and F4/80 staining, suggesting increased pancreatic inflammation, relative to Controls.

Conclusion: Maternal BPA exposure has sex- and dose-specific, but relatively mild, effect on metabolic health of the third generation offspring. While some effects we observed in first and second-generation offspring persist in third generation, other effects disappear. Interestingly, the third generation offspring appear to be developing compensatory mechanisms to BPA exposure effects. We are currently investigating the mechanisms underlying these novel observations.

Exposure to antibiotics during the first year of life and childhood growth, obesity and cardiometabolic traits.

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Background: The intestinal microbiota in infants is particularly vulnerable to perturbation. Few human studies have suggested that early life exposure to antibiotic exposure influences microbial diversity and composition and may increase the risk of obesity, but the existing evidence is weak. We aimed to evaluate the impact of antibiotic exposure during the first 12 months of age on weight and height growth trajectories, the risk of overweight and obesity and cardiometabolic risk factors over the first 7 years of life.

Methods: We used prospective data on 705 children participating at the four and seven years’ follow-up in the Rhea birth cohort in Crete, Greece. Antibiotic exposure was assessed using patient-reported medications recorded at the first year follow up. The duration of exposure was determined as all days from the prescribed start to end date or as a single day for prescriptions without a specific ending date. Based on current recommendations, penicillin and amoxicillin were classified as narrow spectrum, while all systemic antibacterial medications were classified as broad spectrum. Children were classified as exposed to antibiotics during infancy if they had received at least one course of antibiotics. Outcomes included repeated weight and height measurements from birth through childhood, and waist circumference, skinfold thicknesses, blood pressure, serum levels of lipids, leptin, and C-reactive protein at 4 and 7 years of age. We assessed associations in adjusted regression and mixed models after adjusting for several confounders.
Conclusions: Infancy antibiotic exposure was associated with higher childhood weight gain and increased risk of obesity.

Results: In total, 224 (31.8%) children received at least one course of antibiotics during the first year of their life, 40 (5.7%) received multiple courses and 139 (19.8%) were exposed to antibiotics during the first 6 months. Any exposure to antibiotics during the first year of life was associated with increased weight SD score [β (95%CI): 0.19 (0.03 to 0.36)] and body mass index (BMI) SD score [β (95%CI): 0.22 (0.04 to 0.41)] from 1 to 7 years of life. The effect of antibiotics on BMI trajectory was stronger from infancy up to 4 years of life [β (95% CI): 0.19 (0.01 to 0.37)] and then it was attenuated [β (95% CI): 0.02 (-0.19 to 0.24)]. Exposure to amoxicillin during the first year of life was associated with 73% higher risk of being overweight or obese at the age of 4 [RR (95% CI): 1.73 (1.17 to 2.59)] and increased waist circumference (cm) at 7 years of age [β (95% CI): -2.67 (-5.32 to -0.03)] and higher CRP levels at the first 6 months of life was associated with lower HDL levels [β (95% CI): -2.67 (-5.32 to -0.03)] and higher CRP levels at age 4 [%change (95% CI): 49% (8% to 105%)] suggesting an association with low grade systemic inflammation.

Conclusions: Infancy antibiotic exposure was associated with higher childhood weight gain and increased risk of obesity.

Prenatal air pollution exposure and attentional function and working memory at 7 years of age

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Background: Pregnancy is a vulnerable period in which environmental exposures can interfere with normal development and may play a crucial role in brain architecture development after birth. Development brain processes in utero that may be influenced by air pollution are neurulation, proliferation, migration, differentiation, synaptogenesis, apoptosis and myelination. Consequently, affection of these processes can impact on brain structures such as prefrontal cortex involved in executive functions like attentional function and working memory.

Methods: We used data from Asturias, Guipuzkoa, Sabadell and Valencia, regions of the Spanish INMA—Environment and Childhood — Project, a population-based birth cohort established between 2003 and 2008. Children were followed from birth to the cognitive assessment. Prenatal NO2 levels at participant residential addresses were estimated using land use regression (LUR) models. Cognitive development at 7 years of age was assessed with the Attentional Network Task (ANT) and the N-back test, in particular, inattentiveness (hit reaction time standard error (HRT(SE)), omission and commission errors), impulsivity (hit reaction time and commission errors), alerting, orienting and conflict attentional networks, working memory (two-back detectability), and superior working memory (three-back detectability). Linear and negative binomial regression models adjusted by child sex and age at the assessment, paternal socioeconomic, and lifestyle variables during pregnancy were used to assess the associations between NO2 and attentional function and working memory outcomes. We used a two-stage approach: i) associations were analysed separately for region and ii) region-specific effect estimates from regression models were combined using random-effects meta-analysis.

Results: Individuals with data on prenatal NO2 exposure and attentional function or working memory were included in this study (n = 1,617). Higher prenatal NO2 levels were associated with an increase of HRT (SE) and higher omission and commission errors [β = 6.12 (95% CI 1.30; 10.93), IRR = 1.08 (95% CI 0.90; 1.27), IRR = 1.97 (95% CI 0.84; 1.29) per each 10 μg/m3 increase in prenatal NO2, respectively]. Individuals with higher prenatal NO2 exposure showed a not statistically significant lower superior working memory capacity [β = -0.04 (95% CI -0.08; 0.01) per each 10 μg/m3 increase in prenatal NO2]. Prenatal NO2 was not associated with other attentional function or working memory outcomes.

Conclusions: Our study suggests that higher exposures to NO2 during pregnancy are associated with inattentiveness but not with impulsivity, working memory or superior working memory in children at 7 years of age. These results are relevant because they highlight the importance of air pollution effects on attentional function which can, among others, affect school performance in those kids whose mother were more exposed during pregnancy.

Breaking the myths: Bidirectional associations between parent perception of child overweight and children’s BMI from ages 2–3 to 14–15 years

M. Wake1, W. Jansen2, K. Kerr3

Background: Many parents do not consider their overweight/obese children to be overweight/obese, and changing this perception is often considered an essential first step to reducing child BMI. Surprisingly, Robinson and Sutin recently showed that correct parent perception of child overweight actually preceded higher weight gain, but did not consider the potential for a bi-directional relationship. Here, we extend Robinson’s analyses within the Longitudinal Study of Australian Children (LSAC) to examine wave-on-wave (1) lagged relationships of parents’ perception of child overweight to child BMI, and (2) lagged relationships of child BMI to parents’ perception.

Methods: LSAC has followed two nationally-representative cohorts with biennial home visits since 2004, when the Baby (B)
cohort (n = 5107, 64% response) were aged 0-1 years and the Kindergarten (K) cohort (n = 4983, 59% response) 4-5 years. Measured BMI z-score and parent perception of child overweight were available for the K cohort at 6 waves (ages 4-5, 6-7, 8-9, 10-11, 12-13, 14-15 years; n = 4632) and the B cohort at 4 waves (ages 2-3, 4-5, 8-9, 10-11 years; n = 4445). We applied a cross-lagged modeling approach using Mplus to examine the two aims (linear regressions to BMI, logistic regressions to parent perception of child overweight), accounting for continuity across waves in BMI, and in parent perception with linear and logistic regression respectively. Models were estimated using maximum likelihood estimation with robust standard errors (MLR), and survey weights applied to account for differential non-response at Wave 1. Unadjusted model results are presented, as adjustment for sex, socio-economic position and having a medical condition did not change the effect estimates.

**Results:** 4632 and 4445 children were included in the cross-lagged models in the K and B cohorts, respectively. The Figure shows that the bidirectional wave-on-wave predictions were strong and consistent between waves and between cohorts. As expected, there were strong associations between BMI z-scores at every wave, and between perceptions of overweight at every wave. All lagged associations were highly significant (p < 0.001). Thus, for every unit increase in BMI z-score, the odds of parents perceiving children as overweight in the next wave ranged from 2.85 (B cohort 2-3 year olds) to 10.4 (K cohort 6-7 year olds), whereas perception of child overweight predicted a BMI z-score that was around 0.2-0.5 higher in the next wave. The obvious bidirectional lagged effects between two subsequent waves were much stronger from BMI z-score than from perception of overweight, as confirmed by Wald tests (all p-values < 0.001). Results were similar for children who were normal weight and overweight at baseline examined separately (not shown).

**Conclusions:** Strikingly large predictive associations from child BMI z-score to parent perception of child overweight far outweigh the reverse associations from parent perception of overweight to higher later BMI. We conclude that: (1) Parents’ perception of overweight seems appropriate to children’s BMI trajectories; (2) Making parents aware of true BMI status seems unlikely to be helpful; and (3) Reducing childhood obesity may require approaches that are not based on changing parent perceptions of overweight.

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**LM2.02.11**

**Breastfeeding and cardiometabolic markers at age 12: a population-based birth cohort study**

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**Background:** It is uncertain whether breastfeeding is associated with cardiometabolic markers in childhood. We investigated whether breastfed children had more favorable levels of cardiometabolic markers at 12 years of age than non-breastfed children and whether the duration of breastfeeding influences these associations.

**Methods:** In 1509 participants of a population-based birth cohort study, cardiometabolic markers were measured by trained research staff at 12 years of age. Duration of breastfeeding in weeks was assessed through parental questionnaires at 3 months and 1 year of age. Multivariable linear regression analysis was used to investigate associations of breastfeeding (any vs. no and duration in categories <3 months, 3-<6 months and >6 months vs. no) with body mass index (BMI, in Z-scores adjusted for age and sex), systolic- and diastolic blood pressure (SBP and DBP, in Z-scores adjusted for age, sex and height) and glycated hemoglobin (HbA1c in mmol/mol), as well as ratios of waist-to-hip circumference (WHpR) and total-to-high-density lipoprotein cholesterol level (TC/HDLc).

**Results:** Breastfed children (n = 1288, 85.3% of the total study population) had a 0.22 SD (95%CI -0.38, -0.06) lower SBP Z-score and a 0.10 SD (95%CI -0.20, 0.00) lower DBP Z-score than non-breastfed children. No associations were observed between the duration of breastfeeding and SBP- or DBP Z-score. Other cardiometabolic markers were not statistically significantly different between breastfed (any breastfeeding or categories of breastfeeding duration) and non-breastfed children.

**Conclusions:** Breastfed children on average had lower blood pressure at age 12 years independent of the duration of breastfeeding. Breastfeeding was not associated with BMI, WHpR, TC/HDLc and HbA1c.

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**LM2.02.12**

**Sex-specific risks on adverse body composition and metabolic outcomes in term born children with extreme birth weights: a narrative review**

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Background: The influence of sex on later risk of adverse metabolic and other health outcomes is quite established, and may be related to early life growth and body composition development. It is not well understood, however, whether these outcomes are differently affected by sex in children born with extreme birth weights (term small for gestational age (tSGA), term low birth weight (tLBW); large for gestational age (LGA) and high birth weight (HBW)). This narrative review aims to evaluate sex differences in development of body composition and metabolic outcomes in infants with extreme birth weights.

Methods: Two search strategies were conducted for the groups from 4 electronic databases and publication dates between 2010 and April 2016.

Results: Sixteen studies were included based on a priori inclusion and exclusion criteria. Only 4 reported the influence of sex (tSGA and tLBW n = 3; LGA and HBW subjects n = 1). Among those infants born tSGA and tLBW, males had a higher fat free mass at 4 and 6 months, and had lower odds of obesity at 4-5 years of age and fat mass at 6-7 years. No differences in metabolic markers between sexes such as impaired glucose, insulin and HbA1C were reported in early infancy. Among neonates born macrosomic, no sex differences were reported in the odds of overweight at 4 years of age. Other studies were sex-stratified, thus no sex-specific information could be inferred.

Conclusion: These results suggest that reported sex-specific risks on anthropometric, body composition, risk of overweight and obesity and metabolic outcomes were not altered by extreme birth weights in term born infants. More research is needed to confirm these outcomes. Future data analysis should focus on sex differences rather than performing sex-stratified analysis.

LM2.06 - Slam session: Studies from developing countries

LM2.06.01

Exposure to tobacco smoke in prenatal and early postnatal life alters infant gut microbiota and increases risk of childhood overweight

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Background: Globally, the prevalence of overweight in children has increased over the past three decades. The association between smoking during pregnancy and overweight in offspring has been reported in a number of studies and confirmed by recent meta-analyses. However, most studies focus only on maternal smoking and fail to adjust for smoking of other household members. Long term exposure to cigarette smoke induces changes in microbial composition and inflammation in the gut of both adult human and mice. In this study, we investigate the effect of household tobacco smoke exposure in prenatal and early postnatal periods on the infant gut microbiota composition and overweight risk at ages 1 and 3.

Methodology: The study population comprised a large subsample of 999 infants enrolled at the Edmonton, Vancouver and Winnipeg sites of the Canadian Healthy Infant Longitudinal Development (CHILD) population-based birth cohort. Smoking exposure status (both maternal and other household members) was collected in both prenatal and postnatal questionnaires and categorized into four groups: no exposure (n = 791, 78.2%); exposure only during pregnancy (n = 15, 1.5%); exposure only postnatally (n = 107, 10.7%); and exposure during pregnancy and postnatally (n = 46, 4.6%). At 1 and 3 years old, weight and height of infants were measured, and age and sex adjusted weight-for-length and BMI (body mass index) z scores were generated according to the WHO criteria. Children with a weight-for-length or BMI z score > 97th centile were classified as overweight/obese. Gut microbial diversity and composition of infants at 3-4 months after birth was assessed using high-throughput 16S rRNA sequencing. Maternal overweight/obesity (classified as BMI ≥ 25.0) was considered as a main covariate for childhood obesity. Other covariates, including ethnicity, mode of delivery, infant sex, breastfeeding, antibiotics exposure and presence of siblings were retrieved from standardized questionnaires completed by mothers. The mediation effect of microbiota measurements was evaluated. Statistical analyses were performed in SAS V9.4.

Results: Exposure to tobacco smoke postnatally only, or during both the pregnancy and postnatal periods, was significantly associated with overweight/obesity at age 1 year (OR: 2.10, 95%CI: 1.13-3.91, and OR: 3.32, 95%CI: 1.42-7.75, respectively) and 3 years (OR: 2.79, 95%CI: 1.46-5.32, and OR: 3.61, 95%CI: 1.36-9.60, respectively). However, the association for household smoke exposure during pregnancy and postnatally was attenuated when adjusted for maternal prenatal smoking. Species richness of Firmicutes and abundance of Ruminococcaceae at 3 months of age was significantly increased in infants exposed to tobacco smoke postnatally or both pre and postnatally (P < 0.05). Independent to tested covariates, the highest tertile of Firmicutes richness provided a two-fold higher risk of overweight/obesity at age 1 and 3 (aOR: 2.28, 95%CI: 1.29-4.01, and aOR: 1.91, 95%CI: 1.01-3.60, respectively). A mediation analysis revealed potential mediation by gut microbiota, especially Firmicutes richness, in the association between postnatal smoking exposure and the risk of childhood overweight at age 1 and 3 (Bootstrap 95%CI: 0.01-0.13, and 95%CI: 0.01-0.09, respectively).

Conclusion: Our study highlights that exposure to household tobacco smoking in early life can alter infant gut microbiota at 3-4 months and may increases risk of childhood overweight and obesity.
Microbiota mediation model for the association between postnatal smoking exposure and childhood overweight

**LM2.06.02**

**Pregnancy glycemic status reflects lifecourse glycemic status of the mother**

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**Background:** Current practice of diagnosis and treatment of Gestational Diabetes Mellitus (GDM) is largely restricted to late pregnancy. It is tacitly assumed that mother’s glucose metabolism was normal before pregnancy. However there is a large body of evidence to show that most of the risk factors of GDM are present from before pregnancy and will influence peri-conceptional programming of diabetes and other Non-Communicable Diseases (NCDs). There is little information on glycemic status of GDM women from before pregnancy.

Pune Maternal Nutrition Study (PMNS) has prospective data in the parents (F0 generation) and in children (F1) from birth to early adulthood. Many F1 girls are married and delivered (F2). This offers a unique opportunity to investigate the association between gestational glycaemia and pre-pregnancy life-course glycaemia.

**Methods:** We studied 797 pregnant mothers (F0) between 1993-96. Maternal glucose measurements were available during pregnancy. Children (F1 generation) were measured at birth, 6yr, 12yr and 18yrs of age for glycemic and anthropometric measurements. Parents were also studied. Girls (F1) who became pregnant underwent a 75 gm OGTT at 28wks gestation. Babies (F2) were measured at birth. We studied the association between 28wks gestational fasting plasma glucose (FPG) in the F1 mothers with their childhood and adolescent FPG and also with parental FPG using simple linear regression analysis.

**Results:** Up to March 2017, 163 F1 girls were married, 132 became pregnant and 94 had an OGTT at 28 wks and have delivered. Ten (10.6%) were diagnosed GDM (IADPSG criteria, FPG ≥ 92mg%, 1hr PG ≥ 180mg%, 2hr PG ≥ 153mg %). GDM were 20 yrs old, and had comparable birth weight (2.6 vs 2.5 kg), pre-pregnancy BMI and body fat% to those in NGT women. However, GDM were more insulin resistant (HOMA IR 1.5 vs 0.8) and had lower disposition index (83 vs 133, p < 0.001, both). They gave birth to heavier babies (3.1 vs 2.7 kg, p < 0.01). In lifecourse analysis, FPG tracked from 6yrs of age to pregnancy through 12 and 18 yrs. Maternal FPG at 28 wks was directly associated with FPG at 18yrs, 12 yrs and 6yrs of age (β = -0.3, p < 0.001), and it was inversely associated with disposition index at 18 yrs and 12 yrs (p < 0.05).

**Conclusions:** The world’s first description of lifecourse evolution of pregnancy glycaemia suggests that it tracks from early childhood and is associated with impaired beta cell function rather than adiposity and insulin resistance. The analysis provides an important clue that GDM women have higher pre and peri-conceptional glycaemia which is a risk factor for programming of diabetes and cardiovascular risk in the offspring. This could be a potential explanation of the failure of current practice of GDM diagnosis and treatment to reduce long term risks in the offspring.

**LM2.06.03**

**Maternal plasma vitamin D concentrations during pregnancy and cardio-metabolic risk factors in the offspring**

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**Background:** Maternal vitamin D status during pregnancy has been shown to influence fetal body composition and metabolic risk. Evidence extending into adult life is lacking. Pune Maternal Nutrition Study, a rural pre-conceptional birth cohort has followed children till young adult age and therefore provides opportunity to explore these associations.

**Methods:** We studied association of maternal anthropometry, nutrition (FFQ) and circulating vitamin D at 28 weeks of pregnancy with neonatal size, body composition (DXA) and metabolic parameters at 6, 12, 18y (n = 662, 356 boys, 306 girls).

**Results:** At pre-pregnancy mothers were ~ 21 years old, weighed 42 kg and were 1.5 m tall, 1/3 had a body mass index < 17 kg/m², indicating severe chronic energy deficiency (World Health Organization 1995). Their plasma vitamin D concentration at 28 weeks of pregnancy was 67.0 ± 23.7 nMol/l (2% deficient <27.5 nMol/l, 20% insufficient <50 nMol/l, 78% sufficient >50 nMol/l). In comparison with sufficient, deficient mothers had significantly larger hip circumference (Avg. 89.7 Vs 86.3 cm) and higher sum of skinfolds (55.5 Vs 42.5 mm, p < 0.05 all) at all trimesters of pregnancy. Their body weight and height were not different. They had higher plasma cholesterol concentration at 28 weeks; their glycaemia and insulin resistance were not different. Deficient
mothers had lower calorie intake (1482 Vs 1703 Kcal/day), lower consumption of milk and non-vegetarian foods but higher intake of dietary calcium (682 Vs 521 mg/day). They had lower physical activity and spent lesser time in activities involving sunlight exposure such as farming.

Offspring of vitamin D deficient mothers had higher weight and head circumference at birth (2.9 Vs 2.6 kg, 34.0 Vs 32.7 cm) and at 6y, 12y than of sufficient mothers; skinfolds at birth were not different. They had higher fat mass (DXA) at 6y (3.5 Vs 3.1 kg) and 12y (6.9 Vs 5.1 kg), higher fat% at 12 y (20.4 Vs 16.8%, p < 0.05 All), their lean and bone measurements were not different. They had higher triglycerides at 18y (74 Vs 61 mg%), higher cholesterol at 12y and 18y (Avg 134.9 Vs 130.5 mg/dl , p < 0.05 All) but glycemia and insulin resistance were not different.

On regression analysis lower maternal vitamin D predicted higher birth weight (R² change 2.1%) and length (R² change 0.7%); higher triglycerides at 12y, 18y (R² change 1.5% both), higher cholesterol and body fat% at 18y (R² change 1.2% both). These associations were independent of maternal calorie intake, physical activity, and dietary calcium intake, skinfolds during pregnancy, parity and gestation at delivery, gender of the child.

Conclusion: In this rural farming Indian community, maternal vitamin D deficiency was rare. Surprisingly it predicted larger birth size though expectedly was associated with higher cardio-metabolic risk in early adulthood. It will be important to define the underlying mechanisms and perform intervention studies.

LM2.06.05
Assessment of abdominal aorta intima media thickness in late preterm appropriate for gestational age and growth restricted fetuses: a comparative cross-sectional study
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Background: Cardiovascular diseases share the topmost burden of mortality worldwide. According to fetal origin of adult atherosclerotic disease hypothesis, cardiovascular derangement appears to originate in-utero in undernourished fetuses secondary to the cardio-metabolic stress they experience. This study investigates the abdominal aorta intima media thickness (aIMT) and aortic diameter (AD) in growth restricted fetuses (GRF) and appropriate for gestational age (AGA) fetuses as a non-invasive marker of future cardiovascular disease risk.

Methods: We conducted a cross-sectional study from February to August 2017 on 29 GRF and 85 AGA singleton fetuses enrolled in the late-preterm at the Aga Khan University, Karachi. The study was approved by the University Ethics Committee. Fetuses with structural and chromosomal abnormalities were excluded. GRF was defined as those whose estimated fetal weight and birth weight were below the 10th centile for that particular gestational age. Abdominal aIMT and AD were obtained in a coronal view between the renal and the iliac arteries using high-resolution Medison Accuvix 20 ultrasound machine with a 3.5 to 5-MHz linear array transducer. Measurement of aIMT was performed offline using digital software by manual placement of calipers on the intima-media surface by two observers separately. aIMT was measured as the distance between the leading edge of the blood intima interface and the leading edge of the media adventitia interface on the far wall of the vessel. AD was measured at the same level of aIMT, between blood intima interfaces at both ends of the vessel. All images were taken at end-diastole of the cardiac cycle. The reading was obtained three times and the mean measurement was analyzed. Inter-rater agreement was calculated by Bland-Altman technique.

Results: Mean maternal age (years) of AGA (30.8 ± 4.3) and GRF (31.2 ± 5.5) did not differ significantly (p value 0.65). Gestational age at ultrasound (weeks) did not differ for AGA and GRF (35.9 ± 2.3 vs 34.7 ± 4.1; p value 0.97). Similarly no difference was observed in gestational age at delivery between the two groups (37.25 ± 1.6 vs 36.3 ± 1.7; p value 0.09). GRF weighed significantly less at birth in comparison to AGA fetuses [2863.5 (±447.6) grams vs 2007.7 (±415.4) grams; p value <0.001]. Mean abdominal aIMT on far wall examination was found to be significantly greater among GRF compared to AGA fetuses [0.44mm (± 0.06) vs. 0.39mm (± 0.07); p-value <0.003]. Inter-rater agreement constituted maximum observations within 95% confidence intervals as excellent measure of agreement (mean difference = 0.004 mm; 95% CI -0.121, 0.130). Multivariable model revealed significant increase of aIMT among GRF (β = 0.040, 95% CI 0.007, 0.073) after adjusting early gestational age at delivery, decreased aortic diameter and increased uterine artery pulsatility index.

Conclusions: GRF demonstrate thicker abdominal aortic intima media as compared to AGA fetuses. This appears to depict vascular remodeling and could predispose them to ischemic vascular disease later in life. Long-term longitudinal studies are required to understand the underlying mechanism of in-utero initiation of vascular changes and its association with cardiovascular disease in adulthood.

Comparison of aIMT between Appropriate for Gestational Age and Growth Restricted Fetuses
The Welcome Baby Project, the first virtual cohort in Brazil: prenatal consultation and exclusive breastfeeding rates.

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Background: Brazil is a very big country and the national health system is unable to provide good care and health information for everyone. Attendance to prenatal care is essential for healthy monitoring of pregnancy, as it can prevent medical complications that contribute to low birth weight babies and all the consequences that this fact can determine to future life. According to official estimates, 60% of pregnant women in Brazil attend less than 7 prenatal visits. Encourage breastfeeding should be a practice constantly renewed in all regions of the world, especially in developing countries. Prenatal and breastfeeding are essential and important conditions for the future of all children. The Welcome Baby Project, the first virtual cohort in Brazil, is an initiative that addresses this concern.

Methods: Based on these data, the Welcome Baby Project took shape and began in October 2014. We selected 642 pregnant women that were in the first trimester of pregnancy. Participation was on a voluntary basis. All pregnant women who were interested, accepted the terms and conditions, and filled out an online form. We followed them in a closed group within Facebook, which was the social network used, until their children were 2 years old. Everyday we provided behavior-changing health information encouraging them to go to prenatal visits. After the children were born, we also encouraged them to breastfeed as well as to correctly introduce supplementary feeding after 6 months.

Results: According to brazilian official data, only 57.1% of women achieved more than 7 prenatal consultations; 32% attended between 4 to 6 consultations and 9.5% from 0 to 3 consultations. Our results found that 89% of pregnant women attended more than 7 prenatal consultations, 9% attended 6 consultations and 2% attended 4 or 5 consultations. There was no correlation between the number of prenatal consultations with educational level (p = 0.691) or income (p = 0.400). The exclusive breastfeeding rate up to 4 months of age in our group was 70%, well above the brazilian average, which is 23.3%. The exclusive breastfeeding rate up to 6 months of age in our group was 44.5%, also well above the brazilian average, which is 9.3%. There was no statistically significant difference related to educational level or socioeconomic status.

Conclusions: This is the first virtual cohort in Brazil, an innovative project in its form and content, using a social network to promote health, clarify important issues and encourage the need of prenatal consultation and exclusive breastfeeding in the first 6 months of life. Social networks can be used as a health promotion tool to encourage the need of prenatal consultation and breastfeeding in all educational and social groups.

Effect of linear growth rate and change in adiposity in childhood and adolescence on blood pressure in Afro-Caribbean youth

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Background: Faster growth velocity during childhood and adolescence may increase blood pressure in adults, although there is a dearth of data among African-origin populations. We evaluated the effect of postnatal linear growth and change in body mass index (BMI) from birth to adolescence on systolic and diastolic blood pressure (SBP and DBP) in Afro-Caribbean youth.

Methods: We used data from a birth cohort in Jamaica (Vulnerable Windows Cohort Study). Children were followed from birth, with anthropometric measurements at six weeks, every three months to age 1-year, and then six monthly. Blood pressure (BP) measurements started at age 1-year and every six months thereafter. Analyses used BP measurements (mm Hg) after age 15 years and up to age 21 years. Growth and adiposity measurements were calculated for the periods: early infancy (0-6 months), late infancy (6 months - 2 years), early childhood (2-8 years), and later childhood (8-15 years). Conditional analyses were used to compute growth rates by calculating how much body size at the end of a growth period differed from that predicted by the body size attained at the beginning of the period using linear regression models. Calculated growth rates were standardized by converting them to z-scores. Linear mixed models were used to estimate the effect of growth rates on BP. Models accounted for repeated measures within individuals with random intercepts and random slopes. Multiple imputation was used to fill in missing values.

Results: Analyses included 366 individuals (162 males, 204 females) with mean age 16.7 years (range 15.0, 21.2 years). At age 15 years, mean height was 172 cm for males and 163 cm for females. Mean BMI was 21.0 kg/m² among males and 22.2 kg/m² among females. In total, 1910 SBP and 1908 DBP measurements were available for analyses (average 5.2 measurements per individual). In bivariate analyses, faster linear growth for the 0-6 months (β = 2.06, p < 0.001) and the 8-15 years (β = 1.54, p < 0.001) periods were associated with higher SBP. Greater increase in BMI for the 0-6 months (β = 1.11,
p = 0.010), 6-month to 2-years (β = 1.38, p = 0.004) and the 2-8 years (β = 1.26, p = 0.001) periods were associated with higher SBP. In multivariable models, after adjustment for age, sex, birth length, gestational age and BMI at age 15, faster linear growth for the 0-6 months (β = 1.00, p = 0.024) remained statistically significant. For change in BMI, after adjustment for age, sex, gestational age, birth length and height at age 15, significant associations of higher SBP remained for increases in BMI from 6-months to 2-years (β = 1.40, p = 0.001), and for 2-8 years (β = 1.07, p = 0.009). For DBP models with similar adjustments, faster linear growth for the 2-8 years period was associated with higher DBP, while greater increase in BMI for the 6-months to 2-years, 2-8 years, and 8-15 years growth periods were significantly associated with higher DBP.  

**Conclusion:** Both faster linear growth and greater rate of increase in BMI were associated with higher SBP and DBP in Afro-Caribbean youth. The association was most consistent in late infancy and the early childhood growth periods.

**LM2.06.08**

**Exposure to Outdoor Air Pollution and Birth Outcomes - Evidence from Sao Paulo’s Western Region Project**

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**Background:** While a growing literature has highlighted the negative associations between maternal exposure to NOx and PM pollution and birth weight, evidence on the effect of ambient air pollution on prematurity remains limited. We use new data on street level air pollution to estimate the associations between NOx and birth outcomes in Sao Paulo, Brazil.

**Methods:** 5,542 birth records from children born at the University Hospital of Sao Paulo between April 2012 and March 2014 were linked to street level NOx and PM2.5 emissions using residential addresses. Primary outcomes analyzed were prematurity (gestational age < 37 weeks), low birth weight (< 2500 grams) and being small for gestational age (SGA). Adjusted and unadjusted linear models were used to assess the associations between prematurity, gestation-adjusted weight and child development overall, as well as by gender.

**Results:** In fully adjusted regression models, we find that each unit increase in the natural logarithm of NOx emissions is associated with a 60 percent increase in the odds of low birth weight (95% CIs [1.163, 2.204]), and a 39 percent increase in the odds of prematurity (95% CI [1.016, 1.905]). We do not find any associations between NOx exposure and SGA.

**Conclusions/Interpretation:** The results presented in this study suggest that residential exposure to NOx emissions (a proxy estimate of traffic-derived pollution) may constitute a major risk factor for both low birth weight and prematurity in Sao Paulo and similarly large urban areas. The potential health benefits of lowering local emission levels seem sizeable.

**LM2.06.09**

**Socio-economic transition in rural India and its impact on health indicators: Pune Maternal Nutrition Study 1993-2013**

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**Background:** Developing (LMICs) countries are facing a rapid change in socio-economic conditions. This has led to the emergence of an epidemic of non-communicable diseases (NCDs, including type 2 diabetes, hypertension, cardiovascular disease, cancer and others) on the background of the unfinished burden of undernutrition and communicable diseases, described as the double burden of disease. Countries like India are particularly affected, and reputedly India is one of the world’s capital of both diabetes and cardiovascular disease. Thrifty phenotype and DOHaD theories highlight the adverse health effects of transition within a lifetime from early life adverse exposures and subsequent relative affluence. The change in socio-economic status (SES) and its indicators may be used to understand and partly quantify the transition but up-to-date, precise, and reliable statistics are few in India.

The prospective data collection in the Pune Maternal Nutrition Study (PMNS) birth cohort in rural Pune in the state of Maharashtra, India provided an opportunity to examine the changes in socio-economic status (SES) in comparison with the state and the national data and its association with body size and cardio-metabolic risk factors.

**Method:** PMNS was set up between 1993-96. SES and biomedical data was collected in the index pregnancy and serially every six years (2001, 2007, 2013) after the delivery of the child, using standardised questionnaires. Comparisons with rural Maharashtra and India were made using data from the National Family Health Survey 1999 and 2006 (NFHS II and III). We followed up 700 families (child and parents) for biomedical information (body size and composition, haematological, biochemical and metabolic-endocrine measurements).

**Results:** The PMNS community was a farming community and participants were relatively undernourished (parents’ BMI ~ 20 kg/m2, birthweight of the child 2.7 kg). The proportion of families with ‘high’ Standard of Living Index (SLI, NFHS) progressively increased from 64% to 77% and to 90% between 2001 and 2013, contributed by increasing availability of piped water, toilets, LPG for cooking, and affluent material possessions (two and four wheelers, refrigerators, TVS, mobile phones etc). The increase in SES in PMNS was faster and greater compared to that in the state of Maharashtra and the national
data. Higher SLI was associated with higher weight, height, BMI and a number of cardiovascular risk factors (glucose, blood pressure, lipids etc). Half of the children were still underweight (BMI < 18.5 kg/m²) at 18 years, ~ 5% overweight and obese, and 28% had prediabetes (ADA criteria). Two thirds of the children have vitamin B12 deficiency and ~ 80% have hyperhomocysteinemia.

**Conclusion:** Our data suggest a rapid socio-economic transition over last 20 years in rural Pune which is faster than the state and the national data. This is associated with higher cardiovascular risk factors including prediabetes and hyperhomocysteinemia. Metabolic, endocrine and molecular studies are under way to define mechanisms contributing to increased NCD risk.

**Results:**

![Distribution of SLI](image)

**Fig 1:** Distribution of SLI scores in the study area at the 6 (2000-02), 12 (2006-08) and 18 years (2013-14) follow-up compared with rural Maharashtra at the NFHS II (1998-99) and NFHS III (2005-06) surveys.

**Methods:**

Intricacies of glucose metabolism and fetal outcomes in undernourished pregnant Indian women

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**Background:** HAPO study showed an overriding importance of fasting hyperglycemia in influencing fetal growth. Most of the recent reports of prevalence of Gestational Diabetes Mellitus (GDM) in India have used a non-fasting Oral Glucose Tolerance Test (OGTT) which has clouded the opinion on the importance of fasting plasma glucose in diagnosis of GDM. We studied serial fasting 75gm OGTTs in pregnant Indian women to assess, 1) the contribution of fasting (FPG) and post glucose glycemia (1hPG, 2hPG) to GDM by the IADPSG criteria, 2) importance of early glucose screening in diagnosis of GDM.

**Methods:**

Hundred eligible women were enrolled (~12 week's gestation). OGTT (75 gm glucose) was performed after an overnight fast at baseline, 24 and 32 weeks of gestation. At each stage, women diagnosed with GDM were treated and did not have subsequent OGTT. Demographic information (age, education, socio economic status) and anthropometry was recorded using standardized questionnaire and methods. Babies were measured within 72 hours after birth.

**Results:**

Mothers were on average 25 years old, 153 cm tall and had BMI of 21.5 kg/m² at ~ 12 weeks gestation. Majority were from lower socio-economic class. Hundred, 72 and 57 OGTTs were performed at 12, 24 and 32 weeks of gestation, respectively. Four women aborted after first visit, 6 withdrew consent, and 20 were lost to follow up. Seventy five women were followed at all the three visits, and 70 delivered in the study hospital. A total of 21 women were diagnosed with GDM: 18 at 12 weeks (16 by FPG, 2 by 1-hPG), 2 at 24 weeks (1 by FPG, 1 by 1-hPG) and 1 at 32 weeks (1-hPG). GDM women were older, taller and more educated than the NGT women. Babies of GDM mothers were heavier (3.0 Vs 2.7 kg) and fatter (sum of skin folds: 8.8 Vs 7.2mm) than those born to NGT. Baby's birth weight was significantly predicted by mother's FPG at the OGTT but not by the 1h-and 2h-PG. Three babies were diagnosed to have congenital anomalies, all of them had GDM mothers; one was aborted early, two were delivered live, of these one died on 8th day.

Twenty mothers (5 GDM) delivered at outside hospitals. They were younger, thinner and had lower glucose. Telephonic interviews revealed: none was diagnosed with diabetes subsequently, and neonatal maturity, weight (2.8 Vs 2.7 kg) and Cesarean delivery rate was no different.

**Conclusion:** There was a high prevalence of GDM in this relatively undernourished population which was diagnosed in early pregnancy and by FPG criteria. Babies of GDM mothers...
had high anomaly rate, were heavier and more adipose. Our findings suggest a significant contribution of pre-gestational dysglycemia to ‘GDM’, and a stronger contribution of fasting than post-glucose metabolism to fetal outcomes. There is a need for large scale studies in India to study relative merits of pregestational Vs gestational screening and a fasting and non-fasting OGTT to diagnose GDM.

**LM2.06.11**

**Prevalence of depressive disorder among members of the New Delhi Birth Cohort - role of early life influences**

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**Background:** Globally, depression is a major cause of disability, with chronic or recurrent depressive patterns leading to impairment of daily activity or even leading to suicide. Almost 1 million suicide deaths occur yearly and for every person completing suicide, 20 or more are at suicide risk (WHO, 2012). Socio-economic and lifestyle factors, demographic conditions and environmental pollution can all cause depression. Among major depressive episodes, 70-80% patients are curable. The main obstacles towards providing care for depression are social stigma, lack of resources and poor availability of depression related data.

**Methods:** The NDBC is a longitudinal follow-up of 8181 children born between 1969-1972 to mothers in a defined area of South Delhi, India. The cohort (F1, N = 2221) has been followed from birth, through infancy and childhood, with studies so far on their parents (F0), spouses and children (F2) largely covering cardiometabolic diseases. To assess the mental health status, 271 adult members (F1) of the New Delhi Birth Cohort (NDBC) were screened by trained staff using Patient Health Questionnaire 9 (PHQ9). Patient health questionnaire-9 (PHQ9) is a 9-item depression module of Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument. Each of the nine items asks about DSM IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for depression diagnosis. Each question contained four scores with respective categories from 0 (not at all) to 3 (nearly every day) and refers to occurrence of the items within last two weeks. The total score, indicates categories of depression- zero score (0), none (1-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). Depression is detected when the score is ≥ 10. Major depression is detected following the criteria recommended by Kroenke and Spitzer. Additional data on environment, demographic conditions, and socio-economic & lifestyle factors were collected using questionnaires.

**Results:** Among 271 subjects, data from 249 (male- 163, female- 86) were complete and were used for preliminary analysis. The results indicate 20.88% (52) are suffering from depression (Score ≥ 10) and 15.26% (38) are suffering from Major Depression. Among the sample population, 71.08% (177) have at least one item affected (Score ≥ 1). Depression is 3.2 times higher among female subjects compared to male subjects. Among females, 27.9% (24) and among males 8.6% (14) of the male population are suffering from Major Depression. Total mean score for the population is 5.45; among females, it is very high at 8.65. Also, a higher percentage of females have reported higher degree of severity of the problem.

**Conclusions:** The prevalence of depression is high among this urban sample population. The burden of depression is several times higher among the female subjects. Major depression cases are also high, especially among females. Socio-economic, lifestyle, demographic and environmental factors can impact people’s mental health in addition to early life adverse influences. The current findings will be assessed in relation to these factors to provide crucial insights for appropriate interventions.

**LM2.06.12**

**Compromised expression of placental ABC transporters in a new murine model of malaria induced-preterm labor**

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**Background:** Gestational malaria (GM) is a worldwide life-threatening disease that kills approximately 100,000 pregnant women and newborns every year. In the Brazilian Amazon this mosquito-borne infectious disease leads to intrauterine growth restriction (IUGR) and elevates the risk of preterm labor (PTL) in about 25% of cases. The ATP-binding cassette (ABC) transporters, actively efflux substrates involved in immunological responses and drug biodisposition at the placental barrier. We hypothesized that maternal exposure to Plasmodium Berghei ANKA, which mimics human malaria in a murine model, impairs placentual transport efficiency through changes in the expression of specific placental ABC transporters.

**Methods:** On gestational day E13.5, C57BL/6 mice (8-10 weeks) were injected intrauterine with Plasmodium Berghei ANKA (5 × 10⁵ infected-erythrocytes, n = 16) or injected with PBS (n = 12) and sacrificed on E18.5. Maternal blood was collected to evaluate levels of parasitemia, whereas placental disks and fetal units were collected, weighed and snap-frozen for qPCR assessment of selected ABC transporters: the lipid Abca1 transporter, and the multidrug resistance
transporter genes: Abcb1a/Abcb1b, Abcc2, Abcc5 and Abcg2. Differences were considered significant at $p < 0.05$.

**Results:** Pregnant mice infected with *Plasmodium Berghei ANKA* exhibited increased maternal spleen weight consistent with an average parasitemia of 16% infected-erythrocytes. *Plasmodium Berghei ANKA* induced PTL in 20% of all infected pregnancies and reduced fetal weight ($P < 0.01$) and fetal/placental weight ratio; mimicking higher rates of PTL and IUGR found in human gestational malaria. Furthermore, placental expression of Abca1 ($P < 0.001$) and Abcb1b ($P < 0.05$) was reduced in *Plasmodium Berghei ANKA* infected pregnancies.

**Conclusions:** In the present study, we established a new model of malaria-induced-PTL, associated with reduced fetal weight, probably as a result of impaired placental efficiency and compromised placental expression of selected ABC transporters involved in lipid and drug transport at the maternal-fetal interface. Since GM is associated with increased risk of adverse long-term neurodevelopment, these changes may lead to yet unexplored consequences in programming of fetal and postnatal metabolism and neurodevelopment.

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**LM2.07 - Slam session: Social inequalities**

**LM2.07.01**

**What risk factors are associated with child developmental inequalities at the start of formal education? Evidence from Born in Bradford**

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**Background:** Large inequalities in children’s development exist at the beginning of their formal education (at 4-5 years). Evidence exists for the deleterious effect of early life risk factors, such as deprivation, ethnicity, parental education and employment on child developmental outcomes. Born in Bradford (BiB), a longitudinal birth cohort study in Bradford, England provides a rich data set to explore these inequalities. This study aimed to assess the association between early life risk factors and three domains of child development: physical; cognitive; and socio-emotional abilities.

**Method:** The study analysed a subset of the BiB sample (3,450 children) who took part in school-based assessments at age 4-5 years. Children undertook assessments of fine motor skills (Tracking, Aiming and Tracing; CKAT battery), vocabulary development (British Picture Vocabulary Scale (BPVS), and Letter Identification (LetterID: Woodcock Reading Mastery battery). Teachers completed a survey of socio-emotional health (Strengths and Difficulties Questionnaire (SDQ)). Early life risk factors were assessed using a baseline questionnaire completed by the children’s Mothers during pregnancy. These included Index of Multiple Deprivation (IMD), ethnicity, Mother’s primary language, Mother’s education, parental employment, receipt of benefits, being up to date with household bills, and number of individuals in household. Data were analysed using Stata 13. Multivariable regression analyses were conducted with the variables from Mothers baseline questionnaire as predictors. Dependent measures included motor (CKAT), vocabulary, letter identification and socio-emotional (SDQ) variables.

**Results:** Analyses of motor variables suggested Mother’s primary language ($beta = -0.09, t = 3.34, p = .001$) and Father’s employment status ($beta = -0.06, t = -2.95, p < .01$) were strong predictors of Tracking abilities; a weaker relationship was noted for number of persons in the household, $beta = -0.06, t = -2.52, p < .05$. Mother’s employment ($beta = -0.07, t = -2.39, p < .05$) and particularly Father’s employment ($beta = -0.07, t = -3.07, p < .01$) were important predictors of Tracking skills. All variables in the model were non-significant predictors of Aiming performance. Results indicated that neither ethnicity nor IMD scores were reliable predictors of any child outcomes with the exception of BPVS, ethnicity: $beta = -0.06, t = -2.79, p < .01$, and IMD: $beta = 0.11, t = 5.17, p < .001$. Other predictor variables associated with BPVS include Mother’s primary language ($beta = -0.06, t = -2.54, p < .05$), education ($beta = 0.07, t = 3.10, p < .01$) and employment ($beta = -0.13, t = -5.03, p < .001$), and number of persons living in household ($beta = -0.05, t = -2.29, p < .05$). Mother’s education ($beta = 0.09, t = 3.85, p < .001$), and Father’s employment ($beta = -0.06, t = -2.93, p < .01$) were important predictors of LetterID. Mother’s primary language ($beta = .06, t = 2.21, p < .05$) and education ($beta = -0.06, t = -2.10, p < .05$) were significant, but weaker predictors of socio-emotional difficulties.

**Conclusions:** Inequalities in child developmental outcomes are evident when children begin formal education. Mothers’ ethnicity and family deprivation level predicted vocabulary development and this measure seemed particularly sensitive to the effects of early life risk factors. Parents whose primary language is not English may need support to help develop this skill in their children prior to starting school given its importance for learning and future educational attainment, whereas letter identification while important for reading and writing is a key skill which may be learnt on starting formal education and inequalities addressed more readily.

**LM2.07.02**

**Establishing a biobank to examine the developmental origins of non-communicable diseases - The ORIGINS Project**

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Background: The ORIGINS Project is a collaborative initiative between Joondalup Health Campus and Telethon Kids Institute to establish a new Western Australian birth cohort. A central objective of ORIGINS is to develop a comprehensive research platform consisting of an extensive Databank and Biobank. This will enable investigations into how, when and why non-communicable diseases develop, through the study of early environments, maternal and paternal physical health and genetics.

Methods: The ORIGINS Biobank will include biological samples (blood, breast milk, urine, saliva, stool, cord blood, for example) collected from ORIGINS Project participants (mothers, fathers and children) from the first antenatal clinic visit until the child is 5 years of age. To ensure the ORIGINS Biobank is word class, we have harmonised with several local, national, and international cohorts. We have collaborated with Western Diagnostic Pathology to develop the procedures to collect the biological samples, process them in required time frames and store them appropriately. Further collaborations have secured additional storage at Harry Perkins Institute of Medical Research South and Edith Cowan University. An ORIGINS Project Biobank Ethics and Governance Framework has been developed. It sets out guidelines and a framework for which biological samples are collected, stored, managed and accessed for research purposes. It also provides guidelines for translation of findings and knowledge that are a result of research utilising the Biobank. A Biobank Governance Committee has been established to independently monitor, review and report on the establishment, management and operation of the Biobank and activities pertaining to ORIGINS Bio resources.

Results and Conclusion: The ORIGINS Biobank will generate many opportunities to explore underlying mechanisms of environmental influences and how these vary with genetic predisposition. It will build substantial future capacity to address critical questions (including genetic, epigenetic, metagenomic and metabolomic studies) in relation to the development of non-communicable diseases.

LM2.07.03

Ethnic variations in relationships between availability, use, and satisfaction with green-space on pre-schooler’s mental wellbeing: Results from Born in Bradford

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Background: Green space is linked to health benefits for adults and children, however, some studies have found positive effects vary across different ethnic or socio-economic groups. This may be due to the way in these groups perceive or use green space. The aim of the current study was to explore the relationship between availability of, satisfaction with, and use of green space on mental wellbeing amongst 4 year old children. A secondary aim was to explore whether ethnicity or socio-economic status moderated any impact of green space on health.

Methods: 2594 women participating in the Born in Bradford cohort study completed strengths and difficulties questionnaires assessing the mental wellbeing of their child. Internalising (comprising peer problems and emotional subscales) and externalising (behavioural difficulties and hyperactivity) scales were calculated (higher score = more difficulties). A sub-sample (N = 832) also completed measures of satisfaction with, and use of local green spaces. The residential ‘greenness’ of local neighbourhoods was calculated using the normalised difference vegetation index (NDVI) across 100m, 300m and 500m buffers of participants’ home addresses (range: -1 least green to +1 most green). Multiple regressions controlling for socio-demographic factors examined relationships between green space and difficulties. Interaction terms explored whether relationships differed by ethnicity or socio-economic status.

Results: Amongst the total sample, residential green space was associated with internalising and externalising difficulties in unadjusted models, however, significant effects disappeared after controlling for socio-demographics, ethnicity, maternal smoking, and maternal mental health. Interaction terms indicated relationships were moderated by ethnicity, but not socio-economic status. After adjustment for confounders we found a significant effect of green space on internalising difficulties amongst South Asian children across all buffer zones (100m: B = -2.35 95%CI -4.20, -0.5; 300m: B = -3.15, 95%CI: -5.18, -1.13; 500m: B = -2.85 95%CI: -4.91, -0.80, N=1504). We found a similar pattern of results in the sub-sample, however, the effects of residential green on children’s internalising difficulties were rendered non-significant when controlling for satisfaction with, and use of, green space. In this final model, satisfaction with local green spaces was related to lower internalising difficulties across both 100m (B = -0.28, 95%CI:-0.06, -0.003) and 300m (B = -0.28, 95%CI:-0.056, -0.002) buffer zones (both N = 344).

Conclusions: The positive effects of green space on children’s mental wellbeing varies by ethnicity. We found satisfaction with green space to be more predictive of behavioural difficulties than availability of green space as assessed by measures such as NDVI. More research is required to understand what features influence satisfaction with local green spaces in order to promote use amongst ethnic minority groups. Urban planners need to focus on quality (in addition to quantity) of urban green spaces in order to promote population health.
Prenatal and preconception subjective distress from the 2016 Fort McMurray wildfire in Canada: Comparison to other disasters

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Background: In May 2016, the wildfires around Fort McMurray (FMM), Alberta, Canada forced the evacuation of 88,000 people, including ~1,250 pregnant women and 600 more within a few months of conception. Our other natural disaster studies (1998 Quebec Ice Storm, 2008 Iowa Flood, 2011 Queensland Flood) document that prenatal or preconception maternal exposure to natural disasters can result in high levels of maternal objective hardship, subjective distress, and negative cognitive appraisals of the disaster; these can have negative effects on pregnancy outcomes and predict adverse developmental trajectories for the newborn, especially neurodevelopmental and metabolic. The 2016 FMM wildfire presents a new opportunity to replicate previous disaster studies, and to test a brief, online intervention. Our overall study goals are threefold: (i) determine whether an expressive writing intervention supports maternal resilience, and test its ability to buffer women and their babies from the effects of disaster-related stress; (ii) develop a new allostatic load index of modifiable maternal stress ‘omics markers for predicting risk and responsiveness to the intervention; and (iii) integrate knowledge engagement so that the processes and outcomes of research are beneficial to community and stakeholders. For this abstract, our goal was to compare the level of subjective distress experienced by the FMM cohort with those observed in other disaster cohorts.

Methods: Subjects are women who were pregnant during the fire, or who conceived since the fire. Recruitment commenced in November 2016 and is on-going, with approximately 200 women recruited by May 2017. Quantitative and qualitative data are collected via a secure online platform. Maternal subjective distress is measured at recruitment using the Impact of Event Scale – Revised to assess post-traumatic stress disorder (PTSD) symptoms, the Peritraumatic Distress Inventory, and the Peritraumatic Dissociative Experiences Questionnaire.

Results: Preliminary results find significantly higher maternal subjective distress relative to our other natural disaster cohorts. Nearly 40% of FMM women reported clinically significant levels of peritraumatic distress, with 42% reporting significant dissociative experiences, at the time of the crisis; these levels are 6.9 and 3.3 times higher, respectively, than those observed in our Queensland Flood cohort, and 10.7 and 5.6 times higher than in our Iowa Flood cohort. PTSD symptoms were also significantly higher in our FMM cohort with 26.4% of women screening positive for PTSD, a rate that is 3 times higher than observed in our Project Ice Storm and 7.5 times higher than observed in the flood cohorts. PTSD rates in FMM were 3.9 percentage points lower than those published following Hurricane Katrina (30.3%), and 10.4 points lower than following the 2010 Haitian earthquake (36.8%). We will report final cohort results at the meeting.

Conclusions: Given the extreme stress, this research will improve understanding of the impact of prenatal stress on maternal and fetal outcomes. Preliminary results suggest that this is the ideal cohort on which to determine the effectiveness of a simple intervention in supporting maternal and fetal resilience. The findings of this study have the potential to inform decision-making and support use of a simple intervention following disasters.

Comparison between PTSD symptoms in FMM cohort and 3 other prenatal disaster cohorts of prenatal maternal stress.

Childhood socioeconomic status and arterial stiffness in adulthood: the Cardiovascular Risk in Young Finns Study

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LM2.07.05

Childhood socioeconomic status and arterial stiffness in adulthood: the Cardiovascular Risk in Young Finns Study

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LM2.07.05

Childhood socioeconomic status and arterial stiffness in adulthood: the Cardiovascular Risk in Young Finns Study

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Background: Increasing evidence supports the importance of socioeconomic factors in the development of atherosclerotic cardiovascular disease. However, the association of childhood socioeconomic status (SES) with arterial stiffness in adulthood has not been reported. Our aim was to determine whether higher childhood family-level SES is associated with lower arterial stiffness in adulthood.

Methods: Data from 2566 participants in the longitudinal Cardiovascular Risk in Young Finns Study was used. Participants had data on family-level SES in 1980 when aged 3 to 18 years who had arterial pulse wave velocity (PWV) and carotid artery distensibility (Cdist) measured 21 or 27 years later in adulthood.

Results: Higher family SES in childhood was associated with lower arterial stiffness in adulthood; Cdist being higher (β-valueSE 0.029 ± 0.008%/10mmHg, p = 0.001) and PWV lower (β-valueSE -0.062 ± 0.022 m/s, p = 0.006) among those with higher family SES in a multivariable analysis adjusted with age, sex and conventional childhood cardiometabolic risk factors. The association remained significant after further adjustment for participant’s SES in adulthood (β-valueSE 0.026 ± 0.010%/10mmHg, p = 0.01 for Cdist and β-valueSE -0.048 ± 0.023 m/s, p = 0.04 for PWV), but attenuated after adjustment for adulthood cardiometabolic risk factors (β-valueSE = 0.015 ± 0.008%/10mmHg, p = 0.08 for Cdist and β-valueSE -0.019 ± 0.02 m/s, p = 0.38 for PWV).

Conclusions: We observed an association between higher family SES in childhood and lower arterial stiffness in adulthood which can be partly mediated by conventional cardiovascular risk factors in adulthood.

LM2.07.06

Socioeconomic position, obesity and measures of vascular function in mid-childhood: the Longitudinal Study of Australian Children

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Introduction: Low socioeconomic position (SEP) in childhood predicts adult cardiovascular disease mortality, and earlier in life, predicts risk factor burden and poorer vascular function. Associations between low SEP and functional measures during childhood remain poorly understood; this knowledge may facilitate the effective targeting of public health interventions.

We therefore sought to examine the association between SEP and measures of vascular function in mid-childhood.

Methods: Data from 1874 children, 11-12 years of age, participating in the Child Health CheckPoint, nested within the Longitudinal Study of Australian Children, were used to estimate brachial blood pressure, pulse wave velocity, and carotid artery elasticity across a composite measure of family SEP, summarizing parental education, occupation, and household income. Associations were examined using linear regression models. Covariates in regression models included age, sex, pubertal status, BMI, and birthweight.

Results: Socioeconomic position was cross-sectionally associated with age- and sex-specific systolic blood pressure percentiles (1.4 percentile units lower per SD of SEP, 95%CI: 0.2, 2.5, P = 0.02). In age and sex adjusted analyses, SEP was also associated with carotid-femoral pulse wave velocity (0.03/m/s lower per SD of SEP, 95%CI: 0.00, 0.05, P = 0.05) but not carotid arterial elasticity (P = 0.96). Inclusion of pubertal status and body mass index separately attenuated these associations (P > 0.05), suggesting possible mediating effects on the association. Inclusion of birthweight z-score did not alter the results. In a multivariable model including all covariates, BMI z-score remained a significant predictor (P < 0.001) for all vascular function measures.

Conclusion: Socioeconomic position may partly predict vascular function in this cohort of Australian children, and this is potentially mediated through childhood obesity and puberty timing. Future studies should examine the age at which BMI may predict intermediate vascular phenotypes to inform the timing of interventions.

LM2.07.07

Factors affecting placental weight in multi-ethnic women who are at higher risk of developing Gestational Diabetes in the United Kingdom.

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Research question: Placental weight is a measure which reflects many aspects of placental growth. In normal pregnancy, placental weight is related to many aspects of placental function. Little is known on the predictors of placental weight and its relationship between maternal and fetal characteristics in a multi-ethnic cohort who are at higher risk of developing Gestational Diabetes (GDM). This study is a sub-study of the PRiDE:Placenta study.

Methods: The PRiDE:Placenta study is a sub-study of the PRiDE study. Women are at higher-risk of developing GDM recruited in early pregnancy (mean gestational age at recruitment: xx weeks) and delivered between Jan 2013 – Apr 2017. Maternal
and offspring characteristics were recorded, including detailed anthropology and placental weight. Placenta weight was obtained within 24-hours of delivery.

**Results:** Of the 1192 deliveries during this period, 617 had complete data including placental weight. Participants of PRiDE: Placenta study were recruited at the mean gestational age of xx weeks. Their mean (±sd) characteristics were: age = 31.2±5.44 years, BMI = 29.8±11.3Kg/cm², height = 1.52±0.43cm and waist circumference (WC) = 98.3±29.6cm. 13.1% were current smokers. Mean birth weight was 3285 ± 886g. Mean fasting and 2-hour post-load glucose at the time of Oral Glucose Tolerance test (OGTT; mean duration: xx weeks) were 4.2 ± 1.2 and 5.4 ± 2.0 mmol/l, respectively. Mean placenta weight was 644.5 ± 148.6g.

Placental weight, gestational age, fasting and 2-hour post-load glucose were independent predictors of birth weight after adjustment for height, BMI and smoking status (all p < 0.001). Birthweight (p < 0.001) and 2-hour post-load glucose- (p = 0.016) independently predicted of placental weight after adjustment for all above factors and explained 40% variation in placental weight. Maternal adiposity (BMI, WC and height), smoking status or gender did not impact on placental weight. Maternal adiposity (BMI, waist circumference or skin folds), smoking status or glucose did not predict placental weight.

**Conclusion:** Placental weight, along with gestational age and glucose were independent predictors of offspring weight, after adjusting for all maternal characteristics. Placental weight in turn is preserved across different maternal characteristics except 2hr post-load glucose. Whilst majority of the factors affecting placental weight are not known, our findings highlight the importance of studying placental characteristics to accurately predict offspring weight. Further work is needed to study the associations between antenatal placental volume measured by ultrasound and its impact on placental and offspring weight.

**LM2.07.08**

**Child resiliency at 2 years given exposure to poor maternal mental health: results from the All Our Families pregnancy cohort**

C. Tough

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**Background:** Children who are experience care from a mother with poor mental health are at greater risk for developmental delays in early childhood. Despite the adverse outcomes associated with this exposure, some children do not have developmental problems and exhibit resilience, suggesting there are factors that can play a protective role. Identifying the factors that protect children against early developmental delay among those exposed to mothers with poor mental health can inform prevention and early intervention strategies. This study identifies factors that protect children against development delay at age 2 in the presence of poor maternal mental health.

**Methods:** We analyzed data from a community sample of 1596 women who participated in the All Our Families pregnancy cohort. Participants completed comprehensive questionnaire data during mid-pregnancy, late pregnancy, four months postpartum, 1 year postpartum and 2 years postpartum and provided access to obstetrical and birth record data. Protective factors for child development at age 2 in the midst of poor maternal mental health were identified using multivariate logistic regression modeling.

**Results:** At age 2, 18% of children were classified as developmentally delayed, 15% with behavioral problems and 13% with delayed social-emotional competencies. Among children whose mothers were experiencing poor mental health, factors that were protective against delayed development at age 2 included having a mother with higher social support during pregnancy, more relationship happiness with their partner, and higher parenting self-efficacy. Protective factors for social-emotional development included having a mother with higher relationship happiness, higher parenting self-efficacy and being able to fall asleep in less than 30 minutes. Protective factors for behavioral problems included having a mother who reported higher optimism during pregnancy, less difficulty balancing family, work and other responsibilities, being able to fall asleep in less than 30 minutes and sleeping through the night by age 2.

**Conclusions:** To positively impact early child development among families where the mother has ongoing mental health problems, public health, early intervention and parenting programs could focus on strategies that support interpersonal relationships, parenting confidence and sense of competence. Parents could be supported with strategies that establish good sleep habits.
health in adulthood in a longstanding Aboriginal Birth Cohort in Australia.

Methods: The sample comprised a total of 686 Aboriginal babies born at the Royal Darwin Hospital between 1987 and 1990. At birth, birthweight was measured and data was gathered about the families and their living conditions. A follow-up was conducted in adulthood with a mean age of 25.4 years. At follow-up, prevalence of cardiovascular health metrics was assessed and each participant received an AHA score between 0 and 7. The role of socioeconomic factors at birth and area-level socioeconomic disadvantage in adulthood was analysed.

Results: The mean total AHA scores in the cohort were 3.9 for males and 3.5 for females (P = 0.04). Female gender was directly associated with ideal cholesterol levels (OR 2.7, P = 0.0008) and ideal blood pressure (OR 6.5, P < 0.0001) and inversely associated with ideal levels of physical activity (OR 0.22, P < 0.0001). Living in an area of low socioeconomic disadvantage level at follow-up was inversely associated with ideal cholesterol levels (OR 0.32, P = 0.01) and ideal blood pressure levels (OR 0.13, P = 0.0007). Being born to a family with more than six children was directly associated with ideal BMI levels (OR 3.67, P = 0.03). Maternal obesity (BMI > 30) was directly associated with ideal levels of physical activity (OR 5.2, P = 0.02) and inversely associated with ideal cholesterol levels (OR 0.16, P = 0.006) and ideal blood pressure levels (OR 0.11, P = 0.002). Low maternal BMI (<18.5) was directly associated with ideal BMI (OR 1.87, P = 0.01) and ideal cholesterol levels (OR 1.47, P = 0.03). In multivariable analyses, no significant association was found between birthweight and the seven cardiovascular health markers.

Conclusions: Significant differences were found between males and females regarding physical activity, cholesterol and blood pressure levels. Family size, maternal nutritional status and area-level disadvantage independently predict cardiovascular health in adulthood. These factors could be of significance when assessing cardiovascular health in the Aboriginal population and important in reducing the gap in cardiovascular disease morbidity and mortality between the Aboriginal and the non-Aboriginal populations.

LM2.07.11

Socioeconomic disadvantage, gestational immune activity, and neurodevelopment in early childhood

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Background: Children raised in economically disadvantaged households face increased risks of poor health in adulthood, suggesting that inequalities in health have early origins. However, the mechanisms involved are unclear. From the child’s perspective, exposure to economic hardship may begin as early as conception, in part via maternal neuroendocrine-immune responses to prenatal stressors, which adversely impact neurodevelopment.

Methods: We investigate whether socioeconomic disadvantage is associated with gestational immune activity—which plays a key role in fetal brain development—and whether such activity is associated with offspring neurodevelopment. We analyzed concentrations of five immune markers in 3rd-trimester maternal serum (interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α) from 1,494 participants in the New England Family Study in relation to the level of maternal socioeconomic disadvantage and their involvement in offspring neurologic abnormalities at 4 months and 1 year.

Results: Median concentrations of IL-8 were lower in the most disadvantaged pregnancies (-1.53 log(pg/mL); 95% confidence interval (CI): -1.81, -1.25). Offspring of these pregnancies had significantly higher risk of neurologic abnormalities at 4 months (odds ratio (OR) = 4.61; CI = 2.84, 7.48) and 1 year (OR = 2.05; CI = 1.08, 3.90). This was, in part, accounted for by fetal exposure to lower maternal IL-8, which predicted higher risks of neurologic abnormalities at 4 months (OR = 7.67; CI = 4.05, 14.49) and 1 year (OR = 2.92; CI = 1.46, 5.87).

Conclusions: Findings support the role of maternal immune activity in fetal neurodevelopment, exacerbated in part by prenatal exposure to socioeconomic disadvantage. This finding reveals a potential pathophysiologic pathway involved in the intergenerational transmission of socioeconomic inequalities in health.

LM2.07.11

Pregnant women of South Asian origin have higher prevalence of symptoms suggestive of anxiety and depression in early pregnancy.

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Research Question: Maternal anxiety and depression are known to adversely affect maternal outcome and offspring's health. However, little is known on the prevalence of these in women from Black and Minority Ethnic (BME) communities in the UK. We studied the ethnic specific prevalence and factors contributing to anxiety and depression.

Method: A sub-study of the ongoing prospective multi-ethnic cohort in the UK, ‘Micronutrients in Pregnancy as a Risk factor for gestational Diabetes and Effects on mother and baby (PRiDE) study’ was utilised to explore this. We analysed the
data from the first 3571 women who participated in this PRiDE-Wellbeing sub-study. PRiDE is an early pregnancy cohort of women of high metabolic risk in the UK. Self-reported anxiety (Generalised Anxiety Disorder Assessment, GAD7), depression (Patient Health Questionnaire, PHQ9) and wellbeing (Warwick-Edinburgh Mental Well-being scale, WEMWBS) questionnaires were collected at first trimester (mean gestational age: 12 weeks) and at the time of oral glucose tolerance test (OGTT) (mean gestational age: 27 weeks).

**Results:** The study population comprised: 16.3% South Asians (SA), 73.6% White Caucasians (WC) and 11.1% others. Their mean age: 31.6 (± 5.5) years and BMI: 29.1 (± 9.9) kg/m² were at the time of recruitment.

Both anxiety [mean ± SD: 4.0 ± 4.70 vs. 3.5 ± 4.6; p = 0.03] and depression [mean ± SD: 5.3 ± 4.5 vs. 4.6 ± 4.1; p = 0.006] scores were higher in SA in comparison with WC in early pregnancy. Age, South Asian ethnicity, marital status, employment and lower household income were the independent predictors of anxiety. Similarly, for depression, age, employment and lower income were independent predictors. However, at the time of OGTT (24-28 weeks) there are no differences in the anxiety [mean ± SD: 3.5 ± 4.2 vs. 3.5 ± 4.5; p = 0.910] or depression [mean ± SD: 4.3 ± 3.8 vs. 4.4 ± 4.1; p = 0.75] scores between SA and WC. Wellbeing was similar in SA and WC in early [mean ± sd: 49 ± 16.5 vs. 49 ± 13.8; p = 0.41], as well as at the time of OGTT [mean ± SD: 50 ± 15.2 vs. 50 ± 13.6; p = 0.97].

**Conclusion:** SA ethnicity, Age and lower household income are associated with higher levels of anxiety in high-risk pregnant women in the early stages of pregnancy. Ethnicity plays a lesser role in depression than anxiety. In both ethnic groups, the scores improved in later pregnancy. Interestingly, wellbeing scores were similar between the ethnic groups. Questions in the self-reported WEMWBS scale are positively worded and hence more suitable for general population such as the participants of this cohort. This may explain the differences seen between PHQ9, GAD7 and WEMWBS. Further studies are needed to evaluate the impact of these scales in early pregnancy and the relative changes of these scores on post-natal depression and offspring’s health.

**PA2.09 - Bone health and osteoporosis**

**PA2.09.01**

**Early origins of osteoporosis**

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Osteoporosis is a skeletal disease characterised by low bone mass and susceptibility to fracture. Preventive strategies against osteoporotic fracture can be targeted throughout the life course. Although there is evidence to suggest that peak bone mass is inherited, current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk. Evidence has begun to accrue that fracture risk might be modified by environmental influences during intrauterine or early postnatal life: (1) Epidemiological studies which confirm that subjects who are born light and whose growth falters in the first year of postnatal life, have significantly lower bone size and mineral content, at age 60 to 75 years; (2) Cohort studies demonstrating that subsequent lower trajectories of childhood growth are associated with an increased risk of hip fracture among such men and women; (3) Detailed physiological studies of candidate endocrine systems which might be programmed have shown that birthweight and growth in infancy alter the functional settings of the GH/IGF-1, and vitamin D/PTH axes; (4) Studies characterising the nutrition, body build and lifestyle of pregnant women which relate these to the bone mass of their newborn offspring, have identified a number of important determinants of reduced fetal mineral accrual: these include maternal smoking, excessive weight bearing physical activity in late pregnancy, and low maternal fat stores. More recently, maternal vitamin D insufficiency during mid and late gestation has been associated with bone mineral content and areal BMD in the offspring at age 9 years. As a consequence, large randomised controlled trials of vitamin D supplementation in pregnancy have been instituted and the results of these will inform public health interventions aiming to reduce the frequency of maternal vitamin D deficiency.

**PA2.09.03**

**Mendelian Randomisation shows circulating maternal vitamin D and calcium may be causally associated with birth weight**


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**Background:** Observational studies have shown positive associations between maternal vitamin D or calcium levels and birth weight, though these may be explained by confounding. We therefore decided to investigate whether these traits in the mother were associated with birth weight of the child.

**Methods:** We used UKBiobank (48,632 participants), ALSPAC (7,853 participants) and EFOSCH (746 participants) data to perform Mendelian Randomisation using trait-specific SNPs. We constructed three weighted allele scores (WAS), one for vitamin D synthesis (2 SNPs), vitamin D metabolism (2 SNPs) and for Calcium (7 SNPs), using genome-wide significance SNPs previously reported by published GWAS. Weights from those GWAS were used in our independent data sets. Causative estimate associations were calculated using the ratio estimator, which is equivalent to the inverse-variance weighted method. We used MR-Egger in sensitivity analyses to
check for pleiotropy, I-squared to assess heterogeneity between SNP effects and “leave-one-out” analysis to check for strong influences of individual SNPs. We also used ALSPAC and EFSOCH data to adjust for fetal genotype, and compared WAS-own birth weight (i.e. fetal) with maternal WAS-first child birth weight associations in UKBiobank.

**Results:** Using the ratio estimator, we calculated that a 10% higher maternal 25[OH]D level (synthesis score) was causally associated with a 15g (95% CI: 5g to 26g) higher birth weight, and a 1SD higher calcium level was causally associated with a 45g (95% CI: -5g to 96g) higher birth weight. The equivalent result for 25[OH]D level metabolism was 1g (95% CI: -7g to 9g). Vitamin D results were similar with the inverse-variance weighted and MR-Egger methods. For calcium, there was evidence of pleiotropy, and single SNP influences. There was no evidence (either from conditional analyses or from comparisons of maternal vs fetal WAS-birth weight associations) that the results were driven by association with fetal genotype.

**Conclusion:** Our results suggest that higher maternal vitamin D synthesis causes higher birth weight. Further research is required to explore the extent to which supplements of vitamin D and/or calcium might be useful for attaining optimal birth weight.

**PA2.09.04**

A genome-wide association meta-analysis implicates adrenal steroidogenesis in the process of skeletal maturation


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**Background:** Advanced or delayed physiological age can influence significantly health and disease processes. Physiological age can be assessed through several parameters, typically with skeletal age (SA) determined on carpal bones. We performed the first genome-wide association study (GWAS) meta-analysis to identify genetic determinants of skeletal maturation in children of school age.

**Methods:** Two cohorts were included in this study, the Generation R Study (GENR), a multicentric birth cohort in Rotterdam, The Netherlands, (N = 3510 children; mean age = 9.79 ± 0.33), and The Bone Mineral Density in Childhood Study (BMDCS: N = 1048; mean age = 11.34 ± 1.79, range: 8 to 13y). Bone age was assessed on hand images using the Greulich and Pyle method by a pediatric radiologist or endocrinologist (BMDCS) and one trained observer (GENR). Standardized residuals of SA were calculated separately for boys and girls in both cohorts and used as outcomes in all further association analyses. Participants were genotyped with Illumina BeadChip technology using HumanHap 610K (GENR) and Human OmniExpressExome (BMDCS) arrays. Both studies were imputed to the 1000GP reference panel. Association between genotypes and SA was tested using linear regression in GENR, and linear mixed models in BMDCS. All models were corrected for age, BMI (and 10 genomic PCs in GENR). The fixed-effects inverse variance method implemented in METAL was used for the meta-analysis. Genome-wide significance (GWS) was set at P < 5 × 10⁻⁸.

**Results:** In GENR, a GWS signal was identified mapping to CYP11B1 on 8q24.3 (synonymous variant; rs6410; beta = 0.15; P = 2.8 × 10⁻¹⁰), and three suggestive signals mapped to 9q21.32 (intergenic; rs1246290; P = 8.5 × 10⁻⁷), 7p12.3 (intergenic; rs18905813; P = 3.6 × 10⁻⁷) and 21q21.1 (intergenic; rs380807; P = 6.7 × 10⁻⁷). Significant evidence of replication was observed in BMDCS for the first two signals (CYP11B1; P = 0.008; 9q21.32; P = 0.05). After meta-analysis only the CYP11B1 signal achieved GWS (P = 1.1 × 10⁻¹¹).

**Conclusion:** We identified one novel locus robustly associated with SA containing CYP11B1. Mutations in CYP11B1 cause congenital adrenal hyperplasia, a disorder presenting with precocious puberty and short stature among other clinical manifestations. These findings potentially implicate a role for adrenal steroidogenesis in the process of pediatric skeletal maturation, opening new avenues to investigate normal skeletal maturation and bone health in general.

**PA2.09.05**

Structural geometry of bones is prominently associated with risk of fracture in children.

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**Background:** Low total body BMD (TB-BMD) is an established risk factor for fractures in healthy children. However, bone strength depends not only on bone mass and density, but also on the structural geometry of bones. Hip structural analysis (HSA) is a technique applied on hip DXA scans to calculate several bone geometry parameters. The aim of our study was to evaluate other bone geometrical parameters that can constitute determinants of fracture risk. Specifically, we examined the association between femoral structural parameters including...
the geometry-derived femoral stress index (FSI) and risk of fracture in children.

Methods: We studied 1,851 children from the Generation R study, with whole body and hip scans measured using the same densitometer (GE-Lunar iDXA) at a mean age of 6.2 years. Hip DXA scans underwent HSA with derivation of FSI. This stress index considers both, bending and axial forces acting on the femoral neck and is adjusted for lean mass fraction. Fractures at any skeletal site were assessed using questionnaire reports obtained before a mean age of 9.8 years. Risk (odds) of fracture was estimated from logistic regression models adjusted for sex, age, weight and ethnicity.

Results: Fractures was observed in 251 children (13.7%). A significant increase in the odds of fracture was observed for every standard deviation (SD) decrease in TBLH-BMD (OR: 1.28 95%, CI 1.05-1.56; P = 0.01). Similarly, an increase in the odds of fracture was observed for every reduction in one SD of femoral neck BMD (OR = 1.23 95% CI 1.06-1.43; P = 0.005) and narrow neck BMD (OR = 1.26 95% CI 1.08-1.46; P = 0.005). The FSI showed the strongest association with fracture, where every increment of one SD in the FSI resulted in 28% increased odds of fracture (OR:1.28 95%CI 1.13-1.45; P = 0.0001). After inclusion of both the FSI and each of the BMD variables in the multiple regression model, only the stress variable remained significantly associated with risk of fracture.

Conclusions: Femoral and total body BMD parameters are associated with fracture in children. The stress index which considers in addition to quantity, the distribution of bone in the region, constitutes a biomechanical assessment which captures fracture propensity of children. These results are tantalizing enough to warrant future investigations designed to evaluate the role of this stress index as an early determinant of fracture later in life.

PA2.09.06

Life-course Genome-Wide Association Study Meta-analysis of TB-BMD Yields Thirty-Six Novel Loci and Identifies Age-specific Effects


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Bone mineral density (BMD) assessed by DXA is used for the evaluation of bone health in children across the total body (TB) and to diagnose osteoporosis in the elderly population measured at the lumbar spine (LS) and femoral neck (FN). To date, more than sixty BMD loci have been identified. To investigate the genetic determinants of TB-BMD variation along the life course and test for age-specific effects we performed a meta-analysis of 30 genome-wide association studies (GWAS) of TB-BMD including 66,628 individuals overall and divided across 5 age-strata of 15 years span. We identified genome-wide significant variants in 80 loci (of which 36 are novel). Overall, approximately 10% of variance in TB-BMD was captured by genome-wide significant variants. Meta-analysis stratified across age bins indicated clear age modulation of the effect of markers in ESRI and RANKL loci on TB-BMD. Pathway and enrichment analysis of the association signals resulted in clustering within gene-sets implicated in the regulation of cell growth and SMAD proteins; overexpressed in the musculoskeletal system; and enriched in enhancer and promotor regions. These findings reveal TB-BMD as a relevant trait for genetic studies of osteoporosis, capable of identifying (novel) variants influencing different bone compartments and contributing to our knowledge of BMD genetic determination across the life course.

PA2.09.07

25-hydroxyvitamin D achieved in response to antenatal cholecalciferol supplementation is associated with common vitamin D related genetic variants


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Objectives: Maternal 25-hydroxyvitamin D [25(OH)D] status in pregnancy has been associated with offspring musculoskeletal health, suggesting optimization of maternal vitamin D status during pregnancy might be beneficial to long-term health.
However, the response to antenatal vitamin D supplementation is highly variable. Single nucleotide polymorphisms (SNP) in genes related to vitamin D metabolism have been associated with 25(OH)D status in non-pregnant adults, but the relationship with the response to gestational vitamin D supplementation has not previously been examined. We assessed whether SNPs in DHCR7 (7-dehydrocholesterol reductase in the skin), CYP2R1 (25-hydroxylase), CYP24A1 (24-hydroxylase) and GC (Vitamin D binding protein) were associated with the response to cholecalciferol supplementation in pregnancy.

Methods: MAVIDOS is a randomised double-blind placebo-controlled trial of 1000 IU/day cholecalciferol from 14 weeks gestation until delivery in women with a baseline 25(OH)D of 25-100 nmol/l. Anthropometry and serum 25(OH)D (DiaSorin Liaison) were assessed at 14 and 34 weeks gestation. Genotyping of rs12785878 (DHCR7), rs10741657 (CYP2R1), rs6013897 (CYP24A1) and rs2282679 (GC) was undertaken using KASP™ competitive allele-specific PCR (LGc Genomics, Hoddeston, UK). Multiple linear regression was performed using an additive model with the homozygous minor allele as the reference group (beta represents the change in outcome per additional major allele), adjusting for a number of previously identified determinants of 25(OH)D.

Results: 712 women (345 cholecalciferol, 367 placebo) were included (95.8% White ethnicity). Only rs12785878 (DHCR7) was associated with baseline 25(OH)D [β = 4.1 nmol/l (95% CI 2.2, 6.1), p < 0.001]. Conversely, rs10741657 (CYP2R1) [β = -4.1 nmol/l (95% CI -7.1, -1.2), p = 0.006] and rs2282679 (GC) [β = 4.4 nmol/l (95% CI 1.2, 7.6), p = 0.007] were associated with achieved 25(OH)D after supplementation, but rs12785878 and rs6013897 were not.

Conclusion: Genetic variation in DHCR7, which encodes 7-dehydrocholesterol reductase in the cholesterol/vitamin D bio-synthesis pathway in the skin appears to modify baseline 25(OH)D. Conversely, the response to antenatal cholecalciferol supplementation was associated with SNPs in CYP2R1 and GC, which may alter 25-hydroxylase activity and vitamin D binding protein synthesis or affinity. Women with more risk alleles may require higher supplement doses to achieve vitamin D repletion in pregnancy.

**PA2.10 - Early growth and adiposity**

**PA2.10.03**

Dynamic prediction of high blood pressure in childhood with Generation R data: a model development study

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**Background:** High blood pressure in childhood strongly tracks into adulthood, which makes it an important risk factor for the development of cardiovascular disease. Identifying children at high risk of developing high blood pressure may enable targeted prevention. Therefore, this study aimed to develop and internally validate a dynamic prediction model for high blood pressure at the age of 10 years that could be applied from birth onwards.

**Methods:** Data were used from 5,359 children in the Generation R Study, a Dutch population-based prospective birth cohort study. High blood pressure was defined as systolic and/or diastolic blood pressure ≥95th percentile adjusted for age, gender and height. (#_ENREF_1) Multivariable pooled logistic regression was used to assess the association between potential predictors from birth to the age of 6 years and high blood pressure at the age of 10 years, using longitudinal information on the predictor body mass index (BMI) of the child. The prediction model was internally validated with bootstrapping.

**Results:** 227 children (4.2%) had high blood pressure measured at a median age of 9.7 years. The strongest predictors were maternal hypertensive disease during pregnancy, maternal educational level, maternal pre-pregnancy BMI, child ethnicity, birth weight standard deviation score (SDS) and the most recently measured BMI SDS. When the model was applied at different ages to predict high blood pressure at the age of 10 years, the area under the ROC-curve ranged from 0.65 (prediction at 3 years) to 0.73 (prediction at 5-6 years).

**Conclusions:** A dynamic model including easily obtainable child and maternal characteristics can predict high blood pressure at the age of 10. This prediction model can be applied at different ages between 6 months and 6 years and could guide targeting primary prevention efforts.

**References**


**PA2.10.04**

Increased obesity parameters are associated with shorter telomeres in 8 year old children

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**Introduction:** Telomere length is considered a biomarker of biological aging. Shorter telomeres and obesity have both been
associated with age-related diseases such as cardiovascular disease and type 2 diabetes. Moreover, in recent years, obesity has been associated with shorter telomeres in adults. In children this association is not well established. In this study we evaluated the association of telomere length with various indices of obesity.

Methods: In this analysis we used children of the HELIX subcohort (n = 1305). Obesity was assessed in 4 different ways: body mass index (BMI z-score), fat mass (z-scores) determined from bioimpedence measurements, waist circumference (z-scores), and subcutaneous skinfold thickness (z-scores) determined as the sum of subscapular and triceps skinfold thickness. Relative telomere length was measured by using real time polymerase chain reaction (qPCR). Effect estimates were calculated using multiple linear models adjusted for relevant covariates (i.e.; age, sex, birth weight, ethnicity, and cohort).

Results: Preliminary analyses show that there is an inverse association between telomere length and BMI, fat mass, waist circumference, and skinfold thickness in 8 year old children (ranging from 5.5-12 years). A one-unit increase in BMI z-score, and skinfold thickness z-score was significantly associated with a decrease in telomere length of -1.3% (95% Confidence interval (CI): -2.3, -0.4) and -0.13% (95% CI: -0.26, -0.01), respectively. Furthermore, each unit increase in waist circumference z-score was associated with borderline significant telomere shortening of -1.1% (95% CI: -2.3, 0.02). Finally, a one-unit increase in fat mass z-score was not significantly associated with telomere length (-0.7%; 95% CI: -1.9, 0.5).

Conclusion: Children with higher obesity scores have shorter telomeres. These findings suggest that obesity may accelerate telomere shortening in children and thus may accelerate aging.

PA2.10.05

Epigenetic marks of in utero exposure to gestational diabetes (GDM) and childhood adiposity outcomes: The EPOCH Study

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Background: We have previously shown that the maternal gestational diabetes mellitus (GDM) is associated with the metabolic abnormalities that are precursors of type 2 diabetes (T2D) in pre-pubertal youth in the Exploring Perinatal Outcomes in Children (EPOCH) Study. We now aim to identify GDM-exposure-associated DNA methylation changes and assess whether such changes are also associated with adiposity-related outcomes.

Methods: We measured genome-wide DNA methylation in peripheral blood collected from 81 GDM exposed and 81 unexposed EPOCH offspring (mean age 10.5 years) using the Illumina’s Infinium Human Methylation 450k BeadChip on bisulfitetreated samples. In all analyses of epigenetic data, we adjusted for child age, sex and race/ethnicity. We also estimated and adjusted for cell counts in whole blood. Differentially methylated positions (DMPs) were prioritized using a combination of our own data and published DNA methylation changes associated with GDM exposure at birth. Differentially methylated regions (DMRs) were prioritized using pathway enrichment analysis. Prioritization was followed by pyrosequencing analysis for technical validation of GDM-associated epigenetic marks and testing for association with adiposity-related outcomes. To maximize power for detecting associations with adiposity outcomes, pyrosequencing was performed on the same 81 GDM exposed offspring used for the genome-wide methylation assessment and 204 unexposed offspring, consisting of 81 used in the genome-wide assessment and an additional 123 unexposed participants.

Results: We identified 105 differentially methylated positions (DMPs) associated with GDM exposure at false discovery rate (FDR) < 10% in peripheral blood with 55 remaining significant after adjustment for cell proportions. Furthermore, analysis adjusted for cell proportions identified additional significant 43 DMPs (FDR < 10%) that were not significant in the unadjusted analysis. The median absolute percent methylation change between exposed and unexposed children was 1.1% (range 0.33-5.0%) with almost equal number of hypo- and hyper-methylated loci (53% hypo-methylated). Protein-protein interaction (PPI) analysis, using Network Analyst, of genes nearest to the 98 GDM exposure-associated DMPs after adjustment for cell proportions identified several of the differentially methylated genes as hubs in a significant PPI; this includes transcription factors CEBPG, CALCOCO2 (NDP52), and E2F6; protein kinases MAP3K11, NTRK1, PRKCE, and RYK; and methyltransferases EHMT1 and SHMT1 (Figure). We also identified 2195 differentially methylated regions (DMRs) at FDR < 5% after adjustment for cell proportions. We prioritized loci for pyrosequencing validation and association analysis with adiposity-related outcomes based on strengths of association and effect size, network and pathway analysis, analysis of cord blood, and previous publications. Methylation in 6 of the 9 (67%) GDM-associated genes was validated and we also showed that methylation of SH3PXD2A is significantly (P < 0.05) associated with multiple adiposity-related outcomes.

Conclusions: GDM exposure-associated DNA methylation changes were in genes that are related to each other by multiple network and pathway analyses, suggesting that our study identified modules of differential methylation. Our findings suggest that epigenetic marks may provide an important link between in utero exposure to GDM and obesity in childhood, and add to the growing body of evidence that DNA methylation is an important cellular mechanism affected by GDM exposure.
Proteinamide exposure during p-protein interactome analysis of genes nearest 98 GDM exposure-associated DMPs after adjustment for cell proportions.

PA2.10.06

Maternal infection and antibiotic use in pregnancy in relation to childhood obesity: A longitudinal birth-cohort study with long-term follow-up

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Background: Maternal use of antibiotics during pregnancy has been reported to be associated with risk of obesity in offspring in the emerging literature. However, it is not clear whether the observed effect was due to the impact of underlying maternal infection, antibiotic use, or both.

Methods: To distinguish the effect of maternal infection from that of maternal antibiotic use during pregnancy, we conducted a birth cohort study examining the associations among 203,999 mother-child dyads with up to 12 years of follow-up (2003 to 2015). We used electronic medical records (EMRs) to ascertain information on maternal infection diagnosis, results of screening for group B streptococcus (GBS), and antibiotic use during pregnancy. EMRs were also used to ascertain anthropometric measurements of offspring. Childhood obesity was defined as BMI ≥ 95th percentile based on age- and gender-specific criteria set by the Centers for Disease Control and Prevention. Mixed effects logistic regression for repeated measurements was used to analyze multiple BMI measurements per child during the follow-up period.

Results: After controlling for multiple confounders, maternal infection alone without antibiotic use during pregnancy was associated with an increased risk of childhood obesity compared to controls without infection. Offspring of mothers who screened GBS positive during pregnancy had a 17% higher risk of developing obesity: odds ratio (OR) = 1.17 (95% confidence interval (CI): 1.10-1.25), compared to offspring whose mothers did not have an infection diagnosis or antibiotic use during pregnancy (unexposed controls). There was also a dose-response relationship with increased number of infection episodes during pregnancy being associated with further increased risk of childhood obesity in offspring: OR = 1.16 for one episode and OR = 1.26 for two or more episodes, respectively. Offspring whose mothers had infections other than GBS (i.e., GBS screening was negative) overall did not have an increased risk of obesity: OR = 1.01 (95% CI: 0.96-1.06). However, those whose mothers had 3 or more infections during pregnancy appeared to have an increased risk of obesity: OR = 1.25 (95% CI: 1.00-1.57). We examined the impact of maternal antibiotic use during pregnancy on childhood obesity separately for antibiotic use with or without concurrent diagnosis for an underlying infection. For antibiotic use with an underlying infection, we used the group of women who had similar infections, but did not use antibiotics, as the reference group to remove the effect of underlying infection so that the effect of antibiotics could be better isolated. Maternal antibiotic use during pregnancy was associated with an increased risk of childhood obesity even after the impact of underlying infection was controlled for: OR = 1.11 (95% CI: 1.06-1.16) for antibiotic use among those with an infection, and OR = 1.12 (95% CI: 1.07-1.17) for antibiotic use among those without an infection. Maternal C-section, BMI, smoking during pregnancy, and other factors were controlled for in the above analyses.

Conclusions: In this large longitudinal birth cohort study, both maternal infection and antibiotic use during pregnancy were independently associated with increased risk of childhood obesity. These findings suggest a long-term impact of in-utero exposures to infections and antibiotics on childhood development and growth.

PA2.10.07

Influence of fetal blood flow redistribution on fetal and childhood growth and fat distribution: the Generation R Study


Erasmus MC, ROTTERDAM, The Netherlands

Background: A suboptimal intrauterine environment leads to fetal blood flow redistribution and fetal growth restriction. Not much is known about childhood growth consequences. Among 1195 pregnant women and their children we examined the associations of fetal blood flow redistribution with birth outcomes, and repeatedly measured fetal and childhood growth and fat mass measures.

Methods: The current study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onwards in Rotterdam, the Netherlands. We measured...
of oocytes. Collected oocytes are then fertilized in vitro and allowed to develop in vitro until they are either frozen or transferred to mothers. There are controversial reports on the adverse impacts of these technologies on early embryos and their potential long-term effects. Using newly developed technological platforms that enable global gene expression and global DNA methylation profiling, we evaluated gene perturbations caused by such artificial procedures. We know that cells in the early embryo produce all cells in the body and are able to respond to their in vitro environment. However, it is not known whether gene perturbations are part of a normal response to the environment or are due to distress and will have long-term impacts. While the mouse is an established genetic model used for quality control of culture media in clinics, the bovine is a large mono-ovulating mammal with similar embryonic kinetics as humans during the studied developmental window. The analysis of transcriptomic and epigenetic data indicate significant impact of the culture environment on the early embryos which may not necessarily result in a postnatal phenotype. These model systems are critical to understand the effects of assisted reproduction without the confounding impact of infertility and without the limitations imposed by the scarcity of donated human samples and ethical issues. The presentation will focus on the comparative biology related to culture of oocytes and embryos on the outcome and a summary of the phenotypes and concerns in relation to the use of ART in humans.

PA2.12.03
Influence of maternal diabetes on the DNA methylation and first embryonic lineages in the rabbit preimplantation embryos

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In early pregnancy maternal diabetes leads to delay in embryo development and changes in nutritional and hormonal signals of the uterine environment. The current study focuses on consequences of maternal diabetes on embryonic tissue formation and its DNA methylation. We investigated the expression and promoter methylation of epiblast lineage specifier Oct4 in 6 day old rabbit blastocysts at early gastrulation stage. The expression of Oct4 was higher in epiblast of diabetic blastocysts, accompanied by upregulation of Nanog and Sox2, suggesting that epiblasts were less differentiated. Moreover the
hypoblast differentiation factors Cer1 and Dkk1 were down-regulated, what is a mark of underdevelopment. Specific methylation of the POUSF1 (Oct4) promoter region was investigated by bisulfite sequencing. The Oct4 promoter was hypomethylated in hypoblasts and trophoblasts of diabetic rabbits, implying also a mark of delay in differentiation. The global DNA methylation of male and female blastocysts from diabetic and healthy rabbits was examined, employing embryoblast and trophoblast tissue separately, using LUMinometric Methylation Assay (LUMA). No significant changes in global DNA methylation were observed between embryonic tissues from healthy and diabetic embryos. Furthermore, we verified that the methyl group donor S-adenosyl methionine (SAM) and the product of the methylation reactions S-adenosylhomocysteine (SAH) were changed in diabetic pregnancy. Concentrations of SAM and SAH were measured by use of a modified liquid chromatography–tandem mass spectrometry in rabbit blood plasma collected at the day 6 post coitum. Oct4 methylation was not caused by global methylation changes. Our data showed that maternal diabetes mellitus affects the Oct4 promoter methylation in a specific way with consequences for Oct4 gene transcription and embryo development. A possible reason for this could be delay in differentiation of the hypoblast tissue what has a consequence on signaling between the hypoblast and epiblast.

PA2.12.04

IVF/ICSI treatment enhances first trimester growth trajectories of human embryonic brain structures

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Erasmus MC, ROTTERDAM, The Netherlands

Background: Early development of the human embryonic brain has been studied extensively over the last decades. Three-dimensional ultrasound facilitates studying the human embryonic brain in vivo, in particular the diencephalon (DTD), mesencephalon (MTD) and left and right telencephalon (TTL/TTR). Recent studies suggest that the rapid and expansive growth of the embryonic brain during early gestation elicits susceptibility to developmental disruptions. In the current study we aimed to investigate whether periconceptional maternal health conditions, including IVF/ICSI treatment, impact the development of embryonic brain structures.

Methods: The study population of pregnant patients was selected from the Rotterdam periconception cohort conducted at the Erasmus MC. Three-dimensional ultrasound (3D-US) examinations were performed at 9 and 11 weeks gestational age (GA). DTD, MTD and TTL/TTR were measured offline in standardized planes using specialized 3D software (4D-view). Verified self-reported questionnaires provided information on periconceptional maternal health conditions. To investigate associations between periconceptional maternal exposures and measurements of embryonic brain structures linear regression models at 9 and 11 weeks GA with adjustment for GA, maternal age, BMI, folic acid supplement use, smoking and mode of conception were used.

Results: 168 patients provided 279 3D-US scans for embryonic brain measurements. Success rates of the measurements of DTD and MTD were all above 67%. Success rates of the telencephalon measurements were above 53%. We found a significant positive association at 11 weeks GA between IVF/ICSI treatment and DTD ($\beta = 0.34$, 95%CI = 0.12;0.56, $p = 0.00$), MTD ($\beta = 0.32$, 95%CI = 0.16;0.49, $p = 0.00$), TTL ($\beta = 0.09$, 95%CI = 0.01;0.16, $p = 0.03$) and TTR ($\beta = 0.10$, 95%CI = 0.03;0.17, $p = 0.01$).

Conclusions: For the first time associations between IVF/ICSI treatment and slightly increased sizes of early human embryonic brain structures are shown. The clinical implications of these small differences of the embryonic brain need further investigation.

PA2.12.05

Neonatal outcomes of transferring of Frozen-thawed Cleavage Embryos with Blastomere Loss

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Background: Despite limited information on neonatal safety, the transfer of frozen-thawed cleavage embryos with blastomere loss is common in women undergoing in vitro fertilization. This study aims to evaluate the pregnancy outcomes and the safety of neonates born following frozen-thawed cleavage embryos with blastomere loss.

Methods: Multicenter prospective study including all frozen-thawed cleavage embryo transfer (FET) cycles was conducted in China. A total of 9,846 transfer cycles with only intact embryos and 2,259 transfer cycles with only blastomere-lost embryos were included. The outcomes of neonates born following the transfer of blastomere-lost embryos were compared to those born following the transfer of intact embryos. FET pregnancy outcomes including implantation rate, clinical pregnancy rate, pregnancy loss rate, pregnancy termination due to fetal defects, stillbirth and live birth rate were assessed. The risk of small/large for gestational age (SGA/LGA) at birth, any congenital anomaly, neonatal respiratory disorder, and neonatal mortality were determined using multilevel logistic regression.

Results: A total of 12,105 FET cycles were included in analysis (2,259 cycles in blastomere loss group and 9,846 cycles in intact embryo group). Compared with FET cycles of intact embryo, embryo with blastomere loss transfers showed significantly poorer outcomes with respect to implantation rate, pregnancy rate and live birth rate. However, following embryo implantation, the two groups were similar with respect to live birth rate per clinical pregnancy. Among the 4229 neonates,
Multiples neonates born from embryos with blastomere loss were at an increased risk of SGA (aOR = 1.50, 95%CI, 1.00-2.25). Similar results were observed among singletons (aOR = 1.84, 95%CI, 0.99-3.37), however, the confidence interval did not exclude the null effect. No association were found between blastomere loss and subsequent occurrence of congenital anomalies or neonatal mortality. However, neonates born from blastomere-lost embryos showed an increased risk of transient tachypnea of the newborn (TTN, aOR = 5.21, 95% CI, 2.42-11.22).

Conclusions: Among infertile women resorted to IVF-ET, transfer of embryos with blastomere loss was associated with a lower rate of implantation, chemical pregnancy and clinical pregnancy. However, once embryos with blastomere loss are implanted, pregnancies appear to have the same probability of progressing to live birth, with no risk of major adverse neonatal outcomes.

Flow chat of the study

PA2.12.06

The effect of supplementation with folic acid in non-pregnant and pregnant mice on the ovarian morphology and embryo development

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Background: Women of reproductive age are recommended to take folic acid (FA) to prevent neural tube defects during pregnancy. There is some evidence that indicates that FA could improve fertility. However, further research is needed to identify the effect of FA supplementation on the ovary and embryo development. The aim of this study is to determine the impact of FA supplementation on ovarian morphology and the potential consequences for the embryo.

Methods: Adult (10w old) female C57BL/6 mice were fed for 4w standard (1 mg/Kg) or high (5 mg/Kg) amounts of FA. The animals were then either culled at diestrus or mated and then culled 3.5 days post coitum (dpc). Embryos were collected and frozen at -80C. One ovary per female was used for qRT-PCR and the other was fixed for histological analysis.

Results: In non-pregnant mice FA supplementation decreased ovarian FSH receptor (24%, P = 0.02), Brca1 (36%, P = 0.004) and BMI1 expression (28%, P = 0.04). However, there were no significant differences in the number of follicles between dietary groups. Pregnant mice showed a 35% lower number of embryos at 3.5 dpc after supplementation with FA (P = 0.004).

Conclusions: These outcomes help to understand how high levels of FA could be detrimental for follicle and embryo development. Periconceptional supplementation of FA modified the expression of genes related to proliferation and the number of embryos available before implantation.

PA2.12.07

Gestational exercise prevents cognitive impairment in rat offspring exposed to maternal high-fat diet


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Background: Metabolic dysregulation, including obesity and diabetes, has been associated with a range of cognitive deficits, from mild cognitive impairment to dementia. Even prodromal metabolic dysregulation is associated with and predictive of cognitive decline, with impairment arising as early as adolescence. Exposure to a high-fat (HF) diet has also been suggested to directly impair cognition in the absence of apparent peripheral metabolic disturbance. Given the current acceleration of maternal obesity and overnutrition rates and parallel globalization of the HF “Western” diet, understanding the consequences of HF diet exposure early in development and the potential for cognition-protecting interventions is crucial.

We previously found that offspring of rats dams that consumed a HF diet (60% kcal from fat) during pregnancy and lactation show hallmark signs of metabolic dysregulation, including increased adiposity, impaired glucose tolerance, and leptin resistance, despite being weaned onto a standard low-fat chow diet (CH). HF offspring also have cognitive deficits, exhibiting compromised performance as adults in tasks of learning and memory.

Exercise has been shown to be a promising intervention in targeting both metabolic and cognitive deficit. However, few studies have assessed the effects of gestational exercise exposure on offspring development, especially against the setting of
maternal HF diet. We used the maternal HF diet rat model and provided half of the dams with voluntary running wheel exercise during gestation only to study the impact of gestational exercise on offspring expression of leptin cognitive performance. We also measured hippocampal gene expression of the leptin receptor (Lepr), as hippocampal leptin signaling has been associated with synaptic plasticity and cognition.

Methods: Pregnant Sprague-Dawley rats were divided into 4 diet-exercise groups: CH-Sedentary (CH-SED, n = 12), CH-Running Wheel (CH-RW, n = 12), HF-SED (n = 11), and HF-RW (n = 10). Chow or HF diet was provided ad libitum throughout pregnancy and lactation. The RW groups had voluntary access to a running wheel in their home cage during pregnancy only. On postnatal day (P)21, all offspring were weaned onto the CH diet. On P22, 1 male and female offspring per litter were killed, blood plasma samples collected for peripheral metabolic hormones, and brain tissue dissected for analysis of hippocampal gene expression. On P80, 1 male and female offspring per litter were tested for cognitive performance in the Novel Object Recognition Test and Barnes Maze.

Results: Body weight and plasma leptin levels were elevated at P22 in both HF-SED and HF-RW animals compared to CH control groups. Both male and female HF-SED offspring displayed impaired recognition and spatial memory compared to CH controls. These cognitive deficits were not observed in HF-RW offspring, with both male and female HF-RW offspring performing comparably to CH controls. Male HF-SED offspring had decreased Lepr expression in the hippocampus at P22, whereas Lepr expression in HF-RW offspring was not different compared to CH-SED.

Conclusion: Together, our results suggest that gestational exercise prevents cognitive impairment in offspring exposed to maternal HF diet and may do so, in part, by normalizing Lepr expression in hippocampus.

PA2.13 - How to turn your cohort into an intervention study

PA2.13.01
How to turn your cohort into an intervention study

E. Barker1, C. Bell2, C. Vogel1

1University of Southampton, SOUTHAMPTON, United Kingdom; 2University of Alberta, EDMONTON, Canada

DOHaD hypotheses are increasingly being tested in population-based intervention studies. This symposium will suggest that existing cohorts formed to study DOHaD phenomena are an excellent basis for these intervention studies. We will present three diverse examples which will be used to illustrate the process of developing interventions from cohort studies.

ENRICH: from cohort study to interventions to improve maternal perinatal health Presenter: R Bell

A cohort study of ~ 2200 pregnant women in Alberta found that ~ 50% of all women and ~ 70% of overweight/obese women gained in excess of gestational weight gain (GWG) guidelines. Women with excess GWG were 3.5 times more likely to retain excess weight postpartum. We need effective strategies promoting appropriate and safe weight management among diverse groups of pregnant and postpartum women. ENRICH is a multi-disciplinary, multi-sectoral collaboration working to address this issue, which aims to increasing awareness of appropriate pregnancy and postpartum weights. We formed partnerships with: Alberta Health Services, who provide universally-available services/resources to women and healthcare providers; two community-based programs servicing vulnerable women; an Aboriginal community; and an international network of research advisors. Each gathered information from women, care providers, and key stakeholders (e.g., men, Elders), and developed, implemented, and evaluated intervention strategies in every setting. Building meaningful DOHaD interventions requires: 1) time to establish and maintain partnerships; 2) rigorous research that is adaptable and responsive to a setting; 3) integrated knowledge translation across settings and locations to advance maternal and child health.

WRAPPED: supporting disadvantaged women to adopt healthier diets Presenter: C Vogel

In a cohort of 832 women of childbearing age in Hampshire, UK, shopping at discount supermarkets which had poorer availability and placement of healthy foods was associated with poorer dietary quality among those who left school aged 16 years, but not amongst those who had completed a degree. As a result of these findings, we have established a partnership with discount supermarket chain, Iceland with over 850 stores UK-wide and used frequently by disadvantaged populations. The WRAPPED (Women’s Responses to Adjusted Product Placement) study is quantifying the impact of a healthier store layout, namely enhancing the availability and placement of fresh and frozen fruit and vegetables, and removing confectionery from checkouts, on the dietary behaviours of women aged 18-45 years.

EACH-B: Engaging Adolescents in Changing Behaviour Presenter: M Barker

LifeLab, a science programme delivered in school to 13-14-year-olds, has demonstrated that adolescents can be engaged in thinking about their health and the health of the next generation. We are now working with this cohort to develop and test a complex intervention designed to motivate and support adolescents aged 13-14 years to improve their diets and physical activity levels. After LifeLab, adolescents will receive support to improve their diets and lifestyles from teachers trained in behaviour change skills, and a specially-designed, interactive smartphone app that involves friends and has game features. The effectiveness and cost-effectiveness of this intervention will be assessed in a cluster-randomised controlled trial in 50 UK schools. If successful, integration of the intervention into the UK school curriculum is planned.
This is true both for personal smoking in adults and for smoking in pregnancy.

Background

Early life may be a critical period for changes in DNA-methylation associated with specific exposures and later-life health outcomes. Many pregnancy, birth and childhood studies have recently started research on the role of DNA-methylation modifications as a potential mechanism underlying the Developmental Origins of Health and Disease, using arrays that measure hundreds of thousands of DNA-methylation markers across the genome (“epigenome-wide DNA-methylation”). Individual studies are usually too small to adequately address this issue. Large sample sizes are required to achieve optimal power in analyses of such large numbers of DNA-methylation sites. To achieve this, collaboration between studies and combined meta-analysis of the available data is needed.

Description of the consortium

The Pregnancy And Childhood Epigenetics (PACE) Consortium is an open consortium that brings together studies with epigenome-wide DNA-methylation data in pregnant women, newborns or children. The primary aim of the consortium is to identify, using joint meta-analysis, differences in DNA-methylation in relation to a wide range of early-life exposures and health outcomes across the life course. Secondary aims are to perform further functional analyses, to study causality of DNA-methylation differences on health outcomes, to contribute to methodologic development in the field, and to exchange knowledge and skills. The consortium currently includes 39 studies with a total of over 29,000 samples with epigenome-wide DNA-methylation data. Studies participate on a project-by-project basis. Recently finished and ongoing projects include meta-analyses of exposures during pregnancy, such as maternal alcohol use, body mass index, gestational weight gain, stress, diet, air pollution, maternal diseases, and smoking. DNA-methylation is also studied in relation to childhood and later-life health outcomes, including childhood anthropometric, cardio-metabolic, neurodevelopmental, respiratory, and allergic phenotypes. This presentation will discuss the set-up of the PACE Consortium and will highlight some recently completed and ongoing projects.

PA2.14 - Pregnancy and Childhood Epigenetics consortium

PA2.14.01

Epigenome-wide association studies in the pregnancy and childhood epigenetics consortium

J.F. Felix

Erasmus MC, ROTTERDAM, The Netherlands

Background

The role of maternal smoking during pregnancy and offspring methylation has been well-documented. Smoking has marked effects on methylation across the genome. At 1,817 mother-child pairs, we meta-analysed the association between pre-pregnancy maternal BMI and methylation at over 450,000 sites in newborn blood DNA, across 19 cohorts (9,340 mother-newborn pairs). We attempted to infer causality by comparing effects of maternal versus paternal BMI and incorporating genetic variation. In four additional cohorts (1,817 mother-child pairs), we meta-analysed the association between maternal BMI at the start of pregnancy and methylation at over 29,000 sites. Within the Pregnancy and Childhood Epigenetics (PACE) Consortium, we meta-analysed the association between pre-pregnancy maternal BMI and methylation at over 9,044 sites throughout the genome. Adjustment for estimated cell proportions attenuated the number of significant DNA methylations such as DNA methylation could contribute, but data are limited.

Methods

Within the Pregnancy and Childhood Epigenetics (PACE) Consortium, we meta-analysed the association between pre-pregnancy maternal BMI and methylation at over 450,000 sites in newborn blood DNA, across 19 cohorts (9,340 mother-newborn pairs). We attempted to infer causality by comparing effects of maternal versus paternal BMI and incorporating genetic variation. In four additional cohorts (1,817 mother-child pairs), we meta-analysed the association between maternal BMI at the start of pregnancy and blood methylation in adolescents.

Results

In newborns, maternal BMI was associated with modest (<0.2% per 1kg/m2, P < 1.06*10^-7) methylation variation at 9,044 sites throughout the genome. Adjustment for estimated cell proportions attenuated the number of significant CpGs to 104, including 86 sites common to the unadjusted model. These 86 sites map to several genes reported to be associated with adiposity-related and/or neuropsychiatric traits. At 7/86 sites, the direction of association was the same in newborns and adolescents. However, we found evidence for a causal intrauterine effect of maternal BMI on newborn methylation at just 8/86 sites.

PA2.14.02

Maternal smoking in pregnancy and offspring methylation

S.J. London

NIEHS, RTP, United States of America

Smoking has marked effects on methylation across the genome. This is true both for personal smoking in adults and for newborn babies born to mothers who smoked during pregnancy. Notably, many of the same specific signals are seen for these two exposures. This talk will cover effects of maternal smoking during pregnancy on methylation in newborns and children, the utility of newborn methylation as a biomarker of maternal smoking during pregnancy, and how methylation functioning as a biomarker of this exposure complicates efforts to examine whether epigenetic effects mediate exposure related health effects.

PA2.14.03

Pre-pregnancy maternal BMI and offspring epigenome-wide DNA methylation: Findings from the Pregnancy and Childhood Epigenetics (PACE) Consortium

C. Sharp¹, L.A. Salas², C. Monnereau³, C. Allard⁴, P. Yousef⁵, T.M. Everson⁵, On behalf Of the PACE Consortium⁶, 7, S.J. London⁷, J Felix³, C.L. Rehон⁸

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Background

Pre-pregnancy maternal obesity is associated with adverse offspring outcomes at birth and later in life. Epigenetic modifications such as DNA methylation could contribute, but data are limited.

Methods

Within the Pregnancy and Childhood Epigenetics (PACE) Consortium, we meta-analysed the association between pre-pregnancy maternal BMI and methylation at over 9,044 sites throughout the genome. Adjustment for estimated cell proportions attenuated the number of significant DNA methylations such as DNA methylation could contribute, but data are limited.
Conclusion: Maternal adiposity may cause modest variations in newborn blood DNA methylation, but the potential biological consequences of these variations are currently unclear.

PA2.14.04
A genome-wide meta-analysis of cord blood DNA methylation and birth weight in 8365 newborns reveals over 1000 differentially methylated sites

L.K. Küpers1, C. Monnereau2, G.C. Sharp3, P. Yousef1, L.A. Salas4, A. Ghantous5, J. Heimovaara6, On behalf Of the PACE Consortium7

1MRC IEU, School of Social and Community Medicine, University of Bristol, BRISTOL, United Kingdom; 2The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, ROTTERDAM, The Netherlands; 3MRC IEU, School of Oral and Dental Health, University of Bristol, BRISTOL, United Kingdom; 4Department of Epidemiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, LEBANON, United States of America; 5International Agency for Research on Cancer, Lyon, France, LYON, France; 6University of Groningen, UMCG, GRONINGEN, The Netherlands; 7Pregnancy and Childhood Epigenetics Consortium

Background: The observational associations of birthweight with later health outcomes are assumed to reflect intrauterine exposures for which birthweight is a proxy. These exposures may exert their effects on birthweight and later health outcomes by intrauterine epigenetic programming, including DNA methylation. Our aims were to explore associations between cord blood DNA methylation and birthweight.

Methods: Using a fixed effects inverse variance-weighted meta-analysis, we studied the associations between DNA methylation in umbilical cord blood (measured using the Illumina Infinium 450K BeadChip) and birth weight in 8,406 newborns from 28 birth cohorts participating in the Pregnancy and Childhood Epigenetics (PACE) Consortium. All analyses were adjusted for newborn gender, gestational age at birth, maternal parity, socio-economic status, smoking during pregnancy, age at birth, pre-pregnancy body mass index, as well as batch effects and estimated blood cell counts. Additionally, we assessed whether methylation levels of the Bonferroni corrected statistically significant sites observed at birth persisted during childhood (n = 1,604 from 6 cohorts), adolescence (n = 2,573 from 7 cohorts) and adulthood (n = 930 from 2 cohorts).

Results: Differential methylation of 1,071 sites, located in or near 833 genes, was associated with birthweight (P < 1.03 × 10⁻⁷, Bonferroni-adjusted cut-off, Figure). For these sites, we observed both positive (45%) and negative associations (55%) between methylation levels and birthweight. The top hit was cg20076442 in the Musculin (MSC) gene (mean difference in birth weight for 10% difference in methylation level = -91.3 g [95% confidence interval = -105.7; -76.9]). We found differential methylation (P < 0.05) for 63 (5.9%), 49 (4.6%) and 41 (3.8%) of these 1,071 sites in childhood, adolescence and adulthood, respectively. These sites had the same direction as in the initial meta-analysis of association with birthweight, suggesting that these differences at birth persisted across childhood and into adulthood.

Conclusions: In this first meta-analysis of epigenome-wide association studies including 8,365 newborns from 28 birth cohorts, we have shown robust evidence for a large number of novel associations between cord blood DNA methylation and birth weight. A small proportion of these associations (4-6%) appear to persist into childhood, adolescence or adulthood, potentially due to lower statistical power compared to the newborn discovery meta-analysis. These results provide the foundations for exploring whether the exposures for which birthweight might act as a proxy (e.g. maternal nutrition, placental function) are causally related to these differentially methylated sites, and whether differential methylation at these sites causally affects future health outcomes, using Mendelian randomization.

Manhattan plot for the meta-analysis results for associations between cord blood DNA methylation and birth weight.

PA2.14.05
Gestational age and DNA methylation profiles of newborns and children; a PACE meta-analysis

S.K. Merid1, E.M. Melén1, On behalf Of the PACE Consortium2

1Karolinska Institutet, STOCKHOLM, Sweden; 2Pregnancy And Childhood Epigenetics Consortium

Background: Preterm birth is strongly associated with increased risk of neonatal morbidity as well as long-term health outcomes in adulthood. Prenatal and perinatal factors have been associated with epigenetic modifications in children. Thus, our aim was to investigate the association between gestational age (GA) at birth and blood DNA methylation patterns in newborns and older children.

Methods: DNA methylation was measured using the Illumina 450K platform in cord blood from 3,935 newborns (GA 186-294 days corresponding to 27-42 weeks) from 17 cohorts and in whole blood from 453 pre-school children at 4-5 ages (4 cohorts), 899 school-age children at 7-9 ages (4 cohorts) and 1032 adolescents at 16-18 ages (4 cohorts) who were born at...
GA between 196-294 days corresponding to 28-42 weeks. All cohorts are involved in the Pregnancy And Childhood Epigenetics (PACE) Consortium. After exclusion of maternal and perinatal complications, epigenome-wide robust linear regression analyses were performed in each individual cohort to assess associations between GA and CpG-specific methylation adjusting for potential confounders including cell-type composition, followed by meta-analyses of all cohorts.

**Results:** In the meta-analyses, 5,825 CpG sites annotated to 3,596 unique genes were associated with GA at FDR < 0.05 in cord blood. After restricting findings to at least 3 significant adjacent CpGs, we observed that 677 CpG sites mapped to 188 unique genes were significantly associated with GA (FDR < 0.05). In older children 1,067 and 90 CpGs were nominally significant (p < 0.05) in at least one and two age groups, respectively. Pathway analyses indicated that the 3,596 genes were enriched for several categories such as biological processes, system development, different signaling pathways, animal organ development, and cell communication processes.

**Conclusions:** We identified 5,825 differentially methylated CpGs associated with GA at birth, but rather few of these CpGs showed a significant association during childhood and adolescence. Among identified genes, we observed enrichment in pathways and processes critical to development.

**PA2.14.06**

DNA methylation and childhood body-mass index


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**Background:** Childhood overweight and obesity are major health problems and are associated with adverse short- and long-term consequences. The etiology of overweight and obesity is multifactorial and may partly originate in early life. An accumulating body of evidence suggests that intrauterine epigenetic programming, through changes in DNA methylation, might be involved. Differences in DNA methylation have been associated with adiposity in adulthood. We aimed to identify cord blood DNA methylation loci associated with childhood body mass index (BMI) in two age groups during childhood by using a large multi-study epigenome-wide association study (EWAS) approach.

**Methods:** We used data from 14 cohorts in the Pregnancy And Childhood Epigenetics (PACE) Consortium, to assess the associations of cord blood DNA methylation with childhood BMI in two age groups: 2-5 years (n = 3,358) and 5-10 years (n = 4,283). DNA methylation was measured using the Illumina Infinium 450K BeadChip. We analysed both separate cytosine-phosphate-guanine sites (CpGs) and differentially methylated regions (DMRs) using Comb-P using inverse-variance weighted meta-analysis. Analyses were adjusted for maternal age, parity, educational level, smoking status and BMI, and gestational age at birth, as well as batch effects and estimated cell proportions.

**Results:** No single CpGs were significantly differentially methylated in cord blood in relation to BMI at age 2-5 years. We observed that methylation at one CpG site was significantly associated with BMI at the age of 5-10 years, using a Bonferroni-corrected genome-wide significance threshold of P < 1.03*10^{-7}. This CpG was annotated to the SFRP5 gene (mean difference in childhood BMI for 10% increase in methylation = 0.96 kg/m^2 (standard error 0.17)). We identified 26 and 47 DMRs in cord blood that were significantly associated (False Discovery Rate P-value < 0.05) with childhood BMI in the younger and older age group, respectively. 2 DMRs were overlapping between the two age groups.

**Conclusion:** We identified one individual CpG and up to 47 DMRs in cord blood that were associated with childhood BMI. As next steps, we will assess the cross-sectional associations of DNA methylation and BMI in childhood, as well as functional annotation of the identified regions.

**PA2.14.07**

DNA methylation signature of smoking in adult lung tissue is enriched for in utero smoke exposure signature

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**Background:** Developmental exposures to toxins can cause altered health and disease in children and adults, driven in part by epigenetic alterations. Emerging evidence shows that cancer is also disease of dysregulated epigenetic reprogramming. As part of the Pregnancy And Childhood Epigenetics (PACE) consortium, we have identified a highly reproducible and specific DNA methylation signature in the cord blood of infants exposed to cigarette smoke. We tested whether this early life tobacco smoke exposure DNA methylation signature is identifiable in lung cancers from smokers compared to non-smokers.

**Methods:** We characterized the smoking-related DNA methylation signature in lung tissue (lung squamous cell carcinoma biopsy) from 68 never smokers, 99 current smokers, and 278 former smokers in The Cancer Genome Atlas (TCGA) using Illumina 450k BeadArray data. We preprocessed the data and performed parallel multiple linear regressions at each probe to test the adjusted association between smoking and DNA methylation. The study sample was 54.4% female and was mean 65.1 years old at diagnosis (interquartile range of age: 59-72). We used Pearson
correlation of effect estimates to compare the new genome-wide smoking results in lung tissue to the previously published cord blood results. Focusing on the top hits, we tested the lung smoking sites for enrichment in the cord blood smoking sites using Fisher’s exact test. We used multiple significance cutoffs for each tissue to assess the robustness of our findings.

**Results:** There were 434,820 probes that overlapped between the cord blood and lung analyses. Across all sites, the lung and cord results were minimally correlated (Pearson’s r = 0.01). At the significance level P < 10^-4, in cord blood there were 3,035 probes associated with smoking and in lung tissue there were 577 probes associated with smoking, including 33 overlapping probes. At this cutoff combination, the adult lung signature was enriched for the infant cord blood signature at P = 1.x10^-19. We will further explore the lung association with recent adult blood smoking meta-analysis results.

**Conclusions:** This study observed that the effects of smoking on cord blood and adult lung cancer tissue were not correlated genome-wide. Among the subsets of sites that were highly associated with smoking in either tissue, there was significant overlap, indicating that epigenetic alterations associated with to smoke exposure are genomic site specific and common across tissues. This analysis supports the use of blood-based biomarkers for exposure assessment at target tissues and their relevance to lung cancer, with potential implications for the developmental origins of health and disease.

![In utero smoke exposure and cord blood DNA methylation: PACE P-value<10^-4](image)

Adult lung smoking DNA methylation signature is enriched for in utero smoke exposure signature

**PA2.15 - Environmental chemicals**

**PA2.15.01**

**Synthetic chemical exposures in early life as obesogens and metabolic risks**

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Substantial effort has been devoted to explaining secular trends in childhood obesity and metabolic risks to unhealthy diet and physical activity. Yet accumulated knowledge to date suggests that increased caloric intake and decreased exercise levels may have a partial role in the pathogenesis of obesity and metabolic risks. Since it is unlikely that the human genome has changed significantly in a single generation to have generated an increased susceptibility to excess weight gain in early life, we are left with the reality that factors in addition to diet and exercise represent important risks for obesity and metabolic disorders. In contrast to diet and physical activity, which can require intensive attention, effort and costs to modify through behavioral and other interventions, government action can fundamentally transform the environmental influences to prevent disease and disability. The costs of regulations to limit environmental obesogens can also be much lower than the benefits to society. The notion that synthetic chemicals in the environment can disrupt metabolism was first and most definitively described with tributyltin, a fungicide used to prevent fouling of the hulls of ships which selectively activates peroxisome proliferator activated receptors (PPARs) and their heterodimeric partners, the 9-cis retinoic acid receptors. Over the past two decades, rapidly accumulating scientific evidence has expanded this mechanistic framework to recognize that multiple pathways can be influenced by an even broader array of synthetic chemicals, with characteristic metabolic disruption across multiple endocrine organs and tissues. Sex steroid pathways have also been proven to produce sex-specific effects on body mass. This presentation will focus on three categories of chemicals for which the evidence in laboratory, animal and human studies is the most convincing: phthalates, bisphenols and persistent organic pollutants. For each, we describe pathways of exposure and methods to limit exposure. We then close with a discussion of the disease burden and costs that can be traced to chemicals that contribute metabolic risks, and opportunities for policy action to reduce exposures to the most hazardous chemicals that may contribute.

**PA2.15.05**

**Environmental chemicals and early childhood growth in the Upstate KIDS Study**

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**Background:** Evidence suggests that prenatal exposure to endocrine disrupting chemicals may influence birth size and have longer term “obesogenic” effects by promoting adipogenesis early in development. Although the mechanisms are not well established, they may include hormonal disruption...
through interference with the estrogen receptor or other pathways. Despite convincing toxicological studies of their influence, epidemiologic evidence has been equivocal partly due to difficulties in obtaining large population based samples.

Methods: The Upstate KIDS Study measured newborn dried blood spot (DBS) concentrations of bisphenol A (BPA), perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) among 1,953 singletons born between 2008 and 2010 whose mothers also provided information on their longitudinal growth. Mothers reported weight and height as measured during pediatric visits from birth through 3 years of age, aided by a child health journal. Chemical concentrations in DBS was measured using liquid chromatography tandem mass spectrometry in previously validated methods accounting for potential contamination from storage and handling. Chemical concentrations were log-transformed. Mean differences per log standard deviation (SD) increase in chemical concentrations (and 95% confidence intervals, CI) for each growth parameter were determined using generalized linear mixed effect models with random effects adjusting for maternal age, pre-pregnancy body mass index (BMI), education, race, insurance status, and infant gender. Addition of other covariates such as neonatal intensive care unit stay, breastfeeding at discharge, gestational diabetes, maternal smoking, and infertility treatment did not alter results and were not retained.

Results: Geometric mean levels (95% CI) of the three chemicals in newborn DBS were 29.1 (11.0-77.1), 2.76 (1.36-5.59), and 2.12 (1.11-4.08) ng/ml for BPA, PFOS and PFOA, respectively. Per 1 SD increase in BPA, increases in trajectory of BMI (0.047 kg/m²; 95%CI: 0.010, 0.085) and weight-for-length (0.05 z-score; 95%CI: 0.012, 0.089) through 3 years of age were observed. These associations appeared to be driven by increased weight (45 grams; 95%CI: 13, 77) and not height. Conversely, PFOS and PFOA were associated with lower BMI (-0.078 kg/m²; 95%CI: -0.12,-0.038 and -0.076 kg/m²; 95% CI: -0.17,-0.051). Similar findings were observed using weight-for-length z-scores. These associations were driven by increased height (PFOA: 0.13 cm; 95%CI: 0.016, 0.25) with no differences seen in weight. Interactions with gender did not reach statistical significance suggesting no sex-specific effects although some associations were stronger in one group versus the other (e.g., BPA for boys associated with BMI at 0.08 kg/m²; 95%CI: 0.03, 0.13 versus for girls 0.01; -0.04, 0.06).

Conclusions: In this first prospective population-based study known to use DBS, we found some evidence that longitudinal weight and height of children from birth through 3 years of age minimally differed by the concentrations of BPA, PFOS and PFOA measured at birth. Neonatal BPA concentration was associated with greater weight while PFOS and PFOA concentrations were associated with thinness. Although findings are limited by one-time assessment of chemical exposures in newborn DBS and magnitudes of associations may not be clinically meaningful, few data have measured the newborn directly rather than relying on maternal plasma or cord blood concentrations.

PA2.15.07

Non-A bisphenol exposures widely prevalent in pregnant women in a population-based cohort in the Netherlands, 2004-5

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Background: Bisphenols and phthalates are omnipresent in our environment. Exposure to pregnant women is of particular interest since bisphenol and phthalate metabolites may lead to adverse health effects in women themselves and their offspring.

Objective: To describe first trimester bisphenol and phthalate urine concentrations and determine nutritional, socioeconomic and lifestyle related determinants.

Methods: In a population-based prospective cohort of 1,396 mothers, we measured first trimester bisphenol and phthalate urine concentrations (samples collected in 2004-2005, median gestational age 12.9 weeks [IQR 12.1-14.4]). We examined associations of potential determinants with log-transformed bisphenol and phthalate concentrations, grouped according to their origin. Outcomes were back-transformed.

Results: Bisphenol A (median 9.24 ng/ml [IQR 3.54-20.25]), bisphenol S (1.66 [0.72-3.56]), and bisphenol F (0.36 [0.17-1.08]) have been detected in 79.2, 67.8 and 40.2% of the population, respectively. Mono-n-butylphthalate (median 16.21 ng/ml [IQR 7.01-31.22]), mono-(2-ethyl-5-hydroxyhexyl)phthalate (12.02 [5.83-23.21]) and monobenzylphthalate (6.59 [3.07-12.91]) have been detected in >90% of the population. Nutritional intake was not associated with bisphenol and phthalate concentrations. Obesity was associated with higher high-molecular-weight phthalate concentrations and the lack of folic acid supplement use with higher mono(3-carboxypropyl)phthalate concentrations (respectively mean differences were 40.74 nmol/l [95% CI 11.69-85.54] and 0.25 ng/ml [0.07-0.52]).

Conclusion: Non-A bisphenol exposure was highly prevalent in pregnant women in the Netherlands as early as 2004-5. Adverse lifestyle factors including obesity and the lack of folic acid supplement use seem to be associated with higher phthalate concentrations in pregnant women. Further studies are needed to assess pregnancy outcome effects of bisphenol and phthalate urine concentrations in pregnant women.

PA2.15.06

Prenatal exposure to perfluoroalkyl substances, immuno-related outcomes, and lung function in children from a Spanish birth cohort study

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Background: Prenatal exposure to perfluoralkyl substances (PFAS) may be associated with immunosuppression and respiratory health during childhood. However, evidence from epidemiological studies is scarce and inconsistent. We studied the association between prenatal PFAS exposure and immune-related outcomes and lung function up to age 7 in the Spanish INMA birth cohort study.

Methods: We assessed perfluorohexane sulfonate (PFHxS), perfluorooctanoate perfluoroctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorononanoate (PFNA) in maternal plasma samples collected during the 1st-trimester of pregnancy (years: 2003-2008). Mothers completed interview-led questionnaires assessing the occurrence (yes/no) of wheezing, chest infections, bronchitis, asthma, and eczema in the previous 12 months at 1.5 (n = 1188), 4 (n = 1193) and 7 (n = 736) years of the child. At ages 4 (n = 502) and 7 (n = 737), lung function was assessed using spirometry by trained personnel. We used multivariate logistic and linear regressions to assess the association between PFAS and immune-related outcomes, and lung function during childhood. Regression models were adjusted for the age and sex of the child, and for maternal characteristics during pregnancy (age, parity, previous breastfeeding, body mass index, region of residence, country of birth, and fish consumption).

Results: PFOS (mean: 5.80 ng/mL) and PFOA (mean: 2.31 ng/mL) were the most abundant PFAS. The prevalence of childhood immune-related outcomes ranged from 3% for asthma-ever up to 41% for wheezing-ever during the study period. At 4 years, PFOS [OR (95 CI %): 0.77 (0.61, 0.96)] and PFNA [0.79 (0.65, 0.95)] were inversely associated with eczema, also PFNA was inversely associated with chest infections [0.74 (0.56, 0.97)] and asthma [0.62 (0.43, 0.90)]. At 7 years, PFHxS [0.79 (0.64, 0.97)] and PFOS [0.77 (0.60, 0.99)] were inversely associated with eczema, and PFOS [0.70 (0.49, 1.00)] and PFNA [0.65 (0.48, 0.87)] were inversely associated with wheezing. No association was observed between PFAS exposure and lung function at any age. There was no evidence of interaction by sex.

Conclusion: In this Spanish birth cohort, higher prenatal PFAS concentrations were associated with lower odds of ever reporting wheezing, chest infections, eczema, and asthma during childhood.

PL2.02 - Global population impact

PL2.02.01

The vicious cycle of pregnancy induced complications and NCDs; it all starts in utero - FIGO GLOBAL VISION

C.N. Purandare

1International Federation of Gynecology and Obstetrics

It has been proposed that the vicious cycle of non-communicable diseases (NCDs) starts in utero. Specifically, intra-uterine stressors, such as maternal undernutrition or placental dysfunction, can initiate abnormal patterns of development and histone modification. Additional postnatal environmental factors, including accelerated postnatal growth, obesity, inactivity, and aging can further contribute to DM risk, potentially via further histone modifications and DNA methylation in critical tissues. Both fetal programming and genetics might play a role in the risk of NCDs. This intra-uterine period, together with the first two years of life, offer an opportunity to address prevention of NCDs in the next generations. This leaves an important role for OB/GYNs through FIGO. Primary, secondary and tertiary prevention could lead to lower risks of NCDs, and specifically pregnancy induced complications and cardiovascular disease. This presentations will focus on the global vision of FIGO in relation to these issues.

PL2.02.02

DOHAD - addressing the science-policy nexus

P.D. Gluckman

Office of the Prime Ministers Science Advisor, AUCKLAND, New Zealand

Both at the international level (first at 2011 at the UN, and most recently at the 2017 World Health Assembly) and in a number of national jurisdictions, DOHAD related policy discourse has been elevated into policy consciousness in the last 5 years. Despite this actual policy initiatives are generally lacking. Science and policy are two very different cultures and I will explore the interface at both global and national levels. The science of DOHAD can be looked at in a narrow or broader framing. Traditionally DOHAD researchers have tended to focus on one biological system - most dominantly the cardio-metabolic axis. The arguments for public policy intervention have largely been made from a normative perspective with there being very little (if any) empirical evidence in human populations to support large-scale policy interventions. The reasons for policy skepticism are many reflecting the diverse inputs and the messy nature of the policy process. Adding to this is ongoing confusion in public health nutrition and the relative failure of the adult obesity community to embrace the developmental perspective. But when looked at through the broader perspective of the life course and shorter-term behavioral and emotional outcomes in childhood the arguments shift and the evidence base gets stronger. DOHAD science will remain a challenge for the policy community if it remains with a narrow
facing. This will not change without compelling empirical evidence for shorter-term benefit (e.g., addressing GDM or maternal perinatal depression or childhood cognitive, health, and behavior). But placed within a life course approach addressing some of the issues that all countries are facing, progress is possible. It is also important to recognize the very different contexts of different populations. The agenda for low and middle-income countries is very different and DOHAD science must be embedded within the broader developmental agenda in part encapsulated in the “every woman, every child” agenda and which then spreads into a number of the sustainable development goals (SDGs). While the SDGs also apply to developed countries, the motivation for policy intervention differs and the opportunities link better to other policy priorities. Big data applied to social sector research will become the mainstay of policy making for such countries and DOHAD researchers will need to link to that community of academic and policy researchers. Traditional DOHAD research is disadvantaged because of its lack of evidence as to effective interventions with short-term benefits and normative arguments abound. However the life-course dimension does impact on the policy community. DOHAD research will need to expand its boundaries to have policy impact.

**PL2.02.03**

Interaction between infection and obesity and gestational diabetes during pregnancy

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Sub-Saharan Africa has over 25 million people living with HIV, most of whom are women of reproductive age. This region accounts for a large proportion of new HIV infections globally. In addition, Sub-Saharan Africa faces increases in the prevalence of obesity and type-2 diabetes mellitus (T2D) and has the greatest proportion of people who have died from T2D before age 60 years. These non-communicable disease burdens not only add to the already substantial morbidity of HIV infection, but the expected increase in T2D and related gestational diabetes mellitus (GDM) and their impact on the next generation, could overwhelm an already strained health system. This constellation of health burdens is particularly exacerbated in South Africa. The aim is to review evidence on the interaction between maternal infection and obesity and GDM during pregnancy and its impact on the newborn.

**PA2.17 – DOHaD Trainees Meeting**

**PA2.17.01**

DOHaD Trainees Meeting

A. Bansal, S. Feuer

DOHaD trainees are comprised of undergraduate students, graduate students, postdoctoral fellows, clinical fellows, and other early-career professionals pursuing research in fetal and developmental origins of health and disease. The DOHaD Trainees Meeting is an open meeting at which all Trainees are welcome. Come meet your representatives on the DOHaD Council, Amita Bansal and Sky Feuer, network with other trainees, and learn more about the benefits of trainee membership. During this hour, we will discuss the multiple opportunities offered to DOHaD trainees - including an opportunity for postdocs to become reviewers for JDOHaD and listen to your feedback and ideas about future opportunities, including novel ways to engage outside of the World Congresses.

**Tuesday October 17th Abstracts poster presentations**

**PO2.01 – Adiposity – life course**

**PO2.01.01**

Sex differences in the association between adverse childhood experiences (ACEs) and adiposity measures in adolescents


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**Background:** Many studies have shown a robust positive association between adverse childhood experiences (ACEs) and overweight/obesity in adults, however the results are inconclusive in adolescents. Sex differences in this association are found not only in adults, but also in adolescents. However, most of the evidence on the relationship between ACEs and adiposity comes from high-income countries, and more studies are needed in low- and middle-income countries, since the prevalence and the socioeconomic distribution of both ACEs and adiposity differs between settings. Thus, in order to explore potential residual socioeconomic confounding, this study aimed to assess the association between ACEs and adiposity measures in adolescents (15 and 18 years) from two cohorts in different socioeconomic contexts (The United Kingdom and Brazil), and to explore whether this association differs according to sex.

**Methods:** This cross-cohort study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC, UK) and the 1993 Pelotas Cohort (Brazil), and the analysis comprised 4,844 adolescents in ALSPAC and 3,924 in Pelotas. Six ACEs were assessed up to age 15 in both cohorts: physical abuse, sexual abuse, domestic violence, parental separation, separation from parents, and maternal mental health problems. At 15 years, body mass index (BMI) and waist circumference...
(WC) were measured, and at 18 years, BMI, fat mass index (FMI) and android fat percentage were assessed. The association between ACEs and adiposity was evaluated using linear regression, stratified by sex, using each ACE separately and then summed into a score.

**Results:** Few associations were found between ACEs and adiposity measures, and they were not consistent across cohorts. After adjustment for possible confounders, in ALSPAC males physical abuse was associated with higher WC at 15 years ($\beta$ 3.46, 95% CI: 1.37, 5.55), and domestic violence and the ACE score were associated with both higher BMI and higher WC at 15 years. In ALSPAC females, the only association observed was between parental separation and higher android fat percentage at 18 years ($\beta$ 0.13, 95% CI: 0.01, 0.26). In Pelotas, an association was observed between separation from parents and lower BMI at both 15 years ($\beta$ -0.66, 95% CI: -1.32, -0.01) and 18 years ($\beta$ -0.74, 95% CI: -1.46, -0.03) in males. In females, no association of ACEs or the ACE score with adiposity measures was observed in Pelotas.

**Conclusions:** Even though little evidence was observed for the association between ACEs and adiposity in adolescence (found mainly in ALSPAC at 15 years), there was some evidence for a stronger association in males. The associations observed between ACEs and adiposity were positive in ALSPAC, whilst in Pelotas the only association observed was negative. Residual confounding or context-specific relationships could explain the different pattern of associations found across the cohorts. Other studies, including in low- and middle-income countries, should investigate other factors that can moderate this association, such as time of occurrence of ACEs, sociocultural factors, biological mechanisms and resilience.

**PO2.01.02**

**Changes in trajectories of adult body mass index in China 1991-2011: evidence from the China Health and Nutrition Survey**

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**Background:** Different body mass index (BMI) trajectories have implications for morbidity and mortality in later life. But evidence on secular trends in BMI trajectories for is limited, especially in countries which are experiencing marked socio-economic and nutritional transitions. We examined how trajectories of adult BMI have changed across different generations in China.

**Methods:** We used (mixed) longitudinal data from the China Health and Nutrition Survey, which have been conducted in 9 provinces varying substantially in economic and health indicators, and have so far had ten waves 1989-2011 (N = 19,000). We derived five cohorts of adults (age $\geq$20 y) born in three-year intervals (1950-53, 1954-57, 1958-61, 1962-65, and 1966-69). Height and weight were measured at each survey. We fitted cubic growth models with random effects to adult BMI, separately for men and women.

**Findings:** Later born cohorts had higher mean BMI levels than older cohorts across all ages. All cohorts entered overweight range for a cut-off of $\geq$24kg/m$^2$, but at increasing younger ages across cohorts: for men at ~ 60 y (cohorts born 1950-57) to ~ 40 y (born in 1962-69), for women at aged ~ 55y (born in 1950-57) to ~ 45y (born in 1958-69). The slope for BMI trajectory became steeper across cohorts in men and did not change in women. The trajectories differed between urban and rural areas and the patterns differed by sex. Men in urban areas had a lower mean BMI in early adulthood than men from rural areas, but gained BMI at a faster rate and had higher BMI from 30y. Women in urban areas had a higher mean BMI in early adulthood, until mid-adulthood (45-50y) when they were overtaken by women from rural areas.

**Conclusions:** While Chinese adults had a lower mean BMI compared to Western populations, their BMI trajectories have changed over 20 years, with a secular trend of increasing BMI at increasing younger ages in more recent generations. Changes of rural/urban differences in BMI trajectories suggest further research in changing patterns of socio-economic differences in disease risk in the Chinese populations.

**PO2.01.03**

**ROLO Kids Step Test: A simple method of estimating cardiovascular fitness and adiposity in 5 year old children**

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**Background:** Children’s cardiovascular fitness has declined worldwide, with children now being 15% less fit than their parents according to the American Heart Association. Cardiovascular fitness is closely related to health and body composition with a strong link being identified between child fitness and metabolic risk factors. There is currently no simple validated measure of fitness in 5 year old children and having a way to reliably estimate this is vital for tracking children’s health.

**Methods:** A cohort of 110 children completed a step test which is based on maximal energy expenditure. Using a 25cm step, the children stepped up and down as many times as possible for 3 minutes. A pedometer was worn to record number of steps. Baseline heart rate was measured before starting stepping, immediately after the 3 minutes then every 30 seconds until it returned to baseline and the length of recovery time was noted. Child anthropometry including height, weight, circumferences and skinfold thickness were collected along with perceived exertion by the child’s mother and perceived effort by two researchers. Statistical analysis involved simple and multiple regression models.
**Results:** Males had a lower heart rate after the step test than females and a faster recovery time (112.6 seconds vs 140.6 seconds). Heart rate recovery time was positively associated with all skinfold measures of triceps, biceps, subscap and thigh (P < 0.01). After adjusting for confounders (including child sex and baseline heart rate), each 1-SD (9.1mm) increment in sum of skinfold thickness corresponded to 4.7 seconds of an increase in heart rate recovery time (95% CI: 0.02, 1.02; P = 0.04).

**Conclusion:** Child adiposity was positively associated with heart rate recovery time after the step test. With heart rate recovery being a proxy for cardiovascular fitness this provides evidence that a stepping test could be used as a valid fitness tool in 5 year old children.

**PO2.01.04**

**Air pollution, noise, green space and overweight in children aged 12 years: the PIAMA birth cohort study**

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**Background:** Increasing childhood overweight and obesity are a major public health problem. Environmental factors may contribute to obesity development in children. There is evidence that exposure to air pollution and noise is associated with a higher body mass index (BMI), whereas exposure to green space may have a beneficial effect on children’s BMI. However, no studies have examined the combined effects of these three spatially correlated environmental exposures on markers of adiposity in children. We therefore investigated the individual and combined associations of air pollution, road traffic noise and green space with overweight. For example, we found an OR of 1.12 [95% CI 0.90-1.39] for NO2, OR 1.03 [95% CI 0.84-1.26] for PM2.5 absorbance, OR 1.15 [95% CI 0.94-1.40] for road traffic noise and OR 0.85 [95% CI 0.68-1.05] and OR 0.87 [95% CI 0.71-1.06] for the average NDVI in the 300m and 3000m buffer, respectively, in single-exposure models. The associations changed only slightly when the other environmental exposures were added in multi-exposure models.

**Conclusions:** Our results do not provide support for adverse effects of air pollution and road traffic noise or beneficial effects of green space exposure on overweight in children aged 12 years.

**PO2.01.05**

**Infant subcutaneous fat and abdominal, pericardial and liver fat assessed by Magnetic Resonance Imaging at the age of 10 years**

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**Background:** Fat mass development in infancy contributes to later adiposity, but its relation to ectopic fat depots is not known. Specific ectopic fat depots may have greater adverse health effects than body mass index (BMI). We examined the associations of subcutaneous fat mass during infancy with general and organ specific fat measures in school-age children.

**Methods:** Among 593 Dutch children from a population-based prospective cohort study, we obtained total subcutaneous fat mass (as sum of biceps, triceps, suprailiacal, and subscapular skinfolds thickness), central-to-total subcutaneous fat ratio (sum of suprailiacal and subscapular skinfold thickness/total subcutaneous fat) at the ages of 1.5, 6 and 24 months. At the age of 10 years, we assessed BMI, and abdominal subcutaneous and visceral fat mass, pericardial fat mass, and liver fat fraction by Magnetic Resonance Imaging (MRI). For all exposure and outcome measures, we created standard deviation scores (SD). To assess the associations of infant subcutaneous fat with childhood general and organ specific fat we used multiple linear regression analyses adjusted for child’s sex and age at MRI measurement, maternal, birth and childhood characteristics.
Results: A 1-SDS higher total subcutaneous fat at 6 and 24 months, and higher central-to-total subcutaneous fat ratio at 1.5 months only, were associated with higher BMI and higher subcutaneous fat mass at 10 years. The strongest effect was observed for the associations of total subcutaneous fat at 24 months with childhood BMI (difference 0.15 [95% Confidence Interval (CI) 0.08, 0.23] SDS) and childhood subcutaneous fat mass (difference 0.16 [95% CI 0.09, 0.23]). Infant subcutaneous fat measures at any time point were not associated with visceral and pericardial fat mass, and liver fat fraction at 10 years.

Conclusions: Our results suggest that infant subcutaneous fat is associated with later childhood BMI and subcutaneous fat, but not with other organ specific fat depots.

PO2.01.06
Growth in early life and the risk of obesity among children in Aruba: a retrospective population-wide cohort study
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Background: Childhood obesity is an increasing health problem worldwide, causing a higher incidence of metabolic syndrome in early life. In Aruba, in 2010, the prevalence of overweight and obesity in boys at age 6 was 17.8% and 8.4% respectively, increasing to 32.4% and 14.9% respectively at age 11. The prevalence of overweight and obesity in girls was 27.6% and 11.7% respectively at age 6 increasing to 33% and 16.4% at age 11. The aim of this study was to identify if obesity was already present in the first 1000 days of life. In addition, early risk factors predicting obesity at the age of 6 and 11 years: rapid weight gain in the first 6 months of life, prematurity, being small (SGA) or large (LGA) for gestational age at birth, were investigated.

Methods: A retrospective population-wide cohort study of children, born in Aruba between 1 January 2001 and 31 March 2005, was conducted. Growth data obtained from White Young Cross and the Department of Health, section Youth Health Care, were converted to BMI-for-age z-scores (BAZs), based on the WHO growth standards, to determine the prevalence of childhood obesity, defined as BAZ ≥2. Logistic regression analyses were performed to evaluate the associations between early risk factors and later obesity.

Results: In total, 41,943 measurements of 5,576 children were analyzed. In the first year of life, 34.4% of the boys and 32.4% of the girls were overweight, of which, respectively 9.3% and 7.5% were obese. The mean BAZ at birth [95% CI] was -0.13 [-0.15-0.04] and -0.07 [-0.15-0.40] for boys and girls, respectively. The mean BAZ [95% CI] for boys and girls, respectively, changed to 0.55 [0.51-0.60] and 0.47 [0.43-0.51] at the age of 2-4 months, 0.41 [0.34-0.47] and 0.32 [0.27-0.39] at the age of 5-7 years and increased to +1.03 [0.94-1.13] and +0.79 [0.71-0.88] at the age of 11 years (See figure). The adjusted OR [95% CI] per unit increase in BAZ during the first 6 months of life for obesity at age 6 years was 1.20 [1.10-1.30]. The adjusted OR [95% CI] of being LGA at birth for obesity at age 6 and 11 years was 3.45 [2.02-5.90) and 2.78 [1.33-5.80], respectively. The associations of prematurity and being SGA with obesity at age 6 and 11 were not statistically significant.

Conclusion: The present study shows that children born in Aruba are heavier compared to WHO standards. Children whose BMI grows faster in the first 6 months are at increased risk of childhood obesity, but being large for gestational age at birth, which can be associated with maternal obesity and gestational diabetes, does give a more profound risk of childhood obesity. Prevention of obesity in Aruba should start in the first 1000 days of life, as is promoted by the WHO. Future research should focus on maternal life style and diet during pregnancy to prevent LGA born infants and early life nutrition to reduce rapid weight gain in the first 6 months of life as risk factors for childhood obesity.

PO2.01.07
Neonatal chronic pain, analgesia and obesity in adulthood: experimental study in rat
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Previous data reported that exposure to a noxious environment in early life increases vulnerability to developing metabolic disorders in adulthood such as metabolic syndrome and obesity. Over recent decades the advances in medicine considerably raised the number of newborns exposed to chronic pain increasing opioids use to induce analgesia. However long-term effects of chronic perinatal pain and analgesia are not yet fully understood. In this study we examined whether a chronic pain in early life can affect body weight, feeding behavior and metabolism in 24-month-old-male-rats. At the same time we investigated the consequences of opioid analgesia. Finally we
Experimentation

A. van Hulst1, G. Paradis2, A. Benedetti2, M. Henderson3

Type 2 diabetes in children aged 10-12 years: the QUALITY

Early weight gain, childhood adiposity and risk factors for type 2 diabetes in children aged 10-12 years: the QUALITY COHORT

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Background: Studies have shown that weight gain early in life is a risk factor for type 2 diabetes in adults, independent of current weight status. In contrast, few studies have examined the pathways that link birth weight, postnatal weight gain and childhood adiposity with subsequent risk factors for type 2 diabetes in early adolescence. The aim of this study is to determine whether birth weight and weight gain during infancy are associated with insulin sensitivity in early adolescence, and to assess potential mediation of associations by childhood adiposity.

Methods: Data from a longitudinal cohort of 630 Quebec (Canada) Caucasian children with a parental history of obesity (QUALITY) were used. In a sub-sample of children born at term, weight and length from 0-2 years of age were obtained and transformed to sex specific weight-for-length z-scores (n = 395). At age 8-10 years, percentage of body fat was measured by dual-energy x-ray absorptiometry, mean daily minutes of moderate-to-vigorous physical activity by accelerometry, and daily hours of screen time was self-reported. Insulin sensitivity was measured by the homeostatic model assessment of insulin resistance (HOMA-IR) and an oral glucose tolerance test-based index (Matsuda insulin sensitivity index (ISI)) at age 10-12 years. Path analysis were used to examine the link between early weight gain, childhood adiposity and later insulin sensitivity while adjusting for potential confounders (sex, gestational age, in-utero exposure to gestational diabetes, hypertension and tobacco, breastfeeding, parental education, lifestyle habits at 8-10 years, and current age).

Results: Higher birth weight was associated with improved insulin sensitivity: 1 z-score increase in weight-for-length at birth was associated with a 7.6% increase in Matsuda-ISI (95% CI: 3.2; 12.1) and 4.9% decrease in HOMA-IR (95% CI: -9.5; -0.3). These associations were independent of postnatal weight gain, childhood adiposity and other covariates. Postnatal weight gain was not directly associated with insulin dynamics, however faster postnatal weight gain was positively associated with adiposity at 8-10 years which in turn predicted decreased Matsuda-ISI and increased HOMA-IR 2 years later. Similarly, higher birth weight, only when not followed by a slow down in postnatal weight gain, was associated with childhood adiposity and subsequent lower insulin sensitivity.

Conclusions: Our results add to the growing body of evidence regarding the importance of prenatal and postnatal weight gain for later type 2 diabetes risk factors in youth. Intervening on determinants of birth weight may be beneficial in terms of later type 2 diabetes risk factors, however adiposity during childhood as a result of higher birth weight or of faster postnatal weight gain may increase the risk for type 2 diabetes.

Individual rearing of mice impairs adolescent growth and increases adult obesity risk.

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Background: Mice are widely used to study the neurobiology of energy balance, metabolic homeostasis and how environmental challenges at different life-stages can influence this regulation. For these purposes and to assess individual caloric intake and energy expenditure, many studies apply solitary housing conditions. The downside is that social isolation can produce chronic psychological stress in mice, and affect thermoregulatory processes. This causes changes in neuroendocrine functioning, baseline anxiety and food intake regulation. Above-mentioned processes may be highly relevant during adolescent life, when fast body growth, affective development and maturation of metabolic organs are established. We therefore hypothesized that individual rearing from weaning onwards alters metabolic development and contributes to later in life vulnerability to obesity and metabolic disease.

Methods: Directly after weaning at postnatal (P) day 21, male C57BL/6J mice were housed in either individual or social...
(n = 2 siblings/cage) housing conditions at 21°C and kept on semi-synthetic (AIN93G based) rodent chow. At P43, one third of the mice from the individually and socially housed groups were sacrificed and the remaining groups were split and either exposed to a moderate western-style diet (WSD, 40En% as fat) or kept on control diet (AIN-93-M, 20En% as fat) until P126. Bodyweight was monitored and energy intake and expenditure were determined using indirect calorimetry during adolescence (P40-42) and adulthood (P105-107). In addition, mice were subjected to a sucrose preference test to assess food reward mechanisms during adulthood (P74-79) and to an elevated plus maze test (EPM) to assess baseline levels of anxiety during adolescence (P39) and adulthood (P92). After dissection at P43 or P126 plasma adipokines, corticosterone and Insulin-like Growth Factor-1 (IGF-1) were measured and body composition was determined by carcass analysis.

**Results:** Compared to socially housed mice, individually housed animals showed reduced body weight gain during adolescence, while energy intake and energy expenditure were increased. At P43 these mice had reduced lean body mass (LBM), but significantly higher white adipose tissue mass (WAT) compared to socially housed mice. In adulthood, the bodyweight gain of individually housed animals exceeded that of socially housed mice, with elevations in both energy intake and expenditure. At P126 the individually housed mice showed higher adiposity, accompanied by a reduced plasma adiponectin/leptin ratio. Adult exposure to WSD amplified these changes and reduced plasma levels of corticosterone and IGF1. Individually housed mice that were exposed to WSD showed the lowest sucrose preference index, suggesting that food reward mechanisms were blunted in this group. Baseline anxiety levels in EPM were reduced by individual housing and by adult exposure to WSD.

**Conclusion:** Individual housing from weaning onwards results in impaired adolescent lean mass development and increased adult adiposity. The latter effects are exacerbated by adult exposure to an obesogenic diet. These effects are associated with mild alterations in reward sensitivity and reduced baseline levels of anxiety, indicating modest consequences for affective functioning. These results suggest that individual rearing of mice can be proposed as a model for programmed adult obesity.

**PO2.01.10**

**Lifecourse developmental trajectories of body mass index - A 46 years follow-up of the NFBC1966**

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**Background:** Propensity to become obese in adulthood varies during the life-course depending on social, biological or lifestyle changes. Recent statistical techniques have allowed exploration of BMI variation over time by identifying heterogeneous groups in populations. Such studies from birth to midlife are scarce. A refined knowledge about the age at onset of obesity as well as duration and intensity of episodes of overweight or obesity is extremely important to understanding the variability in the development of obesity.

**Objective:** To identify BMI developmental trajectories from birth to 46 years in a general population to study groups at risk of early onset obesity.

**Methods:** The study is based on longitudinal data obtained from the Northern Finland Birth Cohort 1966 (NFBC1966). Throughout infancy and childhood, repeated measures of height and weight were collected by the child health and welfare clinic nurses and later by school nurses. From the original paper records, the data has been computerized and integrated into our databases. At 31 and 46 years of age, the cohort members were invited to a clinical examination where their weight and height were measured by trained nurses.

Weight for length z-scores were calculated from birth to two years old and after two years, BMI z-scores were used. Twelve time frames, ranging from birth to 46 years (0, 0.25-1, 1-2, 2-4, 4-7, 7-11, 11-13, 13-17,17-30, 31 and 46), were defined and the corresponding weight for length/BMI z-scores were based on the means over each specific time window. We excluded pre-terms, multiple births (N = 1,406) and data with less than 3 measurements of BMI, giving a final sample size of 8,185 (51% male). A group-based trajectory modeling procedure, using Proc Traj in SAS statistical software, was applied to identify developmental trajectories of BMI z-scores from birth to 46 years old. This method assumes that there are latent underlying groups in the population, following the same behavior over time and each having its own prevalence, intercept and slope. We used a censored normal model, suitable for continuous variables and modeled the trajectories for males and females separately and together. We tested models with 2 to 7 groups, starting with a quartic shape (4th order polynomial). To choose the optimal number of groups, we considered the lowest Bayesian Information Criterion between 2 consecutives models (adding one group at a time). The average posterior probabilities had to be above 0.7 and odds of correct classification above 5. We also took into account a membership probability of 5% minimum if possible, tight 95% confidence intervals and parsimony.

**Results and conclusion:** We observed similar BMI z-score developmental trajectory patterns and proportions in both males and females. The present model includes both genders and identified 5 latent groups (figure) tentatively named as “low stable” (32.3%), “low decreasing” (38.1%), “adolescent obesity maintaining” (14.6%), “childhood obesity decreasing” (11.6%) and “chronic obesity” (3.4%). Identifying BMI trajectories over the life-course is a critical step in understanding the interplay between onset, intensity and duration of obesity and will help apprehending its biological, social and behavioral correlates.
Trajectories of BMI z-scores from birth to 46 years of age in NFBC1966.

PO2.01.11
Infancy growth and BMI at 21 years: the role of home environment in infancy
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Background: Faster infant growth has been related to later obesity in many studies from both developed and developing countries. However, little is known about the possible moderating effects of socio-contextual factors. In a cohort from Santiago, Chile, we evaluated how weight gain, timing of peak growth and growth velocity in the first year of life related to BMI at 21 y and whether the relation varied by stimulation in the home and maternal depression.

Methods: Infants participated in a randomized controlled trial of iron supplementation and were followed at 21y (N = 1000). Infants were singleton, born at term via routine vaginal delivery, had birth weight ≥ 3.0 kg, and did not have iron deficiency anemia at 6 months. Anthropometry (weight and length) was measured monthly between 6 and 12 months; prior measurements were obtained from chart abstraction. We fit a Super Imposition by Translation and Rotation (SITAR) growth curve model, which generates three infant-specific random effects: (1) size (mean weight relative to overall sample weight, grams), (2) tempo (timing of peak growth velocity, months) and (3) velocity (peak growth velocity, grams/month). We used multivariable linear regression to assess the effect of these growth parameters on 21y BMI. Models adjusted for sex, breastfeeding (age at first bottle), socioeconomic status, gestational age, and iron supplementation. We also tested whether the relation between the growth parameters and 21y BMI varied by home environment for developmental nurturing (HOME) and maternal depression risk (CESD).

Results: At 21y, participants were 47.3% male. BMI averaged 26.3 (5.3), with 22.5% obese and 31.2% overweight. Adjusting for covariates, later timing of peak growth in the first year related to higher 21y BMI. Higher relative weight gain also related to 21y BMI but varied by HOME environment. Weight gain positively related to 21y BMI only among infants from more, versus less, nurturing homes. Peak growth velocity was not directly related to 21y BMI. However, we found a statistically significant interaction between growth velocity and HOME score. Among infants from more nurturing homes, faster growth velocity related to lower 21y BMI; with less nurturing homes, faster growth velocity related to higher 21y BMI. There were no statistically significant interactions between growth parameters and maternal CESD score.

Conclusions: Weight gain, timing of peak growth and growth velocity in the first year of life related to 21 y BMI. The associations between 21y BMI, relative weight gain and peak growth velocity varied by HOME environment, suggesting multiple determinants of infant growth. These interesting findings require replication to better understand mechanisms. Evaluating the home environment for developmental nurturing may be an intervention point for prevention of excess weight gain in infancy.

PO2.01.12
Low insulin levels during lactation in rats can protects against obesity in adult life
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Background: Hyperinsulinemia in early life are related to the development of obesity and metabolic syndrome later in life, whereas hypoinsulinemia is implicated with lean phenotype. In this line, the M₃ muscarinic acetylcholine (ACh) receptor (M₃ mAChR) in pancreatic b-cells is essential for maintaining proper insulin release and glucose homeostasis. Here, we evaluated the effects of treatment with a cholinergic antagonist scopolamine butylbromide, during lactation on metabolism of rats submitted to a high fat diet (HF) in adulthood.

Methods: After birth, male Wistar rats received intraperitoneal injection of scopolamine butylbromide, 0.5 mg/Kg body weight (bw)/day during the first 12 days of lactation (Treated Group; T) or saline (Control Group; C). At 60-days-old, the offspring from both group were consumed standard diet (normo fat diet; NF) or high fat diet (HF; 35% of fat) by thirty days. At 90-days-old body weight, food intake, fat tissue accumulation, glucose tolerance were evaluated.

Results: The lean phenotype was observed in rats treated with scopolamine butylbromide during lactation. T group presented lower body weight than C group until 60-days-old (8%, p < 0,01) associated to a lower food intake (14%, p < 0,05). At 90-days-old, T-HF group showed to decrease the body weight (11%, p < 0,001) compared to C-HF, however, no difference was observed in food intake in all groups. The T groups presented lower fat tissue accretion (T-NF 30%; T-HF 14%; approximately, p < 0, 05) compared to C and C-HF respectively. During intraperitoneal glucose tolerant test, the T-HL
animals presented lower glucose levels than C-HL animals (13%, p < 0.01).

Conclusions: Treatment with scopolamine butylbromide during lactation attenuated the development of obesity induced by a HFD diet in adult life.

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PO2.01.13

Exploring the relationship between early and later life exposures and obesity in middle-age: Findings from the Newcastle Thousand Families study

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Background: Obesity prevalence continues to rise partially attributed to various lifestyle factors, however growing evidence emphasises the importance of early life factors in obesity development later in life. Socio-economic status (SES) also plays an important role, with more deprived populations tending to have higher obesity prevalence.

Using life-course longitudinal epidemiological data from a UK post-war cohort (Newcastle Thousand Families study 1947), this project investigates the hypothesis that exposures in early life could predispose an individual to obesity in later life with a focus on the influence of SES.

Methods: Detailed data were collected longitudinally throughout childhood, via self-completion questionnaires and clinical assessment at age 49-51 (n = 412). To explore how early life and adult factors impact on body mass index (BMI) in middle-age (49-51), multivariable linear and non-linear regression methods and path analyses were used. We investigated associations between the early life variables; birthweight, gender, maternal age, breastfeeding, infections and rapid growth in the first year, and adverse events up until the 3rd year, in addition to socioeconomic variables at birth; father’s occupational social class and quality of housing conditions, with both obesity (BMI ≥ 30 kg/m²) and BMI in middle age.

Results: After adjustment, the only early life factors associated with BMI at 50 were older maternal age and infection, whilst no significant associations were identified for birthweight, rapid growth, adversity or housing conditions. Infection in the first year of life was associated with both increased BMI and with increased likelihood of being obese in fully adjusted models. Later life factors of increased physical activity, smoking and higher occupational social class were all significantly associated with both a lower BMI and lower odds of obesity. Path analyses showed that later life lifestyle and socioeconomic factors were influenced by early life SES.

Conclusions: This work demonstrates that maternal age and infection during the first year of life directly explain a higher BMI in middle age, whereas there is an indirect effect of early life socioeconomic status. This highlights the complexity of the factors influencing BMI through the life course.

PO2.01.14

A systematic review of the life course determinants of metabolically healthy obesity

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Background: Obesity is a major public health concern, with the global age standardised obesity prevalence estimated to be 25.7%. However, obese individuals are not one homogenous group, some obese individuals have healthier metabolic profiles and decreased health risks compared to others. The concept of metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) has thus been proposed. Metabolically healthy obesity reflects obese individuals who have healthy metabolic profiles (e.g., healthy blood pressure, blood sugar, and lipid profiles), and therefore display cardiometabolic resilience to obesity. On the other hand, MUO reflects obese individuals who have unhealthy metabolic profiles (e.g., hypertension, hyperglycaemia, and dyslipidaemia), and have been shown to have increased cardiometabolic disease risks compared to those defined as MHO. However, the factors explaining this heterogeneity between obese individuals’ different health status and prospects are not well established. To date, most research focuses on the prognosis, prevalence, and transitioning rates of MUO and MHO. Research which has looked into the factors that account for the differences between MHO and MUO is largely cross-sectional. In comparison, there is a lack of longitudinal studies investigating the associations between certain exposure factors and MHO. It has been highlighted that longitudinal analysis is required to provide greater insight into the life course factors that contribute to the development of MHO or MUO. This study aims to systematically review longitudinal studies investigating the association between life course exposures and cardiometabolic resilience to obesity.

Methods: Electronic databases will be searched using a trialled search strategy. Studies will be included following a double screening process according to strict inclusion criteria. Studies eligible for inclusion will be prospectively measured longitudinal studies, which investigate the association between certain exposure factors and MHO. It has been highlighted that longitudinal analysis is required to provide greater insight into the life course factors that contribute to the development of MHO or MUO. This study aims to systematically review longitudinal studies investigating the association between life course exposures and cardiometabolic resilience to obesity.

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1956, and based on human participants. This systematic review has been registered with PROSPERO (Registration number: CRD42017057992).

**Results:** Key results of included studies will be tabulated, and a narrative synthesis will be conducted. Further, quality of included studies will be assessed using an adapted version of the Newcastle Ottawa scale, and results reported.

**Conclusions:** This review will be the first to summarise the literature on the life course determinants of cardiometabolic resilience to obesity. This information will be important in understanding what we currently know on this subject, and identifying gaps for future research. Importantly, it may highlight which modifiable lifestyle factors could be targeted to delay the onset of cardiometabolic complications among the obese.

**PO2.01.15**

**Faster infancy growth and waist circumference and blood pressure at 21 years**

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**Background:** Rapid infant growth is associated with obesity. However, less is known about how infant growth relates to later waist circumference and blood pressure. In fact, few studies have reported relations between infant growth and obesity-related comorbidities past childhood. In a cohort from Santiago, Chile, we evaluated how infant growth, timing of peak growth and growth velocity in the first year of life related to waist circumference, systolic (SBP) and diastolic (DBP) blood pressure at 21 y.

**Methods:** Participants were from an infant iron supplementation trial aimed to prevent iron deficiency anemia. Original inclusion criteria were birth weight ≥ 3.0 kg, term, vaginal delivery, and no pregnancy complications or health problems. Between 6 and 12 months, anthropometry (weight and length) was measured monthly by research staff; prior measurements were obtained from chart abstraction. At 21y, 1000 participants were reassessed. Waist circumference, SBP and DBP were measured by a research-trained nurse. We fit a Super Imposition by Translation and Rotation (SITAR) growth curve model, which generates three infant-specific random effects: (1) size (mean weight relative to overall sample weight, grams), (2) tempo (timing of peak growth velocity, months) and (3) velocity (peak growth velocity, grams/month). We used multivariable linear regression to assess the effect of each growth parameter on waist circumference, SBP, and DBP. Models adjusted for breastfeeding (age at first bottle), socioeconomic status, gestational age, and iron supplementation.

**Results:** At 21y, the sample was 47.3% male. Waist circumference averaged 79.5 (11.2) in females and 88.0 (11.2) cm in males. Mean SBP and DBP were within the normal range: 112 (11) and 69 (9), respectively. The associations examined did not vary by sex, so estimates for the whole sample are presented. Adjusting for covariates, greater mean relative weight gain (size) related to higher SBP (r = 0.09, p = <0.01) but not DBP (r = 0.02, p = 0.64). In contrast, later timing of peak growth velocity related to higher DBP (r = 0.08, p = 0.02) but not SBP (r = 0.002, p = 0.95). We did not observe a significant relation between peak growth velocity and SBP (r = -0.06, p = 0.08) or DBP (r = 0.04, p = 0.20).

**Conclusions:** Weight gain and timing of peak growth in the first year of life related to 21 y outcomes. Few other studies have evaluated these associations in young adults.

**PO2.01.16**

**Differential associations of subcutaneous adiposity size and shape with all-cause mortality among NHANES III adult population**

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**Background:** Previous studies which investigated on the relationship between fatness and all-cause mortality commonly used Body Mass Index (BMI) as the primary estimator of body fat, which is a crude measure that does not differentiate fat and fat-free mass nor indicate the pattern of regional fat distribution. Increasingly researchers recommend that a more direct fatness measure such as subcutaneous adiposity (SA) (i.e., skinfolds) may provide further information on the associations of fatness with cause-of-death mortality.

**Methods:** To assess the Hazard Ratio (HR) of all-cause mortality by SA (i.e., skinfold measurements), the third National Health and Nutrition Examination Survey (NHANES III) dataset was used, which conducted data collection from 1988 to 1994, and followed for mortality through 2011. Inclusion criteria were: 1) aged between 25 and 75, and 2) includes all four skinfold measurements (i.e., triceps, subscapular, supraspinale, and thigh) as well as BMI. The total number of participants selected were 10,789 individuals (5,282 males). These four skinfold measurements were used to estimate the SA size (overall fat) and shape (regional fat distribution) using Healy and Tanner’s method (HTM) (1981), which statistically divides multiple anthropometric measurements into uncorrelated size and shape values. Therefore, the statistical analysis in the current study was composed of two steps. Step one is HTM, which, again, consists of 4 steps: 1) transform all skinfolds into natural logs, 2) average all the log-transformed data, which is referred as size, 3) calculate differences between the size and each log-transformed skinfold, 4) perform principal component analysis (PCA), which the results then referred as shape. Next step is running Cox proportional hazard model using those calculated size and shape values as covariates with

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other potential covariates (e.g., mortality status, age, race/ethnicity, education, and smoking).

Results: The PCA generated two components for each gender. For male, the first shape components strongly correlated with triceps (positive) and supraspinale (negative), and the second shape component strongly correlated with subscapular (positive) and thigh (negative). For female, the first shape components strongly correlated with triceps (positive) and supraspinale (negative), and the second shape components strongly correlated with thigh only. Those SA size and shape values were categorized based on the age-specific z-scores into quintile groups. For male, all covariates significantly modified the relationship between all-cause mortality and SA size and shape variables, SA size had a U-shaped relationship (HR minimum at the second biggest size quintile), shape1 had a monotonous pattern (HR minimum at the triceps dominant quintile), shape2 had no significant relationship, and BMI had a U-shaped relationship (HR minimum at the middle quintile). For female, all SA size and shape as well as BMI did not show any significant association with HR patterns, although covariates were still significant.

Conclusions: The associations of both SA size and shape with all-cause mortality is supported in male but not female. The results from this study demonstrate for the first time that the HTM used to statistically explain the association between SA and all-cause mortality with the notion of SA size and shape.

Reference: (Healy & Tanner, 1981)

Hazard ratio difference between quintile groups based on SA size, shape, and BMI among male and female adult population aged between 25 and 75 years (NHANES III)

PO2.02 – Cardiometabolic health - Nutrition

PO2.02.01

Resistance exercise combined with regular insulin supplementation after hepatic glucose and lactate metabolism in healthy swiss mice
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Insulin is an important modulator of liver metabolism by decreasing gluconeogenesis and promoting glycogen synthesis, and thus influencing whole-body glucose homeostasis and energy expenditure. Although exogenous insulin has been employed to treat type 1 diabetic patients, which are insulin-deficient, it has been used for many healthy people to promote muscle hypertrophy or prescribed by health professionals in order to lose body weight. As potentially harmful effects of insulin supplementation to non-diabetics are not known, this study studied the effects of resistance exercise combined with regular insulin supplementation on gluconeogenesis in perfused livers of healthy Swiss mice. Thirty-eight animals were have randomly distributed in four groups: Vehicle (VE, n = 8) and Insulin (IN, n = 12 Vehicle trained (VT, n = 10) and Insulin trained (IT, n = 8). The VE and VT groups were treated with saline and the IN and IT group were treated with regular insulin (0.3 U/Kg, ip.) for eight weeks, five days/week. The resistance exercise (VT and IT groups) was has done using a vertical climb with added weight of 90% maximal load. After that, the livers of a part of animals were perfused in situ after six-hour fasting with alanine and glutamine (ala/gln, 4 mM each) to measure glucose, lactate, ammonia and urea and another part of animals were perfused, in the same protocol, with glycerol and lactate to measure glucose production. After 30 minutes of stabilization, the perfusion fluid was collected at the time 0, 4 8 and 10 minutes without substrate perfused and after the livers were perfused by 45 minutes with substrate perfused (alanine and glutamine or glycerol and lactate) and the perfused liquid collected each 5 minutes. The areas under the curve (AUC, in μmol/g liver) for glucose, lactate, ammonia and urea production of the groups were compared by one-way ANOVA test and the basal lactate was compared by two-way ANOVA test both at the significance level of 5%. When perfused with alanine and glutamine we did not find significant difference in the glucose, ammonia and urea AUC production, however, we found difference in the lactate AUC production between the groups VE (2,338 ± 0,109) vs VT (1,229 ± 0,148); VE vs IT (1,152 ± 0,072); IN (2,204 ± 0,228) vs VT; and IN vs IT. We also measure the basal lactate production of the in situ perfused livers and we found significant difference in its production such as showed on the graphic bellow. Therefore, resistance exercise combined with regular insulin supplementation could alter hepatic glucose and lactate metabolism in healthy swiss mice. Although further experiments are required to elucidate the mechanisms by which these alterations could be lead.
Vitamin B12 deficiency triggers adipocyte dysfunction by enhancing triglyceride biosynthesis and pro-inflammatory cytokine production: a new agonist in metabolic disease?

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Background: Vitamin B12 (B12) is an essential micronutrient required for optimal hematopoietic, neurologic and other several metabolic reactions. Longitudinal studies and animal models showed that low maternal vitamin B12 deficiency is associated with the maternal obesity, development of insulin resistance and metabolic syndrome phenotype. Although the mechanisms underpinning metabolic disorders remain poorly defined, it has become increasingly clear that dysregulation of lipids and metabolic inflammation is associated with obesity and its comorbidities. Therefore, the aim of this study is to investigate the role of B12 in lipid regulation and inflammation in human adipocytes.

Methods: Human pre-adipocyte cell line (Chub-S7) and human primary pre-adipocytes were grown to confluence (day 0), differentiated in differentiation media for one week and maintained in nutrition media for next 7 days (day 14). In order to analyse B12 deficiency effects, customized media with different concentrations of B12 (25pM, 100pM, 1nM, 500nM) were used. On day 14, the condition media were collected and the cells were harvested for RNA and protein analysis, and were used. Our data highlights that low B12 induces excess triglycerides biosynthesis and higher gene expression and secretion of pro-inflammatory cytokines, which might lead to adipocyte dysfunction. This link between vitamin B12 deficiency and metabolic inflammation opens new insights into the pathogenesis of maternal obesity and the relevance of micronutrient supplementation for pregnant mothers.

Results: Adipocytes cultured in low vitamin B12 conditions showed significantly increased expression of genes involved in triglyceride synthesis such as Elongation Of Very Long Chain Fatty Acids Protein 6 (ELOVL6), Stearyl-CoA Desaturase (SCD), Glycerol-3-phosphate acyltransferase (AGPAT), acylglycerophosphate acyltransferase (AGPAT), phosphatidate phosphatase (LIPIN1), Diacylglycerol O-Acyltransferase 2 (DGAT2) and in lipid trafficking Fatty acid binding protein (FABP4). Cellular uptake of radio-labelled fatty acid (14C-oleate) for de novo TG biosynthesis assessed by scintillation was significantly higher in low B12 condition. In addition, we also observed that the gene expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) (figure 1d), interleukin-8 (IL-8) (figure 1a), interleukin-18 (IL-18) (figure 1c), transforming growth factor beta (TGF-β) (figure 1e), monocyte chemoattractant protein-1 (MCP-1/CCL2) (figure 1b) and IL1-beta (figure 1f) secretion were significantly increased in low B12 conditions.

Conclusion: Our data highlights that low B12 induces excess triglycerides biosynthesis and higher gene expression and secretion of pro-inflammatory cytokines, which might lead to adipocyte dysfunction. This link between vitamin B12 deficiency and metabolic inflammation opens new insights into the pathogenesis of maternal obesity and the relevance of micronutrient supplementation for pregnant mothers.

Insulin resistance and liver fat assessed by Magnetic Resonance Imaging in children.

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Background: The worldwide prevalence of pediatric non-alcoholic fatty liver disease (NAFLD) is estimated to be 7.6%. It is associated with metabolic disorders such as obesity, insulin resistance and type 2 diabetes. Although the gold standard for diagnosing NAFLD is a liver biopsy, Magnetic Resonance Imaging (MRI) has been described as an accurate and reproducible technique. We aim to examine the association between insulin resistance and liver fat fraction measured by MRI in children at the age of 10 years. We also aim to explore whether the associations of insulin resistance and liver fat fraction are influenced by maternal and childhood socio-demographic, lifestyle and anthropometric factors.

Methods: In a population-based birth cohort study, we collected blood samples at age 10 years, we assessed glucose and insulin levels and we calculated insulin resistance using the homeostasis model assessment (HOMA). Liver fat fraction was obtained from MRI scans at the same age. Spearman’s rank correlation coefficients will be used to estimate the correlations between insulin resistance and liver fat fraction. We will also assess the role of maternal and childhood factors in the associations of insulin resistance and liver fat fraction using linear regression models.

Results: Out of 5706 singleton children that attended the study visit at 10 years, liver fat fraction measured by MRI was available in 3170 children. The median liver fat fraction was
2.0% (95% range: 1.2-5.3%). The blood samples are currently being processed for glucose and insulin concentrations.

Conclusion: We hypothesize that insulin resistance is associated with higher liver fat fraction and therefore with a higher risk of developing NAFLD. The results will be available soon to reject or confirm this hypothesis.

PO2.02.04

Associations of maternal pregnancy, social and lifestyle characteristics and blood pressure at age 4/5 in White British and Pakistani children

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Background: South Asian individuals have substantially higher rates of coronary heart disease (CHD) than White Europeans. High blood pressure (BP) is one of the most important risk factors for CHD and higher diastolic BP has previously been reported in both South Asian adults and children (age 9/10) compared to White European populations. Our research question was whether pregnancy, social and lifestyle maternal exposures are associated with offspring BP at age 4/5 and whether any association differs between White British and Pakistani origin children.

Methods: Born in Bradford is a bi-ethnic prospective cohort study developed to provide evidence about the causes of disease and health outcomes by following the lives of 13818 children born to 12453 mothers in Bradford, UK between 2007 and 2010. For the analyses presented here, data from 1824 Pakistani and 1644 White British mother-offspring pairs were used. All mothers completed an oral glucose tolerance test in pregnancy. We examined associations of maternal early pregnancy BMI, gestational diabetes (GD), fasting and post-load glucose, maternal hypertension (HDP), smoking in pregnancy and maternal education, with BP in offspring at age 4/5.

Results: Pakistani children had lower systolic, but higher diastolic BP (difference in mean -0.17 mmHg; 95% CI -0.88, 0.54 and 1.33 mmHg; 95% CI 0.59, 2.06, respectively) compared to White British children. Maternal BMI and HDP were positively associated with systolic and diastolic BP in Pakistani children, but there was little evidence for an association in White British children (e.g. difference in mean SBP per 1 kg/m² 0.123 mmHg; 95% CI 0.025, 0.219 and 0.054 mmHg; 95% CI -0.033, 0.140 in Pakistani and White British, respectively and p-value for ethnic differences = 0.274). Associations of maternal glucose, smoking and education with BP were consistent with the null hypothesis in both groups.

Conclusions: Our results suggest that ethnic differences in BP are apparent from at least as young as 4/5 years. The associations of maternal BMI and HDP appear more marked in Pakistani children than White British, and other maternal characteristics do not appear to be notable determinants of BP in either group.

PO2.02.05

Paternal cholestasis alters offspring metabolic phenotype and predisposes to hypertension

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Background: Accumulating evidence has shown that not only maternal health during pregnancy, but also the paternal metabolic status at the time of conception may have an impact on the subsequent health of the offspring. Cholestatic liver diseases are metabolic conditions characterised by increased circulating serum bile acid and lipid levels. Ursodeoxycholic acid (UDCA) is the most commonly used treatment for cholestatic diseases. Previous studies have shown that male cholestasis leads to apoptosis in the testis and loss of the blood-testes barrier. In this study we hypothesised that paternal cholestasis affects the testicular homeostasis resulting in altered disease susceptibility in the offspring.

Methods: Fertile male mice were fed a normal chow (NC) diet or 0.5% cholic acid supplemented diet (CA diet) for 10 weeks. At completion of feeding, males were mated to NC-fed females. Females were allowed to give birth and offspring were kept on a NC diet until 12 weeks old, at which point offspring were either kept on a NC diet or challenged with an obesogenic Western Diet (WD) for 6 weeks. Energy balance, morphometric parameters and glucose and lipid homeostasis were assessed in the male offspring. In a subsequent cohort, used the same breeding setup was used and an additional group of paternal feeding with a 0.5% cholic acid + 0.5% UDCA supplemented diet (CA + UDCA diet) was included as a treatment group. Offspring were weaned onto NC and then fed a WD from 12 weeks to 25-29 weeks of age. Systolic and diastolic blood pressure was recorded over a 24 h period using radiotelemetry.

Results: Male offspring of cholestatic fathers challenged with a calorie-rich Western Diet (WD) showed increased energy expenditure (EE) and respiratory exchange rate (RER) during the night (EE: 13.1 vs 11.8 kcal/h/kg; RER: 0.77 vs 0.74; P ≤ 0.01) and day cycle (EE: 11.6 vs 10.5 kcal/h/kg; RER: 0.76 vs 0.73; P ≤ 0.01) compared to matched controls. Increased liver weight (3.0 vs 2.3 g; P ≤ 0.05), fasting insulin levels (3.9 vs 2.5 μg/L; P ≤ 0.05) and serum cholesterol levels (2.9 vs 1.9 mmol/L; P ≤ 0.01) were also observed in these offspring. Male offspring of cholestatic fathers challenged with a WD were profoundly hypertensive at 25-29 weeks old compared to controls during the night (196/159 mmHg vs 145/112 mmHg; P ≤ 0.01) and day cycle (169/137 mmHg vs 136/109 mmHg; P ≤ 0.01). However, paternal CA + UDCA diet...
resulted in blood pressure values comparable to controls during the night (135/97 mmHg) and day cycle (119/86 mmHg).

Conclusions: Our findings suggest that paternal cholestasis alters disease susceptibility in the offspring which is unmasked when challenged with a WD, resulting in a shifted energy balance, metabolic derangements and profound hypertension. Paternal UDCA treatment of cholestasis prevented the development of a hypertensive phenotype in the offspring.

PO2.02.06

In Utero Caffeine Exposure Induces Transgenerational Effects on the Adult Heart.

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It is recognized that the disruption of the intrauterine environment by nutritional or chemical factors may influence the developing fetus resulting in long-term adverse effects in adulthood and subsequent generations. We tested the hypothesis that in utero exposure to caffeine induces transgenerational effects on the heart. We treated pregnant CD-1 dams with caffeine, using doses equivalent to 2-4 cups of coffee, from embryonic day (E) 6.5-9.5 or E10.5-13.5. We observed that embryos exposed to caffeine from E6.5-9.5 (F1 generation) developed a dilated cardiomyopathy phenotype by 1 year of age, which consisted of increased ventricular volume, reduced left ventricular posterior wall (LVPW) thickness, decreased % fractional shortening (% FS), and impaired response to b-adrenergic stimulation. Caffeine altered cardiac gene expression in F1 generation mice, including a 4-fold increase in Myh7 expression. Embryos exposed to caffeine later (E10.5-13.5) were not affected. However, the F2 generation of mice exposed from E10.5-13.5 developed a cardiac phenotype similar to hypertrophic cardiomyopathy, which included increased LVPW thickness, decreased LV volume, and increased % FS. F2 generation mice exhibited changes in gene expression, including a 2.2-fold decrease in Myh7 expression. The F3 generation of mice exposed from E10.5-13.5 exhibited morphological changes in adult hearts, including increased mass. This report shows that in utero caffeine exposure has long-term effects into adulthood and transgenerational effects on gene expression, cardiac function, and morphology. Considering that millions of women consume caffeine during pregnancy, the notion that early embryonic exposure is associated with long-term cardiac abnormalities make these studies of considerable importance.

PO2.02.07

Metformin treatment in obese pregnant mice modulates hepatic fat accumulation and mitochondrial electron transport chain activity in adult offspring livers

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Background: Obesity during pregnancy increases offspring risk to metabolic diseases, such as non-alcoholic fatty liver disease (NAFLD). We have previously shown that maternal obesity caused by feeding a high fat (HF) diet increases offspring risk to NAFLD by decreasing mitochondrial electron transport chain (ETC) complex activity (Bruce et al. Hepatology 2009). The anti-diabetic drug metformin is prescribed in gestational diabetes, which is strongly associated with maternal obesity during pregnancy. We investigated the consequence of maternal metformin treatment in obese pregnant mice on NAFLD severity and hepatic mitochondrial ETC complex activity in male and female adult offspring.

Methods: Female C57BL6J mice were fed control (C, 7% kcal fat) or high fat (HF, 45% kcal fat) diet 6 weeks before conception, and through pregnancy and lactation. Half the dams were given metformin (met, 250mg/kg BW/day) in drinking water throughout pregnancy and lactation. Male and female offspring were weaned onto a C or HF diet, generating offspring groups (n= 3-5 per group/sex) from untreated dams (C/C, C/HF, HF/C, HF/HF) and metformin-treated dams (Cmet/C, Cmet/HF, HFmet/C, HFmet/HF). Offspring were killed at 30 weeks old and livers taken. NAFLD severity was assessed histologically by NAFLD activity score (NAS) and offspring liver mitochondrial ETC Complex I, II, IV activity was determined using ELISA. Data was analysed by two-way ANOVA.

Results: Offspring from HF-fed obese dams have increased NAFLD severity (as defined by NAS) compared with offspring from C-fed lean dams (p<0.05). There was a corresponding reduction in mitochondrial ETC complex activity levels in their livers, particularly Complex II (p<0.01) in HF/HF females. Treating the obese pregnant dams with metformin partly restored the activity levels of the three ETC complexes in the HF/HF female offspring livers but not in the males. NAFLD severity was reduced in female but not in male offspring from metformin-treated HF-fed obese dams. Conversely, giving metformin to C-fed lean dams increased NAFLD severity and failed to rescue ETC Complex I, II and IV activities in both male and female offspring livers.

Conclusions: There is a sexually dimorphic effect of maternal metformin treatment in obese pregnancy on the severity of diet-induced NAFLD in adult offspring - metformin in obese dam reduced female offspring NAS and partially restored ETC complex activity, but had no effect on male offspring. However, metformin in lean pregnancy increases offspring risk of NAFLD in adulthood for both sexes.

Funding: This work is supported by Diabetes UK

PO2.02.08

Perinatal maternal high-fat diet affects the metabolic response to fructose intake during adolescence period of male offspring

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Background: Fructose is metabolized by fructokinase, which is a rate-limiting enzyme for glycolysis and pentose phosphate pathway (PPP). Previous studies have shown that maternal fructose consumption during pregnancy plays an important role in the development of metabolic diseases, such as NAFLD, type 2 diabetes (T2D) and obesity. The aim of this study was to investigate the effect of maternal high-fat diet (HF) on offspring metabolic response to fructose intake during adolescence period of male offspring.

Methods: Female C57BL/6J mice were fed control (C, 7% kcal fat) or high fat (HF, 45% kcal fat) diet 6 weeks before conception, and throughout pregnancy. Male offspring were weaned onto a C or HF diet, generating offspring groups (n= 3-5 per group/sex) from untreated dams (C/C, C/HF, HF/C, HF/HF). Offspring were killed at 30 weeks old and livers taken. NAFLD severity was assessed histologically by NAS and offspring liver mitochondrial ETC Complex I, II, IV activity was determined using ELISA. Data was analysed by two-way ANOVA.

Results: Offspring from HF-fed obese dams have increased NAFLD severity (as defined by NAS) compared with offspring from C-fed lean dams (p<0.05). There was a corresponding reduction in mitochondrial ETC complex activity levels in their livers, particularly Complex II (p<0.01) in HF/HF females. Treating the obese pregnant dams with metformin partly restored the activity levels of the three ETC complexes in the HF/HF female offspring livers but not in the males. NAFLD severity was reduced in female but not in male offspring from metformin-treated HF-fed obese dams. Conversely, giving metformin to C-fed lean dams increased NAFLD severity and failed to rescue ETC Complex I, II and IV activities in both male and female offspring livers.

Conclusions: There is a sexually dimorphic effect of maternal metformin treatment in obese pregnancy on the severity of diet-induced NAFLD in adult offspring - metformin in obese dam reduced female offspring NAS and partially restored ETC complex activity, but had no effect on male offspring. However, metformin in lean pregnancy increases offspring risk of NAFLD in adulthood for both sexes.

Funding: This work is supported by Diabetes UK
Background: Maternal high-fat diet (HFD) during perinatal period is associated with long-term changes in metabolic responses of the offspring, increasing its susceptibility to obesity and metabolic diseases along life. This might contribute to the increased prevalence of obesity among adolescents, in addition to their own nutritional habits. Fructose intake has increased specially in adolescents, and it has been associated with early development of insulin resistance, dyslipidemia, obesity and hepatic steatosis. The latter results from the impact of fructose in the hepatic lipid metabolism, leading to lipid accumulation and oxidative damage. However, it is unknown whether maternal HFD would change the predisposition to develop hepatic steatosis in response to high fructose consumption during adolescence. Here, evaluated the impact of perinatal maternal HFD on metabolic response of the offspring to fructose intake during adolescence period.

Methods: Female Wistar rats received standard (STD - 9% fat) or high fat diet (HF 29% fat) prior mating, throughout pregnancy and lactation. After weaning, offspring received standard chow and, from 25th to 45th day (adolescence period), received water (control) or fructose-drinking water (15%). At 46 days-old, animals were sacrificed, serum and white adipose tissues depots were collected to biochemical analysis and adiposity evaluation, respectively, and liver to evaluation of redox status by enzymatic assays and investigation of autophagy markers by western blotting. Two-way ANOVA was used as statistical analysis, followed by Tukey’s post-test. Statistical significance considered as p < 0.05.

Results: HFD offspring showed higher body weight and adiposity compared to STD offspring. Fructose intake did not change the body weight, but increased the adiposity of STD (1.3-fold) and HFD (1.2-fold) offspring. Maternal HFD promoted hyperleptinemia in offspring, and fructose also increased serum leptin in STD (1.4-fold) and HFD (1.3-fold) groups. Fructose intake increased serum triglycerides in STD (2.4-fold) and HFD (2.0-fold) offspring, but decreased serum cholesterol levels only in the HFD offspring. Higher liver weight was observed in HFD offspring, but fructose intake increased it in both STD and HFD offspring. The HFD disrupted the hepatic redox status by increasing the protein bound carbonyl (3-fold) and thiol content (1.1-fold), regardless of fructose intake. However, the activities of antioxidant enzymes superoxide dismutase and glutathione peroxidase were decreased (20%) by fructose intake only in HFD offspring, highlighting its susceptibility to oxidative stress in response to fructose intake. Some markers of the autophagy process (nucleation and elongation) were analyzed. Autophagy was changed by maternal obesity and fructose intake. The hepatic protein expression of Beclin-1 (nucleation) and ATG12 (elongation) were not significantly different among experimental groups. However, fructose intake increased ATG3 (elongation) expression (2.1-fold) only in STD offspring and reduced ATG12-ATG5 (elongation) (38%) only in HFD offspring. These data suggests impairment of hepatic autophagy process in HFD offspring that received fructose.

Conclusion: The metabolic responses to fructose intake were changed by perinatal maternal diet, promoting differences in hepatic redox status and autophagy process. These observations suggest that perinatal maternal HFD and fructose intake during adolescence period turn the offspring more susceptible to develop metabolic hepatic changes.

PO2.02.09
Maximizing Precision using Quantitative Certification Programs
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Precision Image Analysis, KIRKLAND, United States of America

Background: Precision Image Analysis (PIA) has developed a robust spectrum of quality control measures, including establishing certification programs to ensure the consistency of analysts performing CT and MR post-processing for both clinical and research use. For every type of post-processing analysis, there is a certification program that must be passed before analyses can be performed. Although each program varies in length and complexity, the end goal of all certification programs is to ensure that analysts meet specific qualitative and quantitative standards. Quantitative certification ensures that all measurements performed are standardized and unbiased and meet the established internal consistency thresholds of the lab. This is achieved via a set of “gold standard” exams, the post-processing of which was already completed and overseen by PIA’s medical director. Following standardized training, prospective analysts postprocess exams from the gold standard set independently, the results of which are compared against the gold standard results. Passing criteria are rigorous. For example, for cardiac MRI (CMR), the prospective analyst must achieve less than 7% variance on all five core metrics (left and right ventricular end-diastolic and end-systolic volumes, and left ventricular mass) for five certification studies in a row. The 7% variance threshold being established based on a compendium of published standards from expert sites.

Methods: To establish the effectiveness of the PIA certification program, two CMR-certified analysts independently postprocessed the same set of 30 randomly selected adult CMR exams. Three weeks later they blindly reprocessed the exams again to establish inter- and intra-observer variability metrics for these analysts.

All CMR parameters were calculated in standard fashion using the summation of discs method on ECG-gated short axis CINE acquisitions. The right and left ventricular endocardial and
### Results

**Figures 1 and 2 show PIA’s results.** Limits of agreement and coefficients of variability were calculated for right and left ventricular end-diastolic and end-systolic volumes using the Bland-Altman method. The coefficients of variability were significantly less than the 7% variability threshold used for PIA’s CMR certification, reflecting a success in the training and certification system.

### Conclusions

PIA’s variability results are comparable to multiple published results using manual contour delineation by well-trained observers at expert CMR centers, e.g., Luijnenburg et al’s Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging.

This precision is crucial for accurate diagnostic interpretations, and in particular for longitudinal studies where small follow-up changes, which may be only marginally larger than the standard deviation for each metric, need to be quantified accurately and consistently. Minimizing observer bias and variability is equally important as optimizing imaging protocols. PIA’s certification program has been demonstrated to reduce such biases to levels comparable to other well-established expert CMR centers.

### Methods

**PO2.02.10**

**Effect of maternal high fructose and offspring high fat intake on programmed hypertension in young adult rats**

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**Background:** There is now substantial epidemiological evidence suggesting the origin of susceptibility for metabolic syndromes (MetS) and associated cardiovascular dysfunctions in adulthood can be traced back to the early life. We have previously demonstrated that maternal high fructose diet (HFD) induces programmed hypertension in adult offspring; however, the cellular and molecular signaling contributing to the developmental programming of adult hypertension is not fully understood. There are a number of nutrient sensing pathways, including silent information regulator transcript (SIRT), AMP-activated protein kinase (AMPK), phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR), and peroxisome proliferator-associated receptor (PPAR), located in the central nervous system and are responsible for the detection of sugars, amino acids, lipids and the surrogate metabolite level for the maintenance of metabolic homeostasis. Perturbation of these signaling pathways could lead to MetS and the associated cardiovascular complications. This study was designed to investigate the role of these nutrient sensing pathways in the brain on developmental programming of hypertension in offspring to maternal HFD, and the influence of high fat diet (HFatD) in offspring to these nutrient sensing pathways.

**Method:** Female Sprague-Dawley rats were fed with 60% HFD or normal diet (ND) during gestation and lactation periods. After weaning both HFD and ND offspring were subjected to HFatD or ND from the age of 3 to 12 weeks. Blood pressure was monitored under conscious condition via tail-cuff or radiotelemetry method from week 6 to 12. Expression of nutrient sensing signals in the brain on developmental programming of hypertension in offspring to maternal HFD, and the in vivo high fat diet (HFatD) in offspring to these nutrient sensing pathways.

**Conclusions:** Maternal HFD induced programmed MetS and hypertension that became significant at age of 9 weeks and maintained in young adult at age of 12 weeks. Changes in both metabolic and blood pressure phenotypes were appreciably enhanced in HFD offspring with additional HFatD intake after weaning. Protein expressions of SIRT3, phosphorylated AMPK (p-AMPK), p-Akt and p-PPAR in the hypothalamus were downregulated in the HFD offspring, which were further suppressed in offspring fed with HFatD. These molecular changes were associated with tissue oxidative stress and production of proinflammatory cytokines in the hypothalamus. Oral intake with metformin or resveratrol to HFD + HFatD offspring notably abrogated the suppression of SIRT3, p-AMPK, P-Akt and p-PPAR expressions in the hypothalamus, and alleviated tissue oxidative stress and cytokine production. The same treatments also prevented the programmed hypertension detected in the HFD + HFatD offspring at the age of 12 weeks.

**Conclusion:** These results suggest that by further downregulating the nutrient sensing signaling in the hypothalamus HFatD intake during young adult may exacerbate the programmed MetS and hypertension to maternal HFD. This may associated with the induction of tissue oxidative stress and production of proinflammatory cytokines in the brain. Activation of the nutrient sensing pathways in young adult offspring by metformin or resveratrol could protect against brain oxidative stress and neuroinflammation, leading to programming of hypertension in HFatD offspring to maternal HFD.

### Figures

Figures 1 and 2 show PIA’s results. **Table 1: PIA Inter- and Intra-observer Variability**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Difference ± SD (mL)</th>
<th>Limits of Agreement (mL)</th>
<th>Coefficient of Variability (%)</th>
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PIA Inter- and Intra-observer Variability

### References

- Y.M. Chao, C.N. Weng, C.C. Yang, J.Y.H. Chan. *Kaohsiung Chang Gung Memorial Hospital, KAOHSIUNG CITY, Taiwan*
- Luijnenburg et al. *Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging.*
- SIRT3, phosphorylated AMPK (p-AMPK), p-Akt and p-PPAR in the hypothalamus were downregulated in the HFD offspring, which were further suppressed in offspring fed with HFatD. These molecular changes were associated with tissue oxidative stress and production of proinflammatory cytokines in the hypothalamus. Oral intake with metformin or resveratrol to HFD + HFatD offspring notably abrogated the suppression of SIRT3, p-AMPK, P-Akt and p-PPAR expressions in the hypothalamus, and alleviated tissue oxidative stress and cytokine production. The same treatments also prevented the programmed hypertension detected in the HFD + HFatD offspring at the age of 12 weeks.

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PO2.02.11

Brain oxidative stress in the programming of hypertension in young offspring to maternal high fructose diet

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Background: Metabolic syndrome and associated cardiovascular complications remain to be a major health burden worldwide. Accumulated evidence from both human and animal studies suggests a suboptimal environment during fetal and neonatal development can significantly impact the evolution of adult-onset disease. Our previous results indicate that female rat fed with high fructose diet (HFD) during gestation and lactation induces programmed hypertension in young adult offspring. Underlying mechanism underpin the programmed hypertension to maternal HFD is not well defined. Oxidative stress at the rostral ventrolateral medulla (RVLM), where sympathetic premotor neurons reside, is known to play a pivotal role in sympathoexcitation and hypertension, two traits that are exhibited in the HFD offspring. This study aimed to identify the role of oxidative stress at RVLM in the programmed hypertension in adult offspring to maternal HFD.

Method: Pregnant Sprague-Dawley female rats were fed with 60% HFD or normal diet (ND) during pregnancy and lactation. Blood pressure of offspring was measured at the age of 3, 6, 9, or 12 weeks under conscious condition by tail-cuff or radiotelemetry method. Expression of enzymes for generation or degradation of the reactive oxygen species (ROS) were evaluated by Western blot or immunohistochemistry, which was visualized by confocal microscopy. ROS level was quantified by electron spin resonance spectroscopy. Drugs were chronically infused into the cisterna magna by the use of osmotic minipump.

Results: Maternal HFD fed during gestation and lactation programmed hypertension development in young, male offspring which became notable at the age of 9 and maintained at the age of 12 weeks, alongside the increase in sympathetic vasomotor activity, suggesting the high blood pressure could have its origin from the brain. In the RVLM of HFD offspring, expressions of gp91phox subunit of the NADPH oxidase and angiotensin type 1 (AT1R) receptors were upregulated, while antioxidant superoxide dismutase 2 (SOD2) was downregulated and ROS level was increased. Theses molecular and cellular events preceded the increases in sympathetic vasomotor activity and blood pressure. Intracerebral infusion of simvastatin reversed the gp91phox and AT1R upregulations, SOD2 downregulation and ROS accumulation in RVLM of HFD offspring. The same treatment, applied to HFD offspring at age of 6-9 weeks, also significantly diminished the programmed hypertension in the adult offspring at the age of 12 weeks.

Conclusion: We concluded that oxidative stress at RVLM may contribute to the programming of hypertension in young adult HFD offspring via upregulation of gp91phox and AT1R, as well as downregulation of SOD2. Early life treatment with simvastatin may protect RVLM against oxidative stress and deprogram the development of hypertension in young adult offspring to maternal HFD.

PO2.02.12

Mechanisms involved in the increase of insulin secretion stimulated by a fraction rich in sterebins extracted of Stevia rebaudiana

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Recent studies have shown that the Stevia rebaudiana (SR) plant, besides being a source of non-caloric sweeteners, is also an important source of bioactive compounds with functionalities that may be beneficial in the control of diabetes mellitus. Among the molecules with possible effect on glycemic homeostasis are the estereins, terpenoids present in large amounts in fractions obtained from SR extracts. These substances contribute negatively to the composition of the sensory profile of stevia sweeteners, even present at 0.05% level, so they are usually discarded by industry. This is the first work to evaluate the effects of a stevia fraction rich in sterebins (SSF) on glucose-stimulated insulin secretion (GSIS). In the present study, we tried to evaluate also the mechanisms that lead to the increase of the release of insulin triggered by SSF at different glucose concentrations. We used SSF extracted from SR leaf from the Center for Studies on Natural Products - UEM. The experimental procedures were approved by the Committee of Ethics in Animal Experimentation (CEUA - 8796250415) of the State University of Maringá. To study the acute effects of FTS on insulin production and secretion, islets of Langerhans from Wistar rats were isolated and incubated at different glucose concentrations (5.6, 8.3 and 16.7 mM) in the presence or not of 0.3 μg / mL SSF. Next, was evaluated the ability of SSF to stimulate GSIS in the presence or absence of Forskolin (10 μM), an activator of the enzyme adenyl-cyclase or IBMX (1 mM), a phosphodiesterase inhibitor. The supernatants from the incubations were collected and stored for further measurements of insulin using a radioimmunoassay method. SSF provoked the increase of GSIS only in the islets incubated with 8.3 and 16.7 mM of glucose. There was an increase in the secretagogue effect of Forskolin when incubated in the presence of SSF (34%), but no significant difference was observed when incubated with IBMX. Therefore, SSF stimulates insulin secretion only in the presence of high glucose concentrations by mechanisms not fully understood, but which seem to involve the activation of the adenyl-cyclase or the signaling pathway capable of activating it. This effect can be triggered by compounds present in SR leaves without sweetening properties, such as steroids, which have important functionalities for the treatment of diabetes mellitus.
High fat diet during adolescence induces increased blood pressure in adult rats

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Background/Aims: High fat diet exposition during gestation and lactation periods lead to hypertension later in life. It have been suggested that adolescence is, as well, a susceptible phase for programming to metabolic syndrome. In this context we hypothesised that high fat diet during adolescence may lead to hypertension.

Methods: Adolescent Wistar rats (30 to 60 day-old) were exposed to a high fat diet (HFD, 35% of lard). Control animals had access to normal commercial chow (NFD). Blood pressure, heart rate and pulse pressure were recorded in 120-day-old rats. Student t-test was used to compare groups.

Results: HFD animals showed greater systolic blood pressure levels compared with control animals (127 ± 2.1 vs. 119 ± 1.5 mmHg, respectively, p < 0.05); while diastolic blood pressure was unchanged (HFD: 74 ± 2.0 and NFD: 71 ± 2.1 mmHg, p = 0.27). Pulse pressure tended to be greater in HFD animals compared with control animals (51.7 ± 0.8 vs. 48 ± 1.9 mmHg, respectively, p = 0.05). Heart Rate was similar between groups (HFD: 342 ± 13 and NFD: 361 ± 17 bpm, p = 0.4).

Conclusion: High fat diet exposition during adolescence programs to higher systolic blood pressure later in life, which is an important predictor for risk of cardiovascular and renal disease.

Maternal fructose exposure further increases myocardial remodeling and impaired cardiac function in rat offspring with doxorubicin-induced cardiomyopathy


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Maternal fructose exposure has been found to participate in the developmental programming of cardiovascular system and increased the risk of cardiovascular diseases in offspring. Doxorubicin, an anticancer drug with adverse effect in cardiotoxicity, is frequently used as a chemotherapeutic agent for various malignancies. In this study, we used the Sprague Dawley rat model to examine the impact of maternal fructose intake during pregnancy and lactation on cardiac responses to doxorubicin-induced cardiomyopathy in adult offspring. Six weeks after doxorubicin injection, echocardiographic, histopathological, and biochemical examinations were performed to evaluate the cardiac function and remodeling. Gross and echocardiographic examinations showed that the heart weight and cardiac ejection function were reduced by doxorubicin treatment in offspring, while maternal fructose exposure further increased left ventricular internal diameter end systole (LVID;s) and reduced left ventricular ejection fraction (LVEF). Histopathological examination also indicated that maternal fructose exposure increased the myocardial fibrosis, oxidative stress, and collagen deposition in offspring with doxorubicin treatment. RT-PCR results showed a synergistic effect on increasing myocardial transcription levels of ANP, BNP, and β-MHC by maternal fructose exposure and doxorubicin treatment. Western blotting results also demonstrated that maternal fructose exposure and doxorubicin treatment modulated...
expression levels of apoptosis and oxidative stress-associated proteins. Moreover, the activation of cardiac stress response signalings, including Akt, p38-MAPK, ERK, and mTOR, were found to be regulated by maternal fructose exposure and doxorubicin treatment. In conclusion, results from this study indicated that maternal fructose intake during pregnancy and lactation further increased myocardial remodeling and impaired cardiac function in rat offspring with doxorubicin-induced cardiomyopathy.

PO2.02.15
Maternal Mediterranean diet during pregnancy and offspring longitudinal growth trajectories and cardiometabolic risk in early childhood
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Background: Higher adherence to the Mediterranean diet during pregnancy is associated with lower risk of abdominal adiposity in childhood. However, evidence about the influence of maternal Mediterranean diet on offspring growth and cardiometabolic risk is scarce.

Objective: To evaluate the association between adherence to the Mediterranean diet during pregnancy and offspring longitudinal growth trajectories and cardiometabolic risk in early childhood.

Design: We included 2244 mother-child pairs from the longitudinal cohort study INMA project in Spain. We measured dietary intake during pregnancy using a food frequency questionnaire and we calculated the relative Mediterranean diet score (rMED). We estimated offspring’s body mass index z-score trajectories from birth to 4 years of age using latent class growth analyses. We measured blood pressure, waist circumference and cardiometabolic biomarkers to construct a cardiometabolic risk score at 4 years.

Results: Higher maternal rMED in pregnancy was associated with a lower risk in the offspring to follow a BMI trajectory that departs from a higher birth size followed by accelerated BMI gain (reference trajectory: children with average birth size and a slower BMI gain) (RR 0.68 95%CI 0.47, 0.99); p for trend 0.059). rMED during pregnancy was not associated with the cardiometabolic risk score, its components or related biomarkers, except for waist circumference at 4 years.

Conclusions: Higher adherence to the Mediterranean Diet in pregnancy was associated with lower risk of having an offspring with an accelerated growth pattern. However, this dietary pattern was not associated with offspring cardiometabolic risk at 4 years.

PO2.03 – Epigenetics – Environmental exposures and neurodevelopment
PO2.03.01
Epigenetic differences in cord blood of newborns exposed to antidepressant medication during pregnancy. A study in the Aarhus Birth Cohort
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Introduction: Depression is common during pregnancy and increasing numbers of women are being prescribed antidepressant medications during pregnancy - especially selective serotonin reuptake inhibitors (SSRIs). There is emerging evidence suggesting that maternal use of SSRIs may be associated with an increased risk of congenital defects and adverse neurodevelopmental outcomes. One suggestion is that prenatal exposure to maternal depression or SSRIs might influence offspring health through a mechanism involving DNA methylation. The aim of this study was to investigate the association between SSRI exposure during pregnancy and methylation changes in the cord blood of the newborn.

Material and methods: We measured DNA methylation at over 850,000 CpG sites in cord blood from 176 newborns in the Aarhus Birth Cohort, selected according to maternal depression or SSRI use status. We carried out epigenome-wide association studies to compare DNA methylation between three groups: (1) SSRI use in pregnancy (n = 88); (2) non-medicated depression in pregnancy (n = 44); (3) unexposed = no depression or SSRI use in pregnancy (n = 44). We performed a single-stage regression analysis and a regional analysis adjusting the results for the following covariates: Maternal smoking, parity, maternal age at delivery, the use of other types of medication and socio-economic status (SES), batch effects, and estimated cell composition.

Results: We found 99 unique differentially methylated regions (DMRs) when comparing the three exposure groups. 18 DMRs were specific to the SSRI exposed compared to the unexposed, and 53 DMRs were specific to the depressed, non-medicated group vs. the unexposed. 27 DMRs were specific to
the SSRI exposed compared to the non-medicated, depressed group. 1 DMR was found in both the SSRI exposed group and the depressed, non-medicated group.

**Conclusion:** Prenatal exposure to untreated depression was associated with more differences in newborn DNA methylation than prenatal exposure to SSRIs. Further research is warranted to confirm these findings and investigate causality.

**PO2.03.02**

Identification of genes susceptible to epigenetic change in response to maternal folate supply and in childhood acute lymphoblastic leukaemia

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**Background:** Altered folate metabolism and inadequate maternal folate intake may be associated with increased childhood acute lymphoblastic leukaemia (ALL) risk. Folate provides methyl groups for DNA methylation, the patterns of which are dramatically disrupted in ALL. Differences in maternal folate intake during pregnancy and/or altered folate metabolism may therefore affect DNA methylation, consequently influencing ALL risk.

**Methods and Results:** We investigated the potential aetiological role of maternal folate intake during pregnancy on ALL risk by identifying genes in which methylation changes occur both in response to folate levels and in ALL. We used previously generated DNA methylation array data from a mouse model of in utero folate depletion to identify genes in which methylation is altered in response to inadequate maternal folate intake: in total 591 genes showed altered DNA methylation. From the literature, we identified 2615 differentially methylated genes in ALL. We selected target genes to investigate DNA methylation from the overlap of these two gene lists (n = 60 genes). For 20 ALL patient samples, we quantified DNA methylation by pyrosequencing for 5 selected target genes (ASCL2, HTRA1, KCNA1, SH3GL3, SRD5A2), all of which were highly methylated in ALL samples. Methylation was then assessed for these 5 genes in a nested cohort of 148 cord blood samples from the North Cumbria Community Genetics Project and analysed in relation to maternal and infant red blood cell folate and vitamin B₁₂ concentrations. Linear regression analysis suggests infant cord blood SH3GL3 promoter methylation is inversely related to maternal RBC folate status (p = 0.008), and ASCL2 promoter methylation is inversely related to infant vitamin B₁₂ status (p = 0.016).

**Conclusions:** These findings demonstrate that folate responsive changes in DNA methylation identified in animal studies can be used to determine relevant gene targets in human studies of diseases for which folate intake is an associated risk factor, and that DNA methylation may be one mechanism by which maternal folate intake (and related pathways) may influence ALL risk.

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**PO2.03.03**

Duration of breastfeeding is associated with leptin DNA methylation in 6 months old children

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**Background:** Infant nutrition in the early postnatal period (lactation) has been associated with metabolic programming of children and consequent disease risk in later life, for example obesity. One of the underlying mechanisms responsible for metabolic programming are epigenetic modifications, such as DNA methylation. Changes in leptin (LEP) DNA methylation at a young age could influence appetite regulation and fat metabolism.

**Methods:** The MAternal Nutrition and Offspring’s Epigenome (MANOE) study was set up to assess the effect of maternal nutrition during pregnancy and infant nutrition (breastfeeding vs. formula feeding) on infant DNA methylation in genes related to the onset of obesity. We investigated the effect of the duration of breastfeeding (1 = < 1 month; 2 = 1-3 months; 3 = 3-6 months; 4 = 6-9 months; 5 = > 9 months) on infant LEP DNA methylation in mouth epithelial cells. We measured LEP buccal DNA methylation in 6 and 12 months old children (n = 98) via pyrosequencing. To assess differences in buccal DNA methylation depending on the duration of breastfeeding we used a one-Way ANOVA.

**Results:** We found statistically significant differences in LEP CpG1 buccal methylation at 6 months by duration of breastfeeding (p = 0.038). A post hoc test revealed that the LEP CpG1 methylation level was significantly higher when the mother breastfed 6 - 9 months (12.4±5.7%) as opposed to breastfeeding less than 1 month (p = 0.01, 8.2±2.9%), 1 - 3 months (p = 0.021, 9±4.9%) and 3 – 6 months (p = 0.05, 9.8±4.7%). In addition, higher LEP CpG4 and mean methylation levels were observed when mothers breastfed 6 - 9 months as compared to breastfeeding less than 1 month (CpG4, p = 0.041, 16.2±7.6% vs. 12.1±3.6%; Mean, p = 0.027, 9.8±4.6% vs. 7.2±2.1%). No significant differences between the breastfeeding groups were found for LEP buccal methylation at 12 months.

**Conclusion:** Infant nutrition in the early postnatal period was associated with epigenetic variations in LEP from buccal cells at
Sex differences in neonatal DNA methylation of imprinted genes and executive functioning in early childhood

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Background: There are inconclusive findings regarding the association of DNA methylation in umbilical cord blood and later neurocognitive outcomes in early childhood. Sex-specific methylation patterns are expected given known gender differences in early cognitive development.

Methods: Using umbilical cord blood samples from the Newborn Epigenetic Study, a southeastern US population-based cohort, we assessed differentially methylated regions of imprinted genes and cognitive outcomes at age 5. Mean levels of DNA methylation for the gene and specific CpG sites of Hes1, Meg3, and MMP9 were tested for significant associations with executive functioning (attention and inhibitory control, cognitive flexibility, and working memory), language development- IQ proxy, and cognitive composite scores. Measures came from the NIH Toolbox Cognition Battery: Flanker Inhibitory Control and Attention, Dimensional Change Card Sort, Picture Sequence Memory, and Picture Vocabulary. Adjusted robust regression models controlled for maternal (age, race, education, smoking) and child (age, gestational weeks, and birthweight) factors. Interactions by sex were tested.

Results: There were significant negative associations (p < .05) for specific CpG sites of Hes1 and attention/inhibitory control; Meg3 and working memory; and MMP9 with attention/inhibitory control and IQ. Significant sex differences were observed for males only. Findings are promising given the established functional roles of Hes1 in cognition, Meg3 in brain development, and MMP9 in ADHD.

Conclusion: Pilot study suggests that DNA methylation in umbilical cord blood is associated with later neurocognitive outcomes of executive functioning and language development, especially among males. Results need to be confirmed in a larger sample.

Like father, like son: Investigating the molecular underpinnings by which environmental contaminants change sperm miRNA expression intergenerationally

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PO2.03.04

PO2.03.05

Numerous reports indicate that the prenatal environment can affect the parental germline and influence future generations. Our laboratory has used persistent organic pollutants (POPs) to show that toxicant-induced disorders are transmitted from father to offspring over multiple generations coincident with alternations in sperm DNA methylation, suggesting paternally-mediated epigenetic inheritance. The role of other epigenetic marks is currently unknown. Micro RNAs (miRNAs) interplay with DNA methylation and are of interest due to their regulatory functions, notably in development and differentiation. Here, we hypothesize that prenatal paternal exposure to POps alters miRNA expression in sperm and the sperm of his offspring. We further hypothesize that POps-induced dysregulation of miRNA expression is reduced or prevented by nutritional folic acid (FA) supplementation. To test our hypotheses, four treatment groups of Sprague-Dawley F0 founder females (n = 6) were gavaged with either an environmentally-relevant POps mixture (500 μg/kg) or corn oil (control); in addition, the F0 females received diets containing 1X or 3X FA representing the intake from fortified foods ± additional FA supplementation, respectively. Treatments were administered 5 weeks before reproduction and until parturition. F1 males were bred with untreated females to obtain F2 offspring. Sperm were collected from F1 and F2 males (n = 12) at 150 days of age. For each treatment group, sperm from 4 individuals were pooled in triplicate and total miRNA was extracted using the mirVana™ miRNA Isolation Kit. Sperm miRNA pools were subjected to sequencing with the Illumia MiSeq system with ~ 25 million reads. Prenatal POps exposure tends to reduce overall miRNA expression in F1 sperm because compared to control, 202 miRNAs were down-regulated and 31 were up-regulated. This pattern shifts in the F2 sperm, where POps treatment caused only 36 miRNAs to be down-regulated and 54 up-regulated compared to F2 controls (Figure 1). David 6.8 GO term analysis revealed that the majority of genes targeted by the affected miRNAs are enriched in a wide range of biological processes including signal transduction, programmed cell death regulation, and reproductive system development in both generations. We also investigated altered cellular pathways. PI3K-Akt and multiple cancer-associated pathways repeatedly received the highest gene match score in both generations. We found that 47 differentially-expressed miRNAs, due to POps exposure, were conserved in F1 and F2 sperm, suggesting perturbation of these miRNA networks in an intergenerational fashion. According to GO term analysis, these conserved miRNAs are indirectly involved in the cGMP-PKG signaling pathway, renin secretion, oocyte meiosis and oxytocin signaling. Combining POps + FA led to fewer differentially regulated miRNAs: 143 down-regulated and 10 up-regulated, compared to POps in F1. In F2, 33 miRNAs were down-regulated and 29 up-regulated. We also observed that these conserved miRNAs are indirectly involved in the cGMP-PKG signaling pathway, renin secretion, oocyte meiosis and oxytocin signaling. Combining POps + FA led to fewer differentially regulated miRNAs: 143 down-regulated and 10 up-regulated, compared to POps in F1. In F2, 33 miRNAs were down-regulated and 29 up-regulated. We also observed that...
PO2.03.06

DNA methylation mediates the association of prenatal adversity with risk factors for metabolic disease

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Human and animal studies show intriguing associations between adverse intra-uterine conditions and adult health which may be mediated by changes in epigenetics, such as DNA methylation (DNAm). A systematic epigenome-wide study investigating whether epigenetic changes also mediate the association between adverse intra-uterine conditions and adult health is still missing. Exposure in the womb to the Dutch Famine of 1944+45, a severe 6-month famine, is associated with both DNAm differences and an increase in BMI, serum cholesterol and serum glucose levels in later-life and therefore provides an unique opportunity to investigate the possible mediating role of DNAm. We evaluated whether DNAm measured in whole blood at 342,596 CpG dinucleotides (CpGs) across the genome mediated the association between prenatal famine exposure and metabolic health in 422 individuals exposed to the Dutch Famine in utero and 463 controls from the Dutch Hunger Winter Families Study. To test for mediation, we implemented a 2-step analysis that consists of an epigenome-wide exploration for potential mediators followed by formal mediation analysis. DNAm mediated that association of prenatal famine exposure with adult BMI and serum triglyceride levels (TG), but not serum glucose and other serum lipids. DNAm at PIM3 (cg09349128), which influences cell growth and mitochondrial function, mediates 13.5% of the association between prenatal famine exposure and BMI. DNAm at six CpGs, including TXNIP (cg19693031) and ABCG1 (cg07397296), together mediate 80% of the association between famine exposure and TG. Additional evidence for mediation by DNAm for exposure during early gestation and TG was found at PFKFB3 and METTL8, which are genes linked to glycolysis and adipogenesis respectively. External data showed that DNAm at the identified CpGs is associated with the expression in blood of genes involved in cell differentiation and metabolism and correlated with DNAm in multiple fat depots. The identified CpGs are also associated with metabolic health in other epigenome-wide association studies. In summary, we provide evidence that DNAm may indeed mediate the association between prenatal adversity and later-life metabolic health in humans. The exact causal mechanism linking DNAm and the metabolic end-points associated with prenatal famine exposure still awaits elucidation.

PO2.03.07

Paternal diet may leave imprinting marks in sperm that persist in offspring: Results from the TIEGER study


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Background: Epigenetic inheritance from environmental exposures has been widely studied in animal models and in humans. In most cases, maternal exposures have been considered as a potential cause of epigenetic changes in offspring. We recently demonstrated paternal contribution to epigenetic inheritance in gametes and epigenetically induced risks for chronic disease in offspring. We here explore potential influences from dietary habits on clinical and epigenetic sperm characteristics.

Methods: We collected food frequency data and semen from 69 Caucasian men in NC, USA, aged 18-35. This study is part of The Influence of the Environment on Gametic Epigenetic Reprogramming (TIEGER) study. Dietary exposures included weekly intake of fruits/nuts, vegetables/soups, whole grain bread, meat, seafood/fish, burgers/hot-dogs, pizza, and fries. We explored their potential effects on clinical sperm parameters and DNA methylation levels at 12 differentially methylated genes linked to cell growth and differentiation, mitochondrial function, and metabolism.
regions (DMRs) of the following imprinted genes: GRB10, IGF2, H19, MEG3, NDN, NNAT, PEG11/MEST, PEG3, PLAGL1, SNRPN, and SGCE/PEG10; quantified using bisulfite pyrosequencing. Multiple regression models were used to study the association between dietary patterns and sperm characteristics; we took into account multiple testing.

**Results:** After adjusting for age, obesity and patient status we found significant positive associations between clinical sperm parameters, such as Total Motile Count (TMC), and consumption of healthy food items, including fruits or nuts ($\beta = +0.05$; $P = 0.007$) and vegetables ($\beta = +0.04$; $P = 0.013$). Consumption of fries was associated with lower TMC ($\beta = -0.14$; $P = 0.023$). Eating seafood/fish was related to increased DNA methylation at PEG11/MEST DMR ($\beta = +0.05$; $P = 0.018$). Consumption of pizza and/or fries was associated with increased DNA methylation at IGF2 ($\beta = +0.03$; $P = 0.036$, for pizza; $\beta = +0.05$; $P = 0.033$, for fries) and MEG3-IG DMRs ($\beta = +0.02$; $P = 0.048$, for fries).

**Conclusions:** Our data suggest that dietary habits are associated with differential DNA methylation percentages at imprint regulatory regions in sperm. Notably, at the MEG3-IG DMR we earlier reported a similar magnitude of differential methylation in offspring of obese fathers. Our findings are consistent with the hypothesis that unhealthy lifestyle of a future father affects epigenetic characteristics of his sperm, and consequently influence health in his future offspring. Larger studies are required to confirm our findings.

**PO2.03.08**

**The effect of peri-conceptional maternal folate on DNA methylation at the ZFP57 locus in Gambian offspring**

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**Background:** Season of birth is associated with mortality in a rural Gambian population. After 16 years of age, those born in the rainy season are up to ten times more likely to die prematurely than those born in the dry season. In rural Gambia the rainy and the dry seasons have a direct impact on nutrition and occupational behaviours as well as disease status. The influence of nutritional factors on DNA methylation during foetal development has been suggested as a potential contributing factor to these stark mortality differences. ZFP57 plays a role in establishing genomic imprints in the early embryo and methylation at this gene has been linked to maternal folate concentrations during gestation.

**Methods:** Linear regression was carried out to assess the association between log-transformed maternal folate concentration at conception and DNA methylation ($n = 121$ for both), measured by Z scores of logit-transformed CpG values at the ZFP57 gene locus. ZFP57 methylation was considered at both individual CpG sites and by taking the mean across CpGs at the locus. Covariates available for assessing confounding were limited to maternal age, maternal body mass index and offspring sex. None of these variables satisfied the conditions of being a confounder, and so none were included in any final models. Season of conception (SoC) was then introduced in the regression model, both as an individual parameter and fitted as an interaction with maternal folate concentration, to determine whether this could explain any observed associations.

**Results:** Linear regression models provided no evidence against the null hypothesis of no association between maternal folate concentration at conception and DNA methylation in the ZFP57 gene locus in offspring ($p > 0.6$ for all CpGs), including after adjustment for SoC ($p > 0.4$ for all CpGs). When assessing for interaction between maternal folate and season of conception, a significant interaction was observed ($p = 0.02$). For those conceived in the dry season there was an inverse relationship between maternal folate and DNA methylation (Coefficient = -0.80, 95% CI: -1.62, 0.03, $p = 0.06$), however for those conceived in the rainy season there was a positive association between maternal folate and DNA methylation (Coefficient = 0.36, 95% CI: -0.20, 0.92, $p = 0.2$).

**Conclusion:** Although the overall association between maternal folate and DNA methylation after adjusting for season of conception did not achieve statistical significance, all the coefficients suggested an inverse relationship between folate and methylation. However, we had limited potential to assess the effects of confounding in this analysis. Whilst interesting results have emerged for analyses fitted with an interaction of SoC, we have to be careful in the interpretation of these results given the limited power in this data set.

**PO2.03.09**

**The response of the DNA methylome to maternal overnutrition in the brain of rat offspring in early life and adulthood**

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**Background:** The consumption of a diet high in saturated fat and obesity during pregnancy are known to increase the risk for
offspring to develop a number of adverse health outcomes. In animal models, maternal exposure to high fat diet is associated with dysregulation of the immune system, specifically increasing systemic and neural inflammation. We previously reported gene expression differences in glucocorticoid and immune genes in the brains of adolescent (postnatal day 35) and adult (postnatal day 90) Long-Evans rat offspring from mother rats exposed to a high saturated fat diet 4 weeks prior to conception and throughout gestation and lactation. The offspring of mothers exposed to overnutrition also showed heightened stress responsiveness and increased anxiety, endocrine and behavioural responses linked to the function of limbic brain regions such as the amygdala. These differences could not be attributed to current diet, as all offspring were provided with control diet upon weaning at postnatal day 21. The results highlight the impact of maternal overnutrition on offspring health and brain function. However, biological mechanisms associated with these long-term phenotypic differences remain unknown. Epigenetic modifications, which can modify the transcriptional potential of genes in the absence of variations in gene sequence, have been proposed as mechanisms that may biologically program aspects of phenotype in response to environmental exposures.

**Methods:** We investigated epigenetic modifications associated with maternal overnutrition in the brains of neonatal and adult rats. Dams were fed with HFD during pregnancy and lactation, and were subsequently placed on control diet after weaning. Offspring were sacrificed at postnatal days 7 and 90 and brain regions were sliced out according to taxonomic co-ordinates. Reduced representation bisulfiite sequencing (RRBS) was performed to profile DNA methylation modifications, particularly in gene regulatory elements, in the rat amygdala at postnatal days 7 and 90.

**Results:** While there were methylation differences specific to each period, we found over 1,000 sites that showed significant differential methylation patterns over time (FDR < 0.05). Genes that were associated with these sites were primarily involved in immune response and enzyme regulation according to the Molecular Signatures Database v6.0 (FDR < 0.05).

**Conclusions:** The results of our study provide further evidence of the impact of maternal overnutrition on offspring immune responses. In particular, we detail the DNA methylation differences associated with maternal overnutrition, which may serve to prime offspring for potential immune stressors.

**PO2.03.10**

Epigenetic markers of the intergenerational transmission of stress

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**Background:** Childhood maltreatment has many long-term effects that extend into adulthood, both psychologically as well as physically. In addition, childhood maltreatment may impact following generations, a recognized effect known as the intergenerational transmission of stress. This transmission is thought to occur via changes in child-rearing practices by maltreated parents or by changes in attachment between maltreated parents and their children. Recently, studies have shown that biological mechanisms may play a role as well, with a specific role for stress hormones like cortisol that may influence the epigenetic regulation of both physical and psychological characteristics. An often-studied epigenetic marker is methylation, and both hyper- and hypo-methylation in adulthood have been associated with perinatal stress and childhood trauma. However, when and how these biological mechanisms impact the development of children whose parents have been exposed to childhood trauma remains to be elucidated.

**Methods:** In a longitudinal study of 173 mother-infant pairs, followed since week 37 of pregnancy, we will examine whether retrospective reports of childhood trauma in the mothers are associated with stress-related measures in their children at age 6, and whether any such associations are mediated by changes in prenatal stress, postnatal stress or parenting styles of the mothers. Furthermore, the methylation status of stress-related genes will be examined in the children, to unravel possible underlying biological mechanisms of the intergenerational transmission of stress.

**Results:** Preliminary data will be presented.

**Conclusions:** This study will provide insight in underlying biological and psychological mechanisms in the intergenerational transmission of stress.

**PO2.03.11**

Epigenetic signatures associated with prenatal socio-economic status


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**Background:** The existing literature on childhood socio-economic status (SES) has focused almost exclusively on postnatal influences. However, SES also associates with birth outcomes, suggesting prenatal influences. SES is also associated with antenatal maternal mental health, which strongly predicts the risk of later psychopathology in the offspring. In this study, we use a genome-wide analysis of DNA methylation data from umbilical cord tissue samples to report evidence of an effect of prenatal SES on neonatal epigenome.
Methods: In the Growing up towards Healthy Outcomes (GUSTO) mother-child cohort (N = 977), we interrogated the effects of maternal SES during pregnancy, birth outcomes-related and antenatal maternal mental health-related variables on umbilical cord DNA methylation. Gene pathway analyses were also performed.

Results: Maternal SES was significantly associated with inter-individual variation in DNA methylation. About half of the SES-related VMRs were also associated with birth outcomes or maternal mental health variables. A gene pathway analysis revealed that genes mapped from SES-related VMRs were significantly enriched for pro-opiomelanocortin (POMC) processing pathway in females, but not in males. The POMC pathway mediates behavioral and endocrine responses to stress and is tightly regulated by glucocorticoids. Indeed, we also found that genes mapped to SES-related VMRs in females were enriched for glucocorticoid receptor transcription factor binding sites.

Conclusions: This study provides evidence that maternal SES associates with variation in neonatal inter-individual DNA methylation patterns, suggesting that the development of the fetal epigenome is affected by the socio-economic context of the mother during pregnancy.

PO2.03.12
Comparison of Agilent SureSelectXT Human Methyl and Illumina HumanMethylation Infinium arrays
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Background: The Illumina HumanMethylation Infinium (INF) platform is a well-established method of assessing the methylome and covers ~ 1.6-3% of CpG sites in the genome. In comparison, capture and bisulphite sequence methods can offer increased coverage. The default library for Agilent SureSelectXT Human Methyl (SS) array covers over 9% of the CpGs in the methylome, as well as methylation in a non-CpG context. Researchers undertaking EWAS across a large number of tissue samples have to consider coverage but also sensitivity, margin of error, ease of processing and cost.

We aimed to assess the quality of SS data in comparison with INF data, even at read-depths >100x, suggesting higher resolution INF assesses mostly CpG sites, the SS library captures data on approximately 19-20 million Cs in different contexts, with CpGs more likely to be methylated at all (~57%) compared to CHG and CHH sites (~4%). With a read depth of >20x, hierarchical cluster analysis and principal component analysis was able to differentiate between tissue types and group duplicates together (although samples 3A/B, which had the lowest DNA quantity, appeared more divergent). With regard to agreement in methylation calls between duplicates, 50% of CpG sites were within ±4-6% across the samples. In samples 4A/B, with 30x read depth, 90% of CpG sites methylation calls agreed within 15%. However, in the same pair, INF array has a better level of agreement between duplicate methylation calls, with 98% of CpG sites agreeing within 15%, out-performing SS even at 100x read depth.

To assess the accuracy of SS, 287 CpG sites covered on the SS platform were analysed (using the pyrosequencing current gold standard for assessing CpG methylation) in the same samples. Results from SS were compared to pyrosequencing results and ~95% of CpG sites agreed to within ±15%.

Conclusions: SS easily discerned replicates and tissue types, and differences between replicates suggested high quality data. 1μg of DNA appears to be an adequate input amount. The error between replicates was higher for the SS data than INF data, even at read-depths >100x, suggesting higher resolution for INF. At 30x read depth, SS is likely to cover more than double the number of CpGs available on Infinium EPIC, as well as non-CpG cytosine methylation.

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PO2.03.13

Epigenetic mechanisms linking pre-conceptional nutrition and health assessed in India and Sub-Saharan Africa- the EMPHASIS study

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Background: Animal studies have shown that the peri-conceptional nutritional environment of the embryo affects the establishment of epigenetic signatures regulating fetal development and susceptibility to disease, providing a plausible mechanism to explain the developmental origins of health and disease (DOHaD) in humans. Preliminary evidence from our group and others through observational studies has shown that maternal diet in the peri-conception period predicts DNA methylation patterns in offspring, and that certain genomic locations including those associated with imprinting and metastable epialleles appear to be particularly sensitive. However, a causal link between maternal diet, alterations to DNA methylation status and later life health outcomes is yet to be fully established. The EMPHASIS study will investigate epigenetically mediated links between peri-conceptional nutrition and a range of outcomes measured in children in a randomized controlled trial setting. Insights gained have the potential to make a significant contribution to our understanding of the impact of nutrition on global health and in particular for maternal and child health policy.

Methods: The EMPHASIS study will analyze DNA methylation in children aged 5-9 years, who were born to mothers enrolled in two complementary randomized controlled trials in which mothers were supplemented with micronutrients before conception and into early pregnancy. These are: 1) the Mumbai Maternal Nutrition Project (MMNP), in which women (n = 1100) living in Mumbai slums in India received a daily snack made from micronutrient-rich foods and 2) the Periconceptional Multiple Micronutrient Supplementation Trial (PMMST) in rural Gambia, which supplemented women (n = 350) with multiple micronutrient capsules. We aim to identify DNA methylation differences between children born to the intervention and control groups using the Illumina EPIC array and also pyrosequencing a small number of candidate loci of interest. We will correlate DNA methylation differences with health-related outcomes in the children, including size at birth, post-natal growth, bone growth, childhood body composition, cardio-metabolic risk markers, and cognitive ability. We will be looking for both cross-cohort and cohort-specific effects.

Conclusion: Identifying epigenetic disruptions linking early nutrition to later life health outcomes can ultimately lead to the design of next-generation nutritional interventions for mothers preparing for pregnancy, affecting the health of their children.

PO2.03.14

Epigenetics of developmental conditions and later life ovarian function: A pilot study among British-Bangladeshis

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Background: In prior studies we have shown that developmental conditions influence reproductive health in females. Depending on where they lived as children, Bangladeshi migrant women have different levels of ovarian function. Those who grew up in Bangladesh - with greater exposure to infectious diseases - have consistently lower biomarkers of ovarian function including later menarche, lower reproductive hormone levels and rates of ovulation, and an earlier menopause when compared to those who grew up in the United Kingdom. Lasting epigenetic memories of these early life experiences, including changes in DNA methylation marks, may contribute to this differential reproductive function and raise important questions in the field of epigenetic epidemiology: how stable are such epigenetic memories? Are adult somatic cells, such as buccal epithelial cells, which can be collected without difficulty, suitable for epigenetic screens with the aim to identify early life events, rather than more specific cells, such as ovarian or vaginal tissue which would be invasive to collect? In this ongoing pilot study, we investigate genome-wide and site-specific, cytosine methylation levels in buccal epithelial DNA samples collected from a small, cross-sectional cohort of Bangladeshi migrants living in London.

Methods: Buccal swabs were collected from 40 first- and second-generation, British-Bangladeshi women and genomic DNA isolated. Thirty-two of these DNA samples were analysed using the Infinium MethylationEPIC BeadChip array to interrogate the methylation status of ~ 850,000 cytosine sites. In addition, we established protocols to amplify hairpin bisulfite PCR products to analyse DNA methylation states of CpG/CpG sites on both strands of individual DNA molecules. Such hairpin-PCR data permit the establishment of a Ratio of Concordance Preference (RCP), a new metric to measure epigenetic stability and flexibility of a given genomic locus. Hairpin bisulfite-PCRs were designed for two genes relevant to our project: i) the Luteinizing Hormone/Choriogonadotropin Receptor (LHR) gene, and ii) Progesterone Receptor gene (PGR/NR3C3).

Results: We report results from data derived from the MethylationEPIC BeadChip array approach and the hairpin bisulfite PCRs.
Conclusions: Our migrant studies are unique in the field of human reproductive ecology in examining the potential of the childhood period to influence reproductive function. One of the objectives of our pilot project is to demonstrate the utility of carefully designed, multi-generational, cross-sectional studies to address specific biological questions of interest to epigenetic epidemiologists that can supplement longitudinal studies. Our approach could uncover epigenetic mechanisms influencing regulation of the environmentally sensitive reproductive system in order to illuminate problems across the life course. In addition, one of the CpG sites analysed within the LHR locus contributes to the epigenetic clock, a metric that tracks changes in methylation patterns across the lifespan and correlates remarkably with chronological age. Varying levels of steroid hormones in Bangladeshi women with different life histories make LHR a prime candidate for studies of environmentally mediated epigenetic variability and ageing. Our study will help to shed light on how and why specific periods of the life-course may be vulnerable to epigenetic instability in conditions of life history stress.

PO2.03.15

Homocysteine levels associate with subtle changes in leukocyte DNA methylation: an epigenome-wide analysis

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Background: Homocysteine is a sensitive marker of one-carbon metabolism. Higher homocysteine levels have been associated with global DNA hypomethylation. We investigated the association between plasma homocysteine and epigenome-wide DNA methylation in leukocytes.

Methods: Methylation was measured using Illumina 450k arrays in 2,035 individuals from 6 cohorts. Homocysteine-associated differentially methylated positions (DMPs) and regions (DMRs) were identified using meta-analysis.

Results: Three DMPs cg21607669 (SLC27A1), cg26382848 (AJP1) and cg10701000 (KCNMA1) at chromosome 19, 14 and 10, respectively, were significantly associated with homocysteine. In addition, we identified 68 homocysteine-associated DMRs, the most significant of which was a 1.8 kb spanning domain (TNXB/ATF6B) at chromosome 6.

Conclusions: We identified novel epigenetic loci associated with homocysteine levels, of which specific role needs to be further validated.

PO2.03.16

Epigenetics in early life: placental promoter methylation in DNA repair genes and prenatal exposure to particulate air pollution

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Background: Exposure to particulate air pollution has been linked to carcinogenic insult. DNA repair pathways are able to mend and maintain the correct DNA sequences. However, they have the potential to induce long-term effects when their functioning is compromised. In the context of the developmental origin of disease, we studied the placental mutation rate exemplified by mutations in the Alu gene in association with prenatal PM2.5 exposure. Additionally, we investigated whether placental DNA methylation in the promoter region of key DNA repair genes and tumour suppressor genes was associated with PM2.5 exposure.

Methods: 463 newborn-mother pairs were selected at random from the ENVIRONAGE birth cohort. The placental mutation rate and methylation of key DNA methylation genes including APEX1, OGG1, PARP1, ERCC1, and ERCC4 was assessed. We regressed DNA methylation profiles in association with the prenatal exposure over the entire pregnancy while adjusting for newborns’ sex, ethnicity, maternal age, education, smoking habits, pre-pregnancy BMI, gestational age, date of delivery, and batch effect.

Results: A higher relative placental DNA mutation rate of 2.97% in Alu (p = 0.029) was observed for an interquartile range (IQR) increase of 3.84 μg/m³ in PM2.5 level during the entire pregnancy. The relative promoter methylation of key DNA repair genes in the base excision repair pathway was 9.26% higher in APEX1 (p = 0.008) and 14.79% higher for OGG1 (p = 0.015) for an IQR increment in prenatal PM2.5 exposure. However, no statistical significance was reached for PARP1. In the nucleotide excision repair pathway, a 14.88% increased promoter methylation was observed for ERCC4 (p = 0.005), whereas ERCC1 promoter methylation did not alter significantly with an IQR increment in prenatal PM2.5 exposure. For the same exposure contrast we observed a relative increase of 10.72% (p = 0.001) in methylation for the promoter region of tumour suppressor gene p53, while promoter methylation of tumour suppressor candidate DAPK1 decreased by 13.65% (p = 0.011).

Conclusions: In utero exposure to particulate matter is associated with a higher placental mutation rate in concert with newborn placental epigenetic alterations in key DNA repair and tumour suppressor genes. Future studies are essential to elucidate the persistence of these changes and their role in carcinogenic insults.

PO2.03.17

DNA methylation analysis of neurodevelopmental disorders using disease-discordant monozygotic twins


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Neurodevelopmental disorders such as Autism spectrum disorders (ASD), cerebral palsy (CP) and epilepsy are some of the
most prevalent neurological disorders and are caused by significant damages to the growth and development of the brain or nervous system. Epigenetic modification, such as DNA methylation, has been implicated as both a mediator and potential biomarker for neurodevelopmental diseases. The complex mechanism of action of neurological diseases poses methodological difficulties. Distinguishing the extent of effect of genetics and environment is confounded by a large number of variables. The study of twins, especially monozygotic (MZ) twins, in which genetics, age, sex, parental factors and shared environment are controlled for, has led to significant advances in our knowledge of disease mechanisms. Molecular studies that evaluate the differences in DNA methylation patterns between disease-discordant MZ co-twins open up the possibility of singling out environmental and stochastic effects that contribute to disease aetiology and may facilitate in biomarker development. We are studying DNA methylation within three MZ twin cohorts discordant for a neurodevelopmental disorder. Specifically, cerebral palsy (CP, 15 pairs), autism spectrum disorder (ASD, 22 pairs) and epilepsy (24 pairs). Genome-wide DNA methylation analysis is being performed using Illumina’s Infinium HumanMethylation450 and the EPIC arrays. Statistical and bioinformatics analysis pipelines are used to analyse methylation data. Gene expression and whole genome sequencing data from the cohorts is also being studied, where applicable, to define the genetic networks associated with each disorder. A preliminary analysis of the CP-discordant pairs has been already been performed on DNA from dried blood spots (Guthrie cards) taken at birth. Within-twin pair analysis identified various differentially methylated probes and regions associated gene ontologies such as cell adhesion and inflammation, indicating its significance in CP pathophysiology. This is the first study to access the correlation of epigenomic variations of MZ twins discordant for CP and presents opportunities for future studies of DNA methylation in singletons with CP. Recruitment and methylation analysis using Illumina’s EPIC array for the epilepsy cohort has also been performed. This project hopes to yield informative and powerful results that have implications for research, advice and treatment options for patients suffering from a broad spectrum of neurodevelopmental disorders. Epigenetic analysis at birth can definitively differentiate the cause and effect and may be able to assist in calculating disease risk before the time of onset. Integrating epigenetic data with that from other ‘omic’ platforms will have the power to further refine models of disease mechanisms and biomarkers.

PO2.03.18

Neonatal patterns of DNA methylation differentiate between children who develop early-onset vs low conduct problems: Findings from a prospective, epidemiological birth-cohort

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Introduction: Early-onset conduct problems (CP) are a key predictor of antisocial behaviour and poor mental health across the lifespan. Compared to other children, those who develop early-onset CP show greater genetic vulnerability as well as more severe exposure to environmental stressors – beginning in utero. Yet, little is known about the biological processes through which these genetic and environmental factors jointly influence risk for early-onset CP. Recent work in animals and humans suggests that epigenetic mechanisms, such as DNA methylation, may be at play.

Aims: This is the first study to investigate genome-wide DNA methylation patterns associated with early-onset CP, based on prospective, longitudinal data spanning pregnancy to late childhood. Specifically, we examined (i) whether neonatal patterns of DNA methylation differentiate children who go on to develop early-onset vs low CP; (ii) whether these patterns remain temporally stable and further distinguish between children who persist vs desist in CP over time; and (iii) whether the identified DNA methylation patterns associate with genetic and prenatal risk factors.

Study Population: The study was based on 260 youth (51% female) drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC), who either followed an early-onset (n = 174) vs low (n = 86) CP trajectory between the age of 4-13. All children had available DNA methylation data at repeated time points (Illumina 450k platform; birth: cord blood, age 7: whole blood).

Methods: Data was analyzed in R and Mplus, adjusting for sex and estimated cell-type proportions. First, we ran a genome-wide analysis to investigate DNAmethylation patterns at birth prospectively associated with an early-onset vs low CP trajectory. Significant hits were functionally characterized using ENCODE data and GO pathway analysis. Second, we examined whether these DNA methylation patterns remained significant at age 7, and whether they further distinguished between early-onset children who persist (n = 91) vs desist (n = 83) in CP over time. Third, we investigated potential influences on the identified DNA methylation loci, by testing associations with (i) known genetic variation, and (ii) prenatal exposures (maternal stress exposure, substance use and diet).

Results: Methylomic variation across seven sites at birth (FDR < 0.05) differentiated children who develop early-onset vs low CP, including sites annotated to MGLL – a gene involved in pain perception and endocannabinoid signaling. Sub-threshold associations with MAOA, BDNF and FKBP5 were also observed. These associations were specific to birth (i.e. not significant at age 7), so that DNA methylation patterns in these loci did not further differentiate early-onset children who persist vs desist in CP over time. While none of the identified loci at birth were linked with known mQTLs, several were associated with prenatal exposures.

Conclusions: Findings lend novel insights into epigenetic correlates of conduct problems, highlighting birth as a potentially sensitive window of biological vulnerability for early-onset CP. Given that the postnatal environment is also important for development, future research should examine...
whether environmental experiences during childhood may modify these early epigenetic patterns, moderating risk for long-term CP.

PO2.04 – Pregnancy complications and prematurity

PO2.04.01

Adult pre-pregnancy weight change and risk of developing hypertensive disorders during pregnancy
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Background: While the association of pre-pregnancy body mass index (BMI) and hypertensive disorders during pregnancy (HDP) is well documented, little is known about the relationship between pre-pregnancy weight change over the reproductive course of life and the risk of developing HDP. In a population-based cohort study, we examined the impact of adult pre-pregnancy weight change on the development of HDP.

Methods: We included 2914 women, surveyed about every three years since 1996, from the 1973-78 cohort of the Australian Longitudinal Study on Women’s Health. Women without hypertension or HDP were followed-up between 2003 and 2012. Generalized estimating equations, which account for correlations in repeated pregnancies of a woman, were used to assess the effect of baseline BMI (mean age 20 years) and pre-pregnancy weight change on the incidence of HDP. The full models were adjusted for time-varying (sociodemographic, lifestyle and reproductive) factors.

Results: Over 9 years of follow-up, 301 incident cases of HDP (6.3%) were reported from 4813 pregnancies. Overweight and obese women at the baseline survey were 1.67 [95% CI: 1.3, 2.2] and 2.15 [95% CI: 1.4, 3.3] times more likely to develop HDP than normal weight women, respectively. Compared with stable weight (loss or gain up to 1.5%/year) women, those who gained at least 2.5% weight gain at baseline were 2.24 (95% CI: 1.3, 3.7) times more likely to develop HDP. Women who reported annual weight loss (>1.5%) between baseline and the average age of 24 years were 46% [95% CI: 0.4, 0.8] less likely to develop HDP.

Conclusions: Pre-pregnancy weight gain is associated with an increased risk of HDP, whereas early adult weight loss is associated with lower risk of HDP.

PO2.04.02

The value of the 24-hour proteinuria in evaluating the severity of preeclampsia and predicting its adverse maternal outcomes

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Background: In 2013, ACOG renewed their guidelines of hypertensive disorder in pregnancy and lowered the position of proteinuria in both diagnosis and severity evaluation of preeclampsia. However, large sample clinical data are still lacking in China to support these changes.

Methods: Eleven hospitals in ten provinces across China were chosen, in which 1738 pregnant women complicated by hypertensive disorders of pregnancy (HDP) with the records of 24h-proteinuria were enrolled. They were allocated into four groups: Patients with maximal quantified proteinuria <0.3 g/24h (Group 1, n = 328); patients with maximal quantified proteinuria ≥0.3 g/24h and <2.0 g/24h (Group 2, n = 638); patients with maximal quantified proteinuria ≥2.0 g/24h and <5.0 g/24h (Group 3, n = 353); patients with maximal quantified proteinuria ≥5.0 g/24h (Group 4, n = 419). Logistic regression analysis were conducted to assess the differences in maternal outcomes between different subgroups of 24-hour proteinuria. The multivariable risk prediction model of adverse maternal outcome for HDP was established with ROC curve and its predicted value was assessed.

Results: Thrombocytopenia, severe hypoproteinemia, cerebral or visual symptoms and severe hypertension showed statistical significance after adjustment (P ≤ 0.001). Thrombocytopenia and cerebral or visual symptoms were more frequent in Group 3 and Group 4 than Group 1 and Group 2 but no differences were found between Groups 3 and 4 or Group 1 and Group 2. The renal insufficiency and increased liver enzyme between all groups were similar (P = 0.801 and 0.125 respectively). Maternal complications were more frequent in Groups 3 and 4 than in Groups 1 and 2 (Group 3 vs. Group 1, OR = 3.559 (1.067-10.571); Group 4 vs. Group 1, OR = 3.628 (1.189-11.086); Group 3 vs. Group 2, OR = 2.845 (1.155-7.003); Group 4 vs. Group 2, OR = 3.082(1.304-7.288)). However, no significant difference was found between Groups 4 and 3 or between Groups 2 and 1. The proteinuria ≥2g/24h had an area under the receiver operating characteristics curve (AUC ROC) of 0.668 (95% CI 0.632-0.705) for predicting adverse maternal outcome. After adjusting for the effects of other symptoms, signs and laboratory test, it was the independent risk factor and predictor factor of the adverse maternal outcome (OR = 3.505,
95% CI 2.431-5.049, P < 0.001). The final risk prediction model included: the proteinuria \( \geq 2g/24h \), renal insufficiency, thrombocytopenia, abnormal liver function, palpitation or suf-focation, upper abdominal pain and delivery weeks. It had an AUC ROC of .811 (95% CI 0.781-0.841, P < 0.001).

**Conclusions:** The 24h proteinuria correlates with adverse maternal outcomes, but the difference was approximately 2.0g/24h. It may not be meaningful to distinguish whether the 24h proteinuria was \( \geq 2.0g \) or \( \geq 5.0g \). The proteinuria \( \geq 2g/24h \) is an independent predictive factor of adverse maternal outcomes in preeclampsia, but its individual predictive value is limited. The risk prediction model is effective in assessing the risk of adverse maternal outcomes in patients with HDP.

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**PO2.04.03**

Maternal infections and preeclampsia: a systematic review of epidemiological literature

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**Background:** Globally, preeclampsia affects 5-8 percent pregnancies and is one of the leading causes of perinatal morbidity and mortality worldwide. So far no causative factor has been identified. Recently, efforts have been made to explore the possible role of infection in the development of preeclampsia. We carried out a systematic review to determine the association between *Helicobacter pylori* (*H. pylori*), Cytomegalovirus (CMV) and *Chlamydia pneumoniae* (*C. pneumoniae*) and development of preeclampsia.

**Methods:** We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines and searched PubMed, EMBASE and Web of Science (WoS) for articles in the English language. Search terms included infections, bacterial infections, viral infections, *H. pylori*, CMV *C. pneumoniae*, preeclampsia, eclampsia, pregnancy induced hypertension and gestational hypertension. Additionally, studies were added after manual searches by reviewing the reference lists of the selected articles. Articles included cross-sectional, case control and cohort studies. Eligible studies included those 1) with original data, 2) which used a recognized definition of preeclampsia that followed guidelines of relevant organizations or societies i.e. the American College of Obstetrics and Gynecology, the International Society for the Study of Hypertension in Pregnancy, and the National High Blood Pressure Education Program, 3) which described the techniques of detection of infectious agents or antibodies, and 4) which included at least one of the three microorganisms of interest as exposure. The individual studies were grouped in categories corresponding to the three microorganisms and synthesis of results was carried out accordingly. Some studies did not report odds ratio (OR) so we had to calculate using the available information. We assessed studies for risk of bias.

**Results:** Initial search results identified 1031 studies. After applying selection criteria 16 studies were eligible for the full review. These studies used either serological tests and/or PCR for the evidence of infection. Four studies explored the association between *H. pylori* and preeclampsia and each found a significant association [Adj OR: 9.2 (2.8-30)], [OR: 2.9 (1.1-7.8)], [OR: 3.8: (1.2-11.8)], and [AdjOR: 2.7 (1.1-6.6)]. Of the four studies investigating the relationship between CMV and preeclampsia, two showed significant association [OR: 1.9(1.4-2.7)] and [OR: 7.2 (p.02)] while three out of ten studies found a significant association between *C. pneumoniae* and preeclampsia [AdjOR: 5.3 (1.4-20)], [AdjOR: 3.1(1.8-7.9)] and [OR: 4.1(1.1-15.6)]. Maternal age and parity were the most commonly controlled factors. Not all studies reported or controlled for the confounding factors. The risk of bias (ROB) assessment found six studies at low ROB, nine at serious risk and one had moderate risk; bias due to confounding was the most common serious flaw.

**Conclusions:** Some evidence exists which supports the relationship between PE and maternal infections especially for *H. pylori* and to a lesser extent for CMV. The role of *C. pneumoniae* in the development is not supported strongly by the existing literature. More research is needed particularly for the role of CMV and *C. pneumoniae* to develop a strong and conclusive body of evidence.

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**PO2.04.04**

Low birth weight and prematurity trends from 2005 to 2014: experience from a public maternity hospital in Athens, Greece

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**Background:** Low birth weight (< 2500 grams), due to preterm birth or restricted fetal growth, is an important predictor of neonatal mortality/morbidity, inhibited growth and
cognitive development, as well as chronic diseases later in life. This study aimed to examine changes in low birth weight rate from 2005 to 2014 and investigate related parameters.

**Methods:** Our retrospective study reviewed birth records of 14,923 neonates, born in a public maternity hospital in Athens, Greece, concerning maternal age, delivery mode and neonatal gender, birth weight, gestational age factors. Univariable analysis tested the association of birth weight and gestational age with time periods 2005-2009 and 2010-2014. Multivariable logistic regression analysis identified factors independently associated with low birth weight.

**Results:** During the 10-year study period, low birth weight rate increased from 6.7% to 11.5%. Prematurity rose from 8.1% to 12.7%, comprising mainly late preterm (34-36+6 weeks) neonates (6.3% to 9.2%). Furthermore, during the same period, the rate of cesarean sections (CS) rose from 41.8% to 55.5% and maternal age ≥ 35 years from 21.2% to 36.7%. Comparing the time period 2010-2014 to 2005-2009, a 21.3% increase of low birth weight (p < 0.001) and an 11.8% increase of prematurity rate (p = 0.027) was noted. Among term neonates (aged ≥ 37 gestational weeks), a 17.2% increase in low birth weight - though not statistically significant (p = 0.150) - was also observed. Multivariable logistic regression analysis identified female gender, maternal age ≥ 35 years and CS to be independent risk factors for low birth weight.

**Conclusions:** In our 10-year study, a statistically significant increase in low birth weight and prematurity was associated with female gender, maternal age ≥ 35 years and birth by CS. Although these findings could be related to high risk pregnancies and early induction of labor, other unidentified parameters, such as maternal diet, physical activity, stress, environmental pollution and particularly socioeconomic factors (economic crisis from 2009 and onwards) should be considered, taken that full-term neonates also presented with a decline in birth weight. Low birth weight associated with infant catch-up growth may have long-term consequences on adult health; therefore, efforts to combat decreased fetal growth and associated factors are urgently needed.

**PO2.04.05**

**Z-score differences for assessment of growth based on cross-sectional growth charts do not reflect weight gain in preterm infants**

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**Background:** Growth of preterm infants is often assessed by z-score differences and it is suggested that a change in z-score reflects weight change. Current z-scores are calculated using references based on birth weights of pregnancies with known gestational age (GA). A significant proportion of pathological pregnancies skews the distribution of percentiles and affects the z-score calculation. Larger distances are seen between percentiles and standard deviations from 24 to 30 weeks followed by a decrease until term age. A physiological explanation for the resulting fluctuation of weight gain suggested when following the 3rd and 10th percentile curves is lacking. It is hypothesized that the current z-score differences approach has a systematic error indicating growth restriction in infants even they grow with desired rates.

**Objective:** To test the hypothesis, in a large-scale data set, that the assessment of growth by z-score differences in preterm infants is affected by GA and birth weight percentile reference data.

**Methods:** This observational study included 6832 (male = 3429) VLBW infants from German Neonatal Network (2009 to 2015). For each infant, z-score differences and weight gain from birth to discharge was calculated. Weight gain expressed as ratio of weight gain/reference growth rate (50th percentile, Fenton 2013) for the corresponding observation period. Primary outcome is the homogeneity of z-score differences versus weight gain.

**Results:** In male infants the correlation between z-score differences and weight gain is weak R² = 0.56, the inter-individual variation is high, up to a factor of 5 with a median (IQR) deviation from line of identity of 0.36 (0.17;0.58). Z-score differences are affected by birth weight percentile and GA. A significant proportion n = 761 (22%) of infants with negative z-score differences had higher weight gain than in utero (Fig.1A). An adjusted z-score differences that reduces the confounding effect of GA decreased the deviation to 0.05 (0.02;0.08) from line of identity (R² = 0.99) (Fig.1B). Analysis for females showed similar results.

**Conclusions:** This study supports the hypothesis that z-score differences, which is used to assess growth, is confounded by skewed reference data. This is primarily due to the fact that cross-sectional data of interrupted pregnancies with pathologies have been used to create birth weight charts. New z-score references optimized for GA showed a high correlation with weight gain and should be used when growth of infants born at different GA is compared.
Child protection actions among children born preterm - the contribution of developmental disorders and intellectual disability

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Background: Prematurity predisposes to out-of-home care (OHC) as a child protection action, in particular during early childhood. Furthermore, children born preterm have more often developmental disorders or intellectual disabilities (DDID), which may contribute to that risk. The aim of this study was to assess whether child’s DDID diagnosed in childhood contributes to preterm subjects’ more frequent entries to OHC.

Methods: We identified singletons (n = 223 615) of five gestational age (GA)-categories born between Jan 1st 1987 and Sep 30th 1990 from the Finnish Medical Birth Register. Register of Child Welfare provided follow-up data, since Jan 1st 1991, (7650 first placements outside home, 3.4%) until 18th birthday. The data on any DDID (n = 1 139, 0.5%) came from The Finnish Care Register for (Inpatient) Health Care. [Table] We analyzed the effect of GA on OHC by Cox regression, stratified by index child’s (IC) birth year.

Results: We compared hazard ratios (HR) for OHC to those born at full term (39 to 41 gestational weeks) unchanged in other GA-categories, to 1.41 (CI; 1.17-1.70) in early preterm group leaving HRs < 0.001 for all. When further adjusted for DDID, HR attenuated to 36), and 1.13 (CI; 1.07-1.20) for early term (37 to 38), P-value (CI) for placement were 1.50 (CI; 1.24-1.81) for early pre-term (23 to 33weeks), 1.27 (CI; 1.14-1.41) for late preterm (34 to 36), and 1.13 (CI; 1.07-1.20) for early term (37 to 38), Pvalue < .001 for all. When further adjusted for DDID, HR attenuated to 1.41 (CI; 1.17-1.70) in early preterm group leaving HRs unchanged in other GA-categories, P value < .001 for all.

Conclusions: As compared to full term children, children of other GA-categories are predisposed to out-of-home care. Only a small portion of that risk of early preterm birth may be mediated via child’s developmental disorders and intellectual disabilities.

First trimester bisphenol and phthalate urine concentrations, placental dysfunction, blood pressure patterns during pregnancy and risks of gestational hypertensive disorders

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Background: Exposure to bisphenols and phthalates during pregnancy is hypothesized to lead to early placental maladaptations and subsequent increased risks of higher blood pressure in pregnancy and gestational hypertensive disorders.

Objective: To examine associations of urinary bisphenol and phthalate concentrations in early pregnancy with placental function markers, blood pressure patterns during pregnancy, and risks of gestational hypertensive disorders.

Methods: In a population-based prospective cohort study among 1,431 pregnant women, we measured bisphenol and phthalate urinary concentrations in early pregnancy [gestational age median 13.1 weeks (inter-quartile-range 12.1–14.5)]. Placental angiogenic markers (placental growth factor (PIGF), soluble fms-like tyrosine kinase (sFlt)-1), placental vascular function measures (umbilical artery pulsatility index (PI), uterine artery resistance index (RI), notchting, and placental weight) and blood pressure were measured in different trimesters. Information on gestational hypertensive disorders was obtained from medical records.

Results: First trimester bisphenol concentrations were not associated with placental angiogenic and vascular function measures or blood pressure patterns during pregnancy. Each log unit increase in high molecular weight phthalate metabolites was associated with placental and maternal haemodynamic outcomes. The observed association of first trimester phthalate metabolites concentrations were not associated with gestational hypertensive disorders.

Conclusion: First trimester bisphenol and phthalate concentrations was not consistently associated with placental and maternal haemodynamic outcomes. The observed association of first trimester phthalate concentrations with placental angiogenesis biomarkers needs further replication.
Background: Twin pregnancies are at significantly increased risk for prematurity and intrauterine growth restriction (IUGR), two conditions characterized by low birth weight, which is considered a risk factor for impaired nephrogenesis, normally completed between 32 and 36 weeks of gestation. At the end of this period, each kidney has a number of nephrons that can vary widely, in correlation with birth weight. Once the nephrogenesis has stopped, there is no possibility of forming new nephrons later in life. In this study we investigated renal volumes and urinary Cys-C in a cohort of twins classified in different groups (preterm and at term, with and without IUGR) in order to evaluate the single or the combined impact of prematurity and IUGR on renal development /damage, eliminating maternal conditions.

Methods: this study was carried out on 30 twins at 30-40 days of corrected age. Urinary Cys-C levels were measured using The ELA DetectX® Human Cystatin C kit. Whole kidney and renal cortex volumes were assessed with ultrasounds (Vocal II; Software, GE).

Results: Multiple regression analysis showed the strongest correlation between renal volume and birth weight (p < 0.00001). IUGR twins showed urinary Cys-C levels significantly higher than those found in the respective preterm twins, in conjunction with a reduced renal volume.

Conclusions: the increased levels of Cys-C in the urine of neonates with IUGR, significantly associated to a reduced renal/renal cortex volumes. IUGR condition affected the volume and the renal functionality in a more definitive way than prematurity; a high percent of preterm twins not affected by IUGR, at 30-40 days of corrected age, did not show statistically significant difference from newborns at term.

PO2.04.09
On the consequences of adapting pregnancy to adverse environments: implications of ancestral placental malaria for pregnancy complications and cardiovascular disease
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Introduction: It is notable that gestation has not received more attention in the context of human evolution and genetics, given that pregnancy has emerged as a period with potential to influence disease development across generations. Nonetheless, Homo sapiens has, like all species, continuously adapted to the local environment. The most prominent force of such recent selection is arguably P. falciparum, which has been endemic in Africa for 10,000 years, is the most lethal of human malaria parasites, and the cause of placental malaria. The selection of traits for hemoglobinopathies due to their protective effect against P. falciparum infection is well known. However, as placental malaria increases the risk of fetal loss, the parasite is not only a cause of clinical malaria in pregnant women but may also affect the natural selection of fetuses. Through altered balancing selection, this has the potential to also influence the risk of pregnancy complications and cardiovascular disease (CVD) in the offspring. Noticeably, populations of Sub-Saharan ancestry appear to have increased risk of several pregnancy complications and CVDs. Furthermore, as several pregnancy complications are associated with increased risk of maternal CVD later in life, pregnancy has been framed as a “stress-test” of the maternal cardiometabolic phenotype. Thus, synthesizing knowledge of placental development, placental malaria, and CVD development with evidence of genetic adaptation in certain populations has the potential to inform etiological research on pregnancy complications and CVD.

Proposed Framework: I propose that ancestral polygenic adaptation to placental malaria contributes to a higher relative risk for pregnancy complications in an environment free of P. falciparum. Furthermore, as many genes have pleiotropic effects throughout the life course, ancestral adaptation contributes to increased risk of CVD compared to individuals with no ancestral exposure. The proposed framework comprises three main components. The first component – placental malaria as a force of natural selection in pregnancy – has been previously suggested, but has not been comprehensively studied. The second component – the specific consequences of ancestral polygenic adaptation to placental malaria for disease development – has not previously been suggested. The third and final component – the potential to leverage evidence of positive selection in the genome of populations ancestrally exposed to placental malaria to better understand the cause of pregnancy complications and CVD – is novel and have potentially broad implications. These insights could facilitate the identification of biological pathways relevant for pregnancy complications and CVD through study of positive selection in populations ancestrally exposed to placental malaria.

Conclusion: I propose that ancestral adaptation of pregnancy to placental malaria contributes to a higher relative risk of pregnancy complications and CVD through pleiotropic effects of relevant genes. For this framework to be relevant, it is important to acknowledge the historical context of hypotheses based on ancestry, avoid unfounded determinism, and separate evidence from speculation. Nonetheless, the proposed hypothesis might facilitate further insight in the causal architecture of pregnancy complications and CVD, potentially leading to a reduction of disease regardless of ancestry.

PO2.04.10
Role of maternal infections in the development of preeclampsia in Michigan USA
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Background: Preeclampsia (PE) is a pregnancy-related condition which affects maternal and newborn health significantly. No causative factor has been identified. Some research has suggested a possible role for past infection with Helicobacter pylori, cytomegalovirus and/or Chlamydia pneumoniae in the development of PE. We conducted this research to explore the role of these microorganisms in the development of PE.

Methods: We conducted a nested case-control study in Lansing, MI, USA using The Archive for Child Health (ARCH), a pregnancy cohort of about 900 women with enrollment at about 13.4 weeks of gestation, and archived blood and urine in pregnancy. We matched cases of PE (diagnosis from birth certificate and medical record) to unaffected controls on: maternal age (±3 years), maternal race, parity and gestational age at first pregnancy blood withdrawal. Using conditional logistic regression, we examined the association between immunoglobulins (IgGs) of the three microorganisms and other covariates of interest (especially smoking and BMI) and PE status.

Results: 21 cases were matched to two to three controls each (52 controls) Two (9.5%) cases and three (5.8%) controls were found positive for anti H. pylori IgGs in plasma; Seven cases (33.3%) and 15 (28.9%) controls had anti CMV IgG in plasma; thirteen (62%) cases and 25 (48%) controls were positive for anti C. pneumoniae IgGs.

Bivariable analysis showed that the odds of being smoker among preeclamptic women was 0.6 times of the odds of being smoker among women without preeclampsia (mOR: 0.6; 95%CI:0.2-2.0); similarly, preeclamptic women in comparison to controls were 8 times more likely to have pre-pregnancy BMI > 30 vs pre-pregnancy BMI < 25 (mOR:7.9; 95%CI:1.6-39.5). Multivariable conditional analysis found non-significantly increased odds of cases being positive for anti H. pylori IgGs (mOR:2.4; 95% CI: 0.2-32.2) and C. pneumoniae IgGs (mOR: 2.3; 95% CI: 0.6-9.1), but there was no higher prevalence of anti CMV IgGs in cases than controls (mOR: 1.4; 95% CI: 0.3-5.6). All analyses controlled for mother’s education, household income and depression. We did not control for pre-pregnancy BMI at final model as it was found as a collider.

Conclusions: Past infection, as determined by presence of IgGs to H. pylori, CMV, and C. pneumoniae in early pregnancy did not show associations with the development of PE in this study. In the future, such studies should be carried out with a larger sample size especially in populations where the prevalence of these infections is high. Future studies should also include serology for anti-CagA antibodies for more extensive exploration of the role of H. pylori, and consider examination of placental tissue for the presence of microbial DNA.

PO2.04.11

Morphometrical placental analysis of maternal hypertensive disorders of pregnancy in a Latin American population

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Background: The multiple aspects of placental growth during critical periods of gestation may be assessed by placental measures, which are also related to specific functional characteristics. Thus, they are useful for epidemiologic studies as indicators of intrauterine developmental aggressions. Placenta weight (PW) and birth weight (BW) may be markers of different types of hypertensive disorders of pregnancy. Although PW is not the ideal indicator of placental function, it frequently is the only one available for population studies. Given the relevance of studies that relate hypertension during pregnancy, alterations in placental growth measures (PGM) and repercussion to newborn health, it is justified to verify such outcomes in different populations. Thus, the objective was to describe placental measures according to hypertension (HT) disorders during pregnancy of a Brazilian birth cohort.

Methods: This was a cohort study of placental morphometry and fetal outcomes of 954 pregnancies at a university hospital in Ribeirão Preto, São Paulo, Brazil, in 2010. Information about clinical and obstetrical characteristics, labor, placental measures placental growth measures and neonatal outcomes were obtained from interviews of the mothers and medical files. The HT types considered were chronic (CHT), gestational (GHT), preeclampsia (PRE) and CHT associated with PRE (CHT + PRE). The following manual measurements of the placenta were performed, according to standard methods: PGM (weight [PW, g], larger and smaller diameters [cm], and thickness [cm]). In addition, eccentricity, shape, area (cm2), volume (cm3), BW to PW ratio and PW to BW ratio were determined. Associations between BW and PGM in pregnancies with and without HT were investigated by multiple linear regression.

Results: Mean maternal age was 27.2 years and mean BMI was 26 kg / m2; 51.7% of the mothers completed 9 to 11 years of education, 39.6% were primiparous, 18.6% smoked, 22.2% had HT, 16.1% had diabetes, and 88.1% performed adequate prenatal care. The frequency of HT types during gestation were: 6.5% CHT, 7.6% GHT, 6.1% PRE, 2.0% CHT + PRE and 77.8% without HT. Mean BW was lower in the hypertensive group (2931g) than in the normotensive group (3078 g, p = 0.016). Mean gestational age was slightly lower with HT (37.5 w) than without it (38.1 w, p = 0.029). There was no difference in the rate of prematurity (p = 0.223). PW, largest and smaller diameters, area and BW to PW ratio were statistically different between the five groups, with the lowest values for preeclampsia; the reminder measures had no difference. BW and PW were correlated in the absence of HT (r = 0, 65, p < 0.001), and greater in the presence of HT (r = 0, 86, p < 0.001). Consequently, in the HT group, 65% of BW variability was accounted for PGM (p < 0.001), and increased...
Subjects and methods: Preterm birth is known to be associated with health and disease later in life. However, significance or influence of early postnatal growth patterns on health status in adulthood is not well known. Therefore, we studied relationship between parameters of body size at birth and those at 3 years of age.

Subjects and methods: Subjects are preterm infants (<32wk gestation) born and admitted at Perinatal Center of Tokai University Hospital during one year period of 2012. They were followed up after discharge until 3 years of age at a follow-up clinic. Data of body weight (BW), body length (BL) and head circumference (HC) were obtained at birth, 2, 6, 12 and 36 months after birth. Correlations of SD scores for BW, BL and HC were analyzed between values at birth and 3 years, and between those at birth and changes in 3 years after birth.

Results: Data from 23 patients (10 males, 13 females) were obtained. Their gestational age ranged 23.1-31.4 (median 28.3) weeks and birth weight 524-1736 (median 1124) grams. There were no significant correlations in all variables between values at birth and at 3 years. However, there were significant inverse correlations between values at birth and changes in 3 years (BW, r = -0.71, p = 0.0001; BL, r = -0.57, p = 0.005; HC, r = -0.43, p = 0.04).

Conclusions: Catch-up growth was almost complete by 3 years after birth. Some infants already showed growth impairment at birth (fetal growth restriction) which never showed catch-up in 3 years. Especially in extremely preterm infants (< 28 wk gestation), influence of postnatal factors on growth should be taken into consideration.

PO2.04.14

Associations between dietary behavior and preterm birth in the Norwegian Fit for Delivery study - interaction with offspring gender

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Purpose: More boys than girls are born prematurely, defined as before completed 37 weeks of pregnancy. The etiology underlying this phenomenon remains unknown, but having a healthy dietary pattern during pregnancy has been associated with lower risk of preterm birth. The purpose of the present study was to investigate potential gender differences in associations between maternal diet during pregnancy and risk of preterm birth.

Methods: 591 healthy nulliparous women participating in the Norwegian Fit for Delivery study were included in this prospective observational analysis. An early pregnancy diet score was constructed from a 43-item food frequency questionnaire completed by participants in early pregnancy. The score comprised 10 subscales broadly reflecting meal regularity, beverages, fruit/vegetables, sweets/snacks, portion size, satiety, and awareness of food labeling. The score ranged from 0-10 and was used to categorize participants into low, medium or high diet quality, respectively. Odds of preterm birth with high and medium vs. low diet score was assessed in a bivariate logistic regression model including an interaction term with diet score*offspring gender.

Results/findings: A total of 34/591 (5.8%) were born prematurely; 24 (71%) boys and 10 (29%) girls. Prevalence of preterm birth was 7.5% among boys and 3.7% among girls. High vs. low diet score was protectively associated...
with preterm birth for both genders combined (OR: 0.24; 95% CI: 0.10-0.57; p = 0.001). Because of a significant interaction with offspring gender (p = 0.035), we ran the analysis stratified by gender. The association between diet and preterm birth in pregnancies with male offspring remained strong (high vs. low score OR: 0.30; 95% CI: 0.12-0.75; p = 0.010, and medium vs. low score OR: 0.09; 95% CI: 0.02-0.42; p = 0.002). There were no preterm births in female pregnancies with high diet score. Medium vs. low early pregnancy diet score was not associated with lower odds of preterm birth of female offspring (OR: 0.70; 95% CI: 0.20-2.52; p = 0.588).

Conclusions: Both high and medium vs. low early pregnancy diet score was associated with lower odds of preterm birth in pregnancies with male offspring. No preterm births occurred in female pregnancies among women with high early pregnancy diet score. Medium vs. low early pregnancy diet score was not associated with preterm birth among female offspring. Maternal diet quality may affect risk of preterm birth differentially according to offspring gender.

PO2.04.15
Maternal exposure to alcohol and nicotine: Is there an effect on chronic disease development at 5-6 years?
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Background: The increase in the prevalence of early signs of non-communicable diseases (NCD) in children is alarming. It can partly be explained by the thrifty phenotype hypotheses, where poor prenatal conditions, nutrition and breastfeeding play vital role in the development of NCDs. These babies have a high prevalence of overweight, obesity and central obesity as adolescents and eventually as adults. Furthermore, children who had rapid infant weight gain are at increased risk for diabetes and cardiovascular disease (CVD) risk factors later in childhood. Small for gestational age (SGA) offspring are often leptin and insulin resistant. Maternal high energy diets during gestation cause offspring to have an impaired hypophagic response to insulin as adults thus reducing the functioning of the arcuate nucleus (ARC), the predominant appetite regulatory site in the brain, neuronal response to leptin and insulin and this results in hyperphagia. In addition epigenetic modifications play a role in determining susceptibility to metabolic diseases. This phenomenon is pronounced during developmental plasticity and shapes the phenotype of organisms.

The aim of project was to identifying the associations between alcohol and nicotine use during pregnancy on birth outcomes, pancreas and kidney size increase in visceral fat and aorta and carotid intima thickness and possible associated risk factors for chronic disease at 5-6 years of age.

Methodology: A prospective cohort study including 340 children aged 5-6 years from the Safe Passage Study who were assessed including anthropometric measurements (weight, height, skinfold thickness, waist and hip circumference). Kidney and pancreas size, visceral fat, aorta and carotid intima thickness using were assessed using ultrasonography. Clinical observations included blood pressure, mean arterial pressure (MAP) and heart rate (HR). The association between the effect of maternal exposure to nicotine and alcohol and organ size was determined as well as the association between organ size and anthropometric and blood pressure, MAP and HR.

Results: Birth weight was significantly lower in the nicotine group when compared to the alcohol exposure group (2844 ±610; 3166 ± 482; p = 0.016). Birth weight was significantly associated with waist circumference in mothers who smoked and used alcohol moderately-continuously during pregnancy (r = 0.301; r = 0.700 at p < 0.01) respectively. However in the exposed group waist circumference showed a stronger correlation with visceral fat compared to the unexposed group (0.539 vs 0.472 at p < 0.01). Aorta intima thickness showed a significant correlation with waist circumference (WC) and in the exposed group WC correlated significantly with systolic blood pressure (0.139 P < 0.01). The difference in pancreas head size almost reached significance if compared between those exposed vs the unexposed.

Conclusions: The results show that the effects of maternal exposure to alcohol and nicotine during pregnancy on birth outcome as well as on organ development had significant consequences for chronic disease risk in later life. These observations were already visible at 5-6 years.

PO2.04.16
Loss of intrinsic tone and impaired vasodilative reaction in Aa. interlobares may contribute to prospective nephron damage in IUGR rats
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Background: Intrauterine growth restriction (IUGR) is a risk factor for arterial hypertension and renal impairment in later life. In industrial countries, placental insufficiency causes the majority of IUGR cases. This study had the aim to identify renal vascular mechanisms potentially contributing to prospective nephron damage in IUGR subjects.

Methods: Pregnant Wistar rats underwent bilateral uterine vessel ligation (LIG) on gestational day 19. Untreated dams served as controls (C). Continuous telemetric measurement of intraaortal blood pressure, heart rate and activity was started in postnatal week 6. In week 9 of life, metabolic examinations were performed for 24 hours. Male animals were sacrificed at the age of 10 weeks. Myographic examinations were carried out in Aa. interlobares and Aa. mesentericae.

Results: LIG animals showed significant (p < 0.01) IUGR without postnatal catch-up-growth. In postnatal week 9,
activity and heart rate were similar, but systemic blood pressure was increased between 5 to 8 mmHg. Metabolic examinations showed significantly (p < 0.05) elevated serum urea and potassium and increased proteinuria, but similar glomerular filtration rate. Mesenteric vessels depicted a significantly reduced reactivity to adrenomedullin. In Aa. interlobares, acetylcholine induced a significantly accelerated vasodilatation. Most interestingly, the physiological increase in intrinsic tone after passive dilatation was completely blunted (p < 0.01) in LIG animals. 

Discussion: Reduced reaction to adrenomedullin in mesenteric vessels might contribute to increased systemic blood pressure after IUGR. Increased sensitivity to acetylcholine and concurrent complete loss of intrinsic tone in interlobaric vessels may predispose to “glomerular flooding”, resulting in proteinuria and probable nephron damage in later life.

PO2.05 – Mental health and socio-economic factors
PO2.05.01
Emotional Status of non-Indigenous Australians from adolescence to young adulthood
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Background: Almost half (45.5%) of Australian adults experience mental illness (psychological distress, affective or substance use disorder) at some point in their lifetime. Although present across the life span, the most vulnerable time begins in adolescence and young adulthood (16 to 24 years). Of particular concern, adolescents and young adults appear to be reluctant to seek advice on how to cope with problems or present to health care services for general health checks, limiting opportunities for early identification of mental illness.

Methods: Non-Indigenous participants from the Darwin, Northern Territory, Australia based Top End Cohort study were recruited in 2007-2009 at age 16-20 years (n=196). Follow-up occurred in young adulthood at age 22-27 years (n=117). Emotional status was assessed at both time points by Kessler-5 and Perceived Stress Scale, along with substance use including alcohol. Analysis was restricted to those with complete data at both time points (n=100). High level of psychological distress was defined as Kessler-5 score ≥ 12 and high perceived stress was defined as ≥ 11 (internal reference, 75th centile).

Results: Women reported higher rates of psychological distress in both at adolescence and young adulthood compared to men. The rate remained the same in women over time; however rates of psychological distress increased in men as they got older. Participants with psychological distress reported significantly higher perceived stress levels both in adolescence and young adulthood, irrespective of gender. After adjusting for gender, those distressed in adolescence were more likely to be distressed in young adulthood (OR 3.78; CI 1.47, 9.74), with a similar trend seen with perceived stress (OR 2.61; CI 0.98, 6.94). A third of participants in adolescence drank alcohol at least once a week with this rate increasing to over half in young adulthood, irrespective of gender. Alcohol use was not associated with distress or perceived stress at either time point.

Conclusions: A third of young adults in this cohort had psychological distress, commencing in adolescence and continuing into young adulthood. The high rate of distress seen in this cohort, almost three times higher than the national rate for non-Indigenous young adults of a similar age, highlights the need for tailored programs addressing wellbeing concerns and lifestyle behaviours commencing in, or before, adolescence. A positive association between psychological distress and perceived stress was evident, suggesting programs should be holistic and examine the underlying causes of stress. Early detection and treatment in adolescence can reduce the long term implications of mental health disorders.

PO2.05.02
Association of Depression and Life Satisfaction with Low Resilience among married women of Karachi, Pakistan
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Background: The concept of resilience is very crucial in promoting positive psychological well-being. However, this construct was never looked among married women of Karachi, Pakistan. Therefore, this study aimed to assess the prevalence and the associated risk factors of resilience in Pakistan. This was the secondary objective of our original project, whose primary objective was validation of resilience scales.

Methods: It was a cross-sectional survey, using the Wagnild Resilience Scale (RS) to assess resilience, Beck Depression Inventory II (BDI-II) for measuring depression and Trait Wellbeing Inventory for determining Life Satisfaction. The

Rates of psychological distress, perceived stress and substance use in adolescence and young adulthood by gender

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sample size (n = 636) for this study was achieved on the basis of our primary objective. Systematic sampling was employed to enroll participants of aged 20 to 40 years living in two urban squatter settlements of Karachi, Pakistan. Prevalence ratio (PR) was computed with their 95% confidence interval.

**Results:** A total of 636 married women participated in the study. The average age of females with low resilience was 29.8 (± 5.7) whereas the mean age of females with high resilience was 31.1 (± 5.7). The prevalence of low resilience among women was 21.9%. Moreover, the prevalence of depression among low resilience group was 43.9% whereas the mean life satisfaction score among females with low resilience was lower than females with high resilience. The females who had low resilience were younger and had no formal/informal education as compared to their counterparts. After controlling for other variables, the prevalence of low resilience was 1.78 times more among depressed females as compared to the non-depressed with a 95% CI: (1.27-2.51). Moreover with every one unit increase in the life satisfaction scores, the prevalence of low resilience decreased 9%. Furthermore, age and informal schooling were also found to be significantly associated with resilience.

**Conclusion:** Depression and life satisfaction are the potential modifiable risk factors for resilience and hence we can improve resilience through interventions that may focus on reducing depression and improving satisfaction towards life. Our study recommends that health care professionals should be educated about these modifiable risk factors to bring about a change in the society and reduce the mental health illness by promoting constructive adaptation.

**PO2.05.03**

The associations of maternal mental health and stress in pregnancy with offspring wheezing and infections

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**Background:** Maternal depression, anxiety and stress in pregnancy have been associated with a wide range of negative outcomes in childhood. Among these are wheezing disorders, as confirmed by a recent meta-analysis (Van De Loo et al, Eur Respir J 2016). In the framework of the Piccolipiù birth cohort we studied the relationship between maternal mental health and stress in pregnancy assessed by the Twelve-item General Health Questionnaire (GHQ-12) and wheezing disorders and infections in 2-years old children. The GHQ-12 is a self-administered screening instrument for mental distress or minor psychiatric morbidity with a main focus on depression. validated worldwide (Goldberg et al, Psychol Med 1997)

**Methods:** Piccolipiù birth cohort started the recruitment in 2011 in 5 centers (Turin, Trieste, Florence, Viareggio and Rome) in Italy. Of the 3338 infants enrolled, 2382 children with at least 24 months of age were analyzed for this study so far. Mothers filled in the GHQ-12 at the end of pregnancy and when the child was 12 months old. The GHQ-12 items, describing mood states over the previous four weeks, were code according to a 4-level Likert scale and then collapsed into two categories (coded 0-1).

Maternal stress was defined as a score of ≥ 5. The relationship between a GHQ12 score ≥ 5 in pregnancy and outcomes was assessed by multivariable logistic regression analyses adjusted for a number of potential confounders (see Table). As mental disorders in pregnancy and stress often continue after birth, in a sensitivity analysis we adjusted also for maternal GHQ-12 at 12 months after delivery. We further adjusted for potential mediators: birth weight, cesarean section, breastfeeding at 6 months, and postnatal maternal smoking.

**Results:** Maternal mental distress (GHQ-12 ≥ 5) had a prevalence of 16.6% during pregnancy, and 6.4% one year after delivery. The prevalence of the offspring outcomes at 12-24 months of age were: wheezing 17.7%, recurrent wheezing 10%, lower respiratory tract infections 21.9%, gastroenteritis 24%. Crude and adjusted associations between maternal stress in pregnancy and outcomes are shown in the table. The adjustment for GHQ-12 at 12 months after delivery and for potential mediators did not change the estimates.

**Conclusions:** We found an association of maternal psychiatric morbidity and distress in pregnancy with offspring wheezing and common infections in infancy. The associations remained also after accounting for postnatal maternal stress. The effects of the combination of prenatal and postnatal maternal distress will be further explored by analyzing separately GHQ-12 scores in different exposure time-windows.

**Table:** Associations between GHQ-12 during pregnancy (cut-off 5) and several outcomes at 12-24 months

<table>
<thead>
<tr>
<th>Outcomes N</th>
<th>OR crude (95% CI)</th>
<th>OR adj (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any wheezing 394</td>
<td>1.65 (1.25;2.17)</td>
<td>1.50 (1.13;1.99)</td>
</tr>
<tr>
<td>Wheezing ≥ 2 episodes 222</td>
<td>1.4 (1.00;2.02)</td>
<td>1.27 (0.88;1.83)</td>
</tr>
<tr>
<td>Lower respiratory tract infections 488</td>
<td>1.37 (1.06;1.79)</td>
<td>1.33 (1.02;1.75)</td>
</tr>
<tr>
<td>Gastroenteritis 534</td>
<td>1.53 (1.19;1.97)</td>
<td>1.53 (1.18;1.97)</td>
</tr>
</tbody>
</table>

* Adjusted for maternal age, citizenship, maternal body mass index, smoking during pregnancy, educational level, parity, maternal history of asthma or atopy, child’s sex, season of birth and center.
PO2.05.04

Adversity in childhood and maternal depression in pregnancy

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Background: Mental health issues during perinatal period result in significant morbidities in women. About one-third of the pregnant women in the Western world experience depression or anxiety during this period. Evidence shows that depression during pregnancy can act as a mediator for postpartum depression. In turn prenatal depression has been found to be associated with previous history of depression and anxiety. This reflects a continuum of symptoms across the pre-pregnancy and perinatal period. In a similar context, adverse experience in childhood provide a more distant exposure and their effect on prenatal depression may suggest a cumulative effect. The primary objective of this analysis is to determine the associated factors of prenatal depression with the Adverse Childhood Experience (ACE), as the main exposure.

Methods: Analysis for this paper comes from a trial which assessed the feasibility of e-screening for maternal mental health. For this community-based randomized controlled trial, pregnant women were recruited from antenatal clinics. Eligibility criteria included women who could speak or read English, were willing to be randomized to e-screening, and willing to participate in a follow-up diagnostic interview. All women completed self-report baseline questions and were telephoned 1 week after randomization by a blinded research assistant for a MINI International Neuropsychiatric Interview. To identify factors associated with prenatal depression, we built a logistic regression model starting with all variables associated with the outcome at P < .20 in the univariable analysis. Stepwise method was used to enter variables into the final multivariable model to estimate adjusted odds ratios (AORs) and 95% CIs.

Results: More than 80% of the participants were older than 25 years, had education beyond high school and had annual incomes of $40,000 Cdn or more. Slightly less than one-fifth (20%) of the women had an ACE score of four or more. Age, education, alcohol consumption and smoking lost significance at multivariable stage and were removed from the model. The final model included: ACE score, ≥ 4 vs < 4, [OR: 1.9; 95%CI: 1.001-3.584], diagnosis of depression before pregnancy [OR: 2.1; 95%CI: 1.2-3.9] and anxiety disorder on the MINI International Neuropsychiatric Interviews (M.I.N.I.) [OR: 9.2; 95%CI: 3.3-25.6].

Conclusions: This analysis explored the independent association of ACE score ≥ 4 with the development of prenatal depression (EPDS ≥ 13). The analysis also found association between previous history of depression as well as anxiety with the prenatal depression. These findings highlight the importance of identifying early adverse experiences in women’s lives as potential contributors to prenatal depression.

PO2.05.05

Through the voice of children: narratives of third generation survivors of maternal death on the Arabian Peninsula

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Background: Maternal mortality is one of the serious public health issues of our time: Over a quarter of a million women died while giving life in 2015. A mother’s death affects the survival of children in low-income settings but is also likely to influence developmental outcomes of surviving children. Against the background of the high maternal mortality in Yemen, the poorest country on the Arabian Peninsula, we aimed to conduct case studies with children following maternal death. The pilot study on children with a special focus on mental health constitutes part of an ongoing epidemiological study of reproductive health among mothers and daughters in Yemen, initiated in Sana’a in 1997.

Methods: The study was conducted in the capital of Sana’a with the help of local midwives. Families where maternal deaths occurred within the past year were identified in the existing cohort and the children interviewed individually or with siblings in their new home. The focus of the study was on children’s own narrated experience. Information about the mother’s and sometimes also grandmother’s death in childbirth had previously been obtained through interviewing family members. Midwives attending the mother’s birth were often friends of the family and introduced interviewers whenever possible. Special care was taken to use a research methodology suitable for interviewing children in vulnerable situations.

Results: The trauma of loss was alive in the minds of children, and loss of mother sometimes evoked loss of grandmother too. Children’s vulnerability within the cultural context of strong taboos surrounding maternal death was a central finding. This ‘culture of silence’ led to feelings of betrayal among the children, who initially believed that their mother was alive. Coping strategies among girls included the reaching out for mother in private notes, identifying mother and even with the fate that she suffered. A blocking out of past duties and taking wholeheartedly the mother’s role in caring for siblings was found. Boys showed signs of psychological distress but even very young tried to succumb to prevailing norms about being a strong man able to keep feelings to himself. As is customary fathers had remarried and the children kept in the care of relatives. Schooling was affected far into the year for children whose mother had died during school-hours, as fear of losing their new caretakers would prevent children from leaving the house.

Conclusions: Our findings indicate that children in families where maternal death occurred are vulnerable to behavioral and emotional problems. The situation of girls must be highlighted early to prevent transmission of reproductive trauma. The DOHaD model implies...
that prevention interventions ought to be focused on preconception and pregnancy mental health. Child survivors of maternal death are possibly among the least noticed in Yemen and likely in similar countries. One of the central principles of the UN Convention on the Rights of the Child is the child’s right to “express opinions and to be heard”. The cultural stigma surrounding maternal death accentuates the need for uncovering this life-changing trauma among surviving children.

PO2.05.06
Socioeconomic inequalities in psychosocial problems in young children: mediation analysis of maternal depressive symptoms during pregnancy, infancy and early childhood.
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Background: Socioeconomically disadvantaged children are more likely to have psychosocial problems. This relationship can be explained by a combination of individual-, familial- and community-level factors. One of the major family-level mediators of socioeconomic status (SES) and children’s mental health problems are maternal mental problems. We lack understanding of how maternal depressive symptoms at different time points during early developmental stages of a child play a role in this regard. Therefore, this study examined the mediating role of maternal depressive symptoms during pregnancy, infancy and early childhood in the association between maternal education and child’s psychosocial problems.

Methods: We included 3410 children of the longitudinal Amsterdam Born Children and their Development (ABCD) study. Mothers and teachers completed the Strengths and Difficulties Questionnaire (SDQ) to assess the child’s psychosocial problems at age 5-6 years. Maternal depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) and Depressive Anxiety and Stress Scale 21 (DASS21). Mediation analysis was done to calculate the direct effect of maternal educational level (indicator of SES) on SDQ total score and indirect effects through maternal depressive symptoms. Adjustments were made for maternal and child characteristics, 95% confidence intervals were approximated with bootstrap procedures.

Results: The mean mother-reported SDQ total score was significantly higher (p < 0.001) for children of low educated mothers (6.7 ± 4.4) compared to children of highly educated mothers (4.5 ± 3.7). The same pattern was found for teacher reported scores (6.5 ± 5.5 vs 4.9 ± 4.4; p < 0.001). Levels of maternal depressive symptoms were higher in low educated mothers during pregnancy, infancy and early childhood. 5.2% of the mothers reported high depressive symptoms during all three periods (chronic depressive symptoms), while 44.3% never reported high depressive symptoms. Chronic depressive symptoms was more common in low educated mothers (9.5%) compared to high educated mothers (3.3%). The mean mother-reported SDQ total score for children of mothers with chronic depressive symptoms was 8.9 ± 5.4. The indirect effect of maternal depressive symptoms in the association between SES and mother-reported SDQ scores was 30.4% (Figure 1). Maternal depressive symptoms during pregnancy had the strongest indirect effect (20.2%). No significant indirect effect of maternal depressive symptoms was found in the association between maternal education and teacher-reported SDQ total scores.

Conclusion: Maternal depressive symptoms during pregnancy mediate the association between low maternal education and child’s psychosocial problems at age 5-6. Early recognition and treatment of maternal depressive symptoms is important to prevent psychosocial problems in children, especially in low SES families.

PO2.05.07
Maternal employment, parental socioeconomic status, and the risk of adverse pregnancy outcomes
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Background: Research on socioeconomic predictors of adverse birth outcomes has focused mainly on maternal characteristics. Much less is known about the role of maternal employment during pregnancy and paternal factors. Maternal employment and parental
education are important socioeconomic markers that may predict birth outcomes in addition to maternal socioeconomic indicators. 

**Methods:** Using data from the Longitudinal Survey of Newborns in the 21st Century in Japan, we estimated the associations of maternal employment during pregnancy, family income, and parental education with low birth weight (LBW) (<2,500 g) and pre-term birth (PTB) (<37 weeks) using logistic regression analyses.

**Results:** A total of 46,039 singleton births were included in the present study. Compared to unemployed women, the adjusted odds ratios (95% confidence intervals [CIs]) for the risk of LBW in women with full and part-time employment were 1.23 (1.11-1.37) and 1.24 (1.10-8.11), respectively. Compared to women with high school-level education, the adjusted odds ratios (95% CIs) in women with junior high school level education were 1.27 (1.04-1.56) for LBW and 1.38 (1.10-1.72) for PTB. In women with university-level education, the adjusted odds ratios (95% CIs) were 0.86 (0.75-0.99) for LBW and 0.91 (0.78-1.06) for PTB. Similarly, for paternal junior high-level and high-school level categories, the adjusted odds ratios (95% CIs) were 1.22 (1.03-1.43) for LBW and 1.18 (0.97-1.42) for PTB. For paternal university-level category, the adjusted odds ratio (95% CIs) were 0.85 (0.77-0.94) for LBW and 0.90 (0.80-1.01) for PTB. Compared to family income levels of 5-7 million yen/year, the adjusted odds ratios (95% CIs) for the category of family income of <3 million yen/year were 1.22 (1.06-1.40) for LBW and 1.36 (1.16-1.59) for PTB. On the other hand, the adjusted odds ratios (95% CIs) for the category of >10 million yen/year were 0.93 (0.77-1.12) for LBW and 0.75 (1.16-1.59) for PTB.

**Conclusions:** Our study suggests that maternal employment during pregnancy, low parental education, and low family income may increase the risk of adverse birth outcomes whereas high parental education and high family income may decrease the risk.

**PO2.05.08**

**Perceptions of pregnancy preparation in socioeconomically vulnerable women: a qualitative study**

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*Erasmus MC, ROTTERDAM, The Netherlands*

**Background:** In the promotion of periconceptional health, appropriate attention has to be given to the perceptions of those who are most vulnerable, such as women with a relatively low socioeconomic status. The aim of this study was to evaluate these women’s perceptions of pregnancy preparation and of healthcare needs in the preconception period.

**Methods:** We conducted semi-structured interviews with women of low to middle socioeconomic status with a desire to conceive, of which a subgroup had experience with preconception care. Thematic content analysis was applied on the interview transcripts.

**Results:** The final sample consisted of 28 women. We identified four types of pregnancy preparation perceptions: (i) perceived possibilities, which included health promotion and seeking healthcare; (ii) perceived objectives, that is, reasons to prepare, which were mostly related to fertility and health concerns; (iii) perceived control, which was expressed as having limited control over becoming pregnant as well as the health of the unborn; (iv) perceptions about the added value of preconception care, reported by women who had visited a consultation, which consisted mainly of reassurance and receiving information.

**Conclusions:** The attained insights into the perceptions of socioeconomically disadvantaged women are valuable in attuning the provision of preconception care. We recommend the proactive offering of preconception care, including information on fertility, to stimulate adequate preparation for pregnancy and contribute to improving perinatal health amongst socioeconomically vulnerable women.

**PO2.05.09**

**Beyond early adversity: Parenting predicts infant health in a community sample**

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**Background:** According to the developmental origins of health and disease (DOHaD) model, the first 1,000 days of life represent a period of increased vulnerability and plasticity in which environmental factors have lasting impacts on biological systems that contribute to later health (Barker, 2004). A growing body of research suggests that early experiences with parents may have important implications for children’s health. In particular, early caregiving adversity—such as parental abuse and neglect—have been linked to child inflammation, abnormal brain development, and risk for cardiovascular and metabolic diseases (e.g., Miller et al., 2011; Shonkoff, 2016). Less is known, however, about how positive parenting may contribute to child health, especially in the first 1,000 days of life. Further, it is important to examine whether the findings reported in high-risk families replicate in community samples, given that a large proportion of patients receiving pediatric care are not high-risk. Thus, this study goes “beyond early adversity” to ask: Does the quality of parental care predict infant health in the first year of life in a community sample?

**Methods:** Participants were 187 healthy mothers and their full-term infants (86 girls), followed from birth to age 1. Mothers’ behavior was observed in a naturalistic setting (home bathing session) when infants were 5 weeks old. Two trained, independent coders rated mothers’ sensitivity and cooperation on a widely used, well-validated measure of maternal care (Ainsworth, 1969); inter-observer reliability was strong (intraclass correlations ≥ .94). Sensitivity and cooperation scores were combined into a composite reflecting overall quality of maternal care. Every month for the first 12 months of the child’s life, mothers completed structured interviews about their infants’ health problems, as well as prescribed antibiotic use (12 total assessments). Infant health problems were categorized into four non-overlapping
domains according to established criteria from the International Classification of Primary Care: respiratory, digestive, skin, and general illnesses and symptoms.

**Results:** For each health outcome, a hierarchical multiple regression was conducted, controlling for health-related covariates that explained at least 1% of the variance. Results are displayed in Table 1. Higher quality maternal care predicted reduced rates of respiratory illnesses, $\beta = -.16, p = .015$, $\Delta R^2 = .03$, and skin illnesses, $\beta = -.19, p = .007$, $\Delta R^2 = .04$, and marginally lower prescribed antibiotic use, $\beta = -.13, p = .083$, $\Delta R^2 = .02$. Effect sizes were small. Maternal behavior was unrelated to digestive and general illnesses, $ps > .05$.

**Conclusions:** Quality of maternal care, even in the absence of adversity, may have important implications for the developmental origins of health and disease. Although ample research has documented the negative health consequences of low-quality parenting, this study is among the few to demonstrate the contribution of positive parenting to child health in a community sample. Results suggest that parenting may be an important point of entry for early prevention and intervention to support children’s health (Britto et al., 2017; Hagan, Shaw, & Duncan, 2008; Perrin, Leslie, & Boat, 2016; Richter et al., 2017).

**Regression Results Predicting Child Health Outcomes**

**PO2.05.10**

**A structured approach to compare different theoretical models in the context of childhood adversity and depressive symptoms**

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**Background:** Researchers examining life course influences on health are often interested in comparing different theoretical models about how exposures combine to affect health. Recently a structured approach has been implemented to investigate whether exposures over the life course relate to later-life outcomes within alternative life course models, e.g. whether a critical period model or an accumulation model is more appropriate. From several plausible hypotheses, the least angle regression (LARS) algorithm selects the hypothesis or hypotheses that explain the most variation in the outcome. This structured approach using LARS lends itself to other areas of hypothesis selection, such as the comparison of different theoretical models to define an exposure of interest.

**Methods:** As a motivating example, and to explore the methodological considerations in applying this method, we examine the association between childhood adversity (0-16 years) and depressive symptoms (21 years) in children of the Avon Longitudinal Study of Parents and Children (ALSPAC) study. Adversity has been conceptualised by a variety of theoretical models using different underlying constructs. We operationalised adversity by twenty-five binary constructs (e.g., sexual abuse). Different combinations of these 25 constructs are then summed to give a total adversity score for five theoretical models (classical adverse childhood experiences (ACE), extended ACE, reduced ACE, deprivation vs threat and risk domains) (see figure). The LARS algorithm is used to identify which combination of adversity constructs and theoretical models explains the most variation in depressive symptoms.

**Results:** The two main challenges when using the LARS approach to compare theoretical models were: (i) reducing the dimensionality of the data to derive the adversity constructs and (ii) handling missing data. 6386 questionnaire items were relevant to the five theoretical models. Each item was recoded to a binary variable. Items were excluded if there was no suitable binarisation, if fewer than 500 people responded or if fewer than 20 people reported the adversity. Subsequently, binary adversity constructs were created by assessing whether someone reported exposure to adversity on any of the items relevant to that particular construct. Finally, per theoretical adversity model, an overall adversity score was calculated by summing exposure to the multiple adversity constructs. Before using the LARS algorithm, it is essential to handle missing data appropriately. The adversity constructs are derived using items from different data sources at several time points, which leads to a high percentage of missingness per construct – thus a complete-case analysis would be inefficient, and potentially biased. A difficulty when using imputation to handle missing data is that the final model is selected by the LARS algorithm and is thus unknown beforehand. In addition, the high number of variables may lead to a high-dimensional imputation model.

**Conclusions:** The structured approach is useful for the examination of the association between complex exposures and health outcomes. Our work builds on previous development of this method to compare alternative life course models by exploring the applicability of this method to the comparison of...
different theoretical models to define an exposure. Methodological considerations when implementing this approach include reducing the dimensionality of the data and missing data.

Overview of the theoretical adversity models. The white boxes describe the constructs that belong to the respective theoretical model in the black box

PO2.05.11

The association between prenatal alcohol exposure and offspring mental health

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Background: Intrauterine alcohol exposure has been reported to be associated with negative cognitive and behavioural outcomes in offspring. However, the findings that are available on mild to moderate alcohol use are inconsistent, and focus less on internalising behaviours than externalising behaviours. The current study investigated the association of maternal drinking during pregnancy with child mental health.

Methods: Participants were adolescents (n = 3,299, mean age = 17.5 years) from the Avon Longitudinal Study of Parents and Children (ALSPAC). Maternal drinking behaviours were obtained at 18 weeks gestation for the number of days alcohol was consumed in the first trimester. The Clinical Interview Schedule-Revised assessed self-reported child mental health, indicating an ICD-10 diagnosis of depression. Logistic regression was used to investigate associations between gestational alcohol consumption and offspring mental health. Paternal alcohol consumption at 18 weeks gestation was included as a negative control comparison.

Results: There was evidence that the number of occasions mothers drank alcohol during their first trimester was associated with offspring depression age 18 (OR for linear trend = 1.18, CI = 1.01-1.39), but this was attenuated in the fully adjusted model (OR for linear trend = 1.11, CI = 0.94-1.31). The number of days fathers drank alcohol during the first trimester was not associated with offspring depression (unadjusted: OR for linear trend = 0.86, CI = 0.72-1.02; fully adjusted: OR for linear trend = 0.87, CI = 0.73-1.03).

Conclusions: Maternal alcohol consumption during pregnancy is associated with offspring depression, but socioeconomic and prenatal risk factors may account for this association. Paternal alcohol use during pregnancy is not associated with offspring depression, suggesting that this may not be an appropriate negative control in this context.

PO2.05.12

Impact of parental cancer on intellectual performance, stress resilience, and physical fitness in late adolescence among boys

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Background: A cancer diagnosis in a parent is a stressful life event, leading to an increased risk of emotional or behavioral problems among the affected children. However, whether parental cancer has an impact on the development of intelligence, psychological adaptability to stress, and physical fitness has rarely been assessed. We aimed to investigate the associations of parental cancer with the intellectual performance, stress resilience, and physical fitness of the affected boys.

Methods: In this Swedish population-based study, we included 465 249 boys born during 1973-1983 who underwent the compulsory military conscription examination around the age of 18. We identified all parents of these boys from the Multi-Generation Register and the cancer diagnoses of these parents from the Cancer Register. Intellectual performance, stress resilience, and physical fitness of the boys were assessed at the time of conscription, and categorized into three levels including: low, moderate, and high (reference category). We used multinomial logistic regression to assess the studied associations.

Results: Overall, parental cancer was not associated with low intellectual performance (relative risk ratio [RRR] 1.02, 95% CI 0.97-1.08), but with higher risks of low stress resilience (1.09, 1.04-1.15), and low physical fitness (1.12, 1.05-1.19). Stronger associations were observed for parental cancer with a poor expected prognosis (low intellectual performance: 1.20, 1.00-1.43; low stress resilience: 1.59, 1.31-1.94; low physical fitness: 1.45, 1.14-1.85), and for parental death after cancer diagnosis (low intellectual performance: 1.11, 1.01-1.24; low stress resilience: 1.29, 1.16-1.43; low physical fitness: 1.40, 1.23-1.59).

Conclusions: Parental cancer, particularly the severe and fatal ones, may result in a higher risk of low intellectual performance, low stress resilience, and low physical fitness during late adolescence among boys.

PO2.05.13

Maternal prenatal anxiety and stress is associated with children’s health: a longitudinal study

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Background: Maternal prenatal anxiety and stress (PNS) have been positively associated to physical health problems in offspring in the first year of life. Whether these associations are transient, persistent, or even progressive over time, is as yet unknown. The goal of the present study is to investigate associations between PNS and child health from 18 months to age 6.

Methods: Mothers were recruited in late pregnancy, and had uncomplicated, singleton pregnancies without physical health problems. At week 37 of pregnancy, mothers reported on their PNS by means of questionnaires, and provided saliva for determination of circadian cortisol concentrations. Children’s illnesses in the preceding year were assessed with the use of maternal reports at 30, 48, 60, and 72 months. Antibiotic use was obtained from medical records between one and six years of age.

Results: Multilevel models (N = 174) showed a positive relation between maternal prenatal general and pregnancy-specific anxiety during late pregnancy and offspring respiratory illnesses and symptoms. Interaction effects with time indicated that more PNS was related to more illnesses until toddlerhood, but not later in life. Furthermore, maternal prenatal cortisol concentrations were related to child digestive illnesses. A steeper maternal cortisol decline over the day was related to more child digestive illnesses, until around three years of age. Finally, children of mothers who suffered more from daily hassles during pregnancy received more antibiotics between one and six years of age. PNS was not related to general and skin illnesses.

Conclusions: Summarizing, this study showed that PNS, was associated with children’s respiratory and digestive illnesses till the age of 3.0-3.5 years. Additionally, more PNS was related to more prescribed antibiotics between one and six years. These findings point in the direction of possible effects of PNS persisting beyond the first year of life and into toddlerhood, but disappearing at older ages.

PO2.05.14

Trajectories of maternal anxiety and child development at three years

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Background: Approximately 17% of children experience developmental problems at school entry. Risk factors for these delays include biological risk factors (e.g. preterm birth), sociodemographic risk factors (e.g. poverty), and psychosocial risk factors (e.g. maternal depression, anxiety). 12 to 24% of women experience depression during pregnancy and approximately 19% suffer from anxiety and depression in the first year postpartum. Maternal anxiety during the early childhood period can have serious consequences and can compromise child development. Existing literature on maternal anxiety has focused on anxiety during the pregnancy or postnatal period and its association with child development. However, few studies have investigated the relationship between maternal anxiety symptoms over time and child developmental delays.

Objective: The aim of this study is to examine the consequences of antenatal and postnatal exposure of maternal anxiety on child global development.

Methods: The All Our Babies (AOB) study is an ongoing prospective pregnancy cohort of mothers and children from Canada. A total of 1983 participants were included in the current study. Study participants completed three questionnaires spanning pregnancy to four months postpartum and participated in the follow up study. Maternal anxiety was assessed using Spielberg State Anxiety Inventory (SSAI). Child development was measured using The Ages and Stages Questionnaires (ASQ) across five domains: Communication; Gross Motor; Fine Motor; Problem Solving and Personal-social. Latent class analysis was conducted to identify trajectories of women’s anxiety across six time points (pregnancy to three years postpartum). Logistic regression was used to explore the relationship between the anxiety trajectories and child developmental delays while adjusting for covariates.

Results: The majority of participants were between 25-34 years (73%), were partnered (96%), had some post-secondary education (92%), had family incomes ≥ $80,000 (73%), and were born in Canada (82%). 10% of children were delayed on two or more ASQ domains at age 3 years. Three distinct trajectories of maternal anxiety symptoms were identified over time: minimal anxiety symptoms (n = 1100, 55%); sub-clinical anxiety symptoms (n = 727, 37%); and persistent high anxiety symptoms (n = 156, 8%). Multivariate analysis showed that mothers assigned to the subclinical or high anxiety symptoms classes were associated with a two fold increased risk of developmental delays in children at 3 years.

Conclusion: With more than 25% of women experiencing poor mental health from conception to one year postpartum, identifying those with subclinical or persistent high symptoms for early intervention may mitigate the risk of child developmental delays.

PO2.05.15

First trimester antenatal depression and anxiety: prevalence and associated factors in an urban population in Soweto, South Africa.

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Background: The prenatal environment, including maternal mental health, is increasingly recognised as having an
important influence on foetal development and later offspring outcomes. Maternal mental health can lead to adverse child outcomes through altered placental function, epigenetic changes in the foetus, and stress reactivity. Depression and anxiety are the most common mental health disorders in pregnancy. Despite this both disorders are under-researched in the first trimester of pregnancy, and especially in Africa. We examine the prevalence of first trimester antenatal depression and anxiety in a cohort of South African women and investigate associated risk factors.

Methods: Data was collected from 946 women (2014-2016) in the Soweto First 1000 Days Cohort (S1000), a prospective pregnancy cohort in Soweto, South Africa. Antenatal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS) with a score of ≥ 13 indicating probable depression. Anxiety was assessed using the short-form of the State Trait Anxiety Index (STAI) with a score ≥ 12 indicating probable anxiety.

Results: Prevalence of antenatal depression was 27% (95% CI 24.2-29.8) and anxiety 15.2% (95% CI 12.9-17.5). Factors associated with antenatal depression and anxiety were predominantly relationship- and family-centred. Women who perceived that their partner made life harder for them had threefold increased odds for depression (OR 3.33 [2.28-4.85] p = 0.000) while those with family stressors had almost double the odds for depression (OR 1.78 [1.22-2.59] p = 0.003) and anxiety (OR 1.75 [1.44-2.69] p = 0.0011).

Conclusions: Antenatal depression and anxiety are reported by a third of women are common early in pregnancy, and partner and family relationship stressors are central. Longitudinal analysis is needed to determine if this is a phase of adjustment to pregnancy or onset of persistent symptomology. Early intervention may have secondary preventative effects and should involve the partner and family.

PO2.06 – Environmental exposures

PO2.06.01

Mechanisms of childhood cadmium toxicity

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Background: Dietary cadmium exposure during pregnancy and early childhood has been linked to impaired growth and cognitive ability, but the underlying mechanisms are largely unexplored. Our aim was to assess how cadmium exposure during pregnancy and childhood may affect different toxicity biomarkers related to growth and development.

Methods: In a prospective mother-child cohort in rural Bangladesh, we measured exposure to cadmium and other metals during early pregnancy and childhood (4.5 and 9 years; n = 522). Cadmium was measured both in blood (erythrocyte fraction; reflecting ongoing dietary exposure) and in urine (reflecting long-term accumulated exposure) using inductively coupled plasma mass spectrometry. Plasma insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH) and biomarkers of nutrition and bone and kidney health were measured at 9 years of age using standard methods in clinical chemistry. Linear regression analyses, adjusted for child gender, hemoglobin, height-for-age Z-score, and socio-economic status at 9 years of age, were used to assess potential associations of blood and urinary cadmium (both log2-transformed) with different markers of toxicity.

Results: In multivariable-adjusted analysis, blood cadmium concentrations (median 0.90 μg/L) at 9 years of age increased with decreasing levels of plasma ferritin [B (95% CI): -5.7 (-10; -1.3)] and folate [-0.39 (-0.74; -0.040)]. Concerning the toxicity markers, blood cadmium was positively associated with plasma Cystatin C [B (95% CI): 0.016 (0.001; 0.031)] and osteocalcin [5.6 (1.9; 9.3)], the latter being most notable in girls. In boys, blood cadmium was also inversely associated with TSH [B -0.46 (-0.92; -0.0024)]. Urinary cadmium (median 0.28 μg/L) at 9 years was positively associated with plasma osteocalcin [B (95% CI) 3.1 (0.20; 5.9)] and creatinine [0.75 (0.11; 1.4) and inversely associated with vitamin D concentrations [mean ± SD: 64 ± 17 nmol/L, B (95% CI) -2.5 (-4.3; -0.78)], regardless of season. In boys, urinary cadmium was also inversely associated with IGF-1 [-4.6 (-8.5; -0.62)]. Blood cadmium at 4.5 years (correlated with that at 9 years, r = 0.68) was positively associated with creatinin [B (95% CI): 0.022 (0.0064; 0.038)] and creatinine [0.80 (0.026; 1.6)], and inversely associated with vitamin D [-4.3 (-6.7; -1.9), ¼ SD]. Urinary cadmium at 4.5 years (correlated with that at 9 years; r = 0.51) was positively associated with albumin-adjusted plasma calcium [B (95% CI): 0.075 (0.021; 0.13)] and inversely with vitamin D [-2.4 (4.1; -0.82)]. Maternal blood cadmium at gestational week 14 was positively associated with child plasma phosphate [B (95% CI) 0.071 (0.021; 0.12)] and inversely associated with TSH [-0.24 (-0.43; -0.048)] at 9 years of age.

Conclusions: Dietary exposure to cadmium in Bangladeshi children appeared to increase with poorer nutrition, probably related to increased gastrointestinal absorption. Children’s cadmium exposure was consistently associated with lower levels of Vitamin D and several bone and kidney biomarkers. Prenatal exposure appeared to mainly affect thyroid function at 9 years of age.

PO2.06.02

Puberty onset in children environmentally exposed to organochlorine compounds

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Background: It has been shown that irregularities in puberty timing are associated with various pathologies in adulthood in both sexes. At the same time prenatal exposures to endocrine disruptors as polychlorinated biphenyls (PCBs), dioxins, organochlorine pesticides and phthalates were linked to puberty onset.

Methods: Cohort of 271 children (157 were girls and 114 were boys) residing in an area highly polluted with agrochemicals, PCBs and furans has been followed from birth to present. Average age of children at examination was 11.6 ±0.4 years (min 10, max 12.7 years, 3, 25, 50, 7 and 97 percentiles: 10.4, 11.5, 11.6, 11.7 and 12.3, respectively). Pubertal maturation using Tanner staging (breast development and pubic hair in girls, external genitalia and pubic hair in boys) was determined. Pubertal onset was defined for boys as external genitalia stage 2 or pubic hair stage 2 or higher. Pubertal onset for girls was defined as either as breast development stage 2 or pubic hair stage 2 or higher. Furthermore, in girls, onset of menarche was recorded. Parents of children answered questions on sociodemographic, environmental and lifestyle factors. As markers of prenatal exposure were measured cord blood levels of PCBs (15 congeners) and organochlorine pesticides (DDE, DDT, β-hCH and HCB) using high-resolution gas chromatography with electron capture detection. With PCBs we differentiated exposure to the sum of PCBs and exposure to DL-PCBs (sum of congeners #105, 114, 118, 123, 156, 157, 167, 189).

Results: In boys we did not find any significant association between prenatal exposure to PCBs, DDE, DDT and HCB, and puberty stages. On the other hand the highest quartile of exposure to β-hCH was associated with increased prevalence of Tanner stage 2+ (4th vs. 1st quartile OR=4.5, p=0.014). In girls we did not observe any association between Tanner stage 2+ and exposure to PCBs, DDE, DDT, β-hCH and HCB, however the time of menarche associated with exposure to DDE (4th vs. 1st quartile OR = 3.1, p=0.088; 3rd vs. 1st quartile OR = 2.3, p=0.209; 2 vs. 1st quartile OR = 4.6, p=0.018).

Conclusions: When considering Tanner stages 2 and higher, commonly accepted as an indicator of puberty onset, we observed an enhancement of sexual maturation in both sexes associated to exposure to β-hCH in boys and DDE in girls. Both agents are known as endocrine disruptors that interfere with action of sexual hormones. The relationship between menarche onset and exposure to DDE in girls appears to be non-monotonic.

PO2.06.04

The outdoor exposome and birth weight association in the HELIX cohort

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Introduction: To date, 4 epidemiological studies have consistently shown an inverse association between prenatal acrylamide exposure and birth outcomes. This implies that prenatal acrylamide exposure may predispose to disease in later life. However, there is no clear biological explanation for this association and thus it is hard to judge the causality of the association, which impairs the use of this observation for acrylamide risk assessment. In the current study, we investigated the association between acrylamide and IGF2, an important driver of prenatal growth, and the interaction between acrylamide and CYP2E1 polymorphisms for the association with birth outcomes. Through this, we aim to contribute data on the mechanism of action of acrylamide and the causality of the inverse relationship between acrylamide and birth outcomes.

Methods: In 74 newborns of the ENVIRONAGE (ENVIRONMENTAL influence ON AGEing in early life) birth cohort, we investigated the association between prenatal acrylamide exposure (acrylamide to hemoglobin adduct levels in cord blood (AA-Hb)) and birth weight, length and head circumference, and IGF2 (n = 68) in cord plasma, measured by a commercial ELISA kit. In addition, we studied interaction with 2 single nucleotide polymorphism (SNPs) in cytochrome P450 2E1 (CYP2E1) (n = 62), rs2480258 and rs915906. These SNPs were analyzed on the Biotrove OpenArray SNP genotyping platform. We used multiple linear regression for the statistical analyses.

Results: For a 10 pmol/g globin increase in AA-Hb, there was a decrease in birth weight of 75 grams (95% CI: -145.6, -6), of 0.32 centimeters (95% CI: -0.69, 0.06) in length, and of 0.29 centimeters (95% CI: -0.56, -0.02) in head circumference. A 10 pmol/g globin increase in AA-Hb was associated with a 20 ng/ml (95% CI: -38, -2) decrease in IGF2 cord plasma levels. There was no statistically significant interaction between acrylamide exposure and birth length and the CYP2E1 SNPs.

Conclusions: This study confirms previous epidemiological studies reporting an inverse association between prenatal dietary acrylamide exposure and prenatal growth. The inverse association between acrylamide and IGFB2 that was investigated for the first time in this study suggests a possible mechanism. Other and larger studies are needed to corroborate this finding.
The exposome is defined as the totality of environmental exposures from conception onwards. The overall aims of the Human Early Life Exposome (HELIx) project are: i) to measure a broad suite of environmental exposures during early life (the early life exposome), ii) to evaluate the exposome’s association with child health outcomes, and iii) to identify omics signatures related to the exposome. Here we evaluate the association between the outdoor exposome and birth weight in the HELIX study, based on data from 31,458 pregnancies collected in birth cohorts from 6 European countries (France, Greece, Lithuania, Norway, Spain, the UK). We considered a large number of outdoor exposure variables (61 variables related to the built environment, air pollution, noise, temperature, UV, and green and blue space) and investigated their association with birth weight and low birth weight. We adjusted all analyses for cohort, gestational age, sex of the newborn, parity, maternal height and weight before pregnancy, mean number of cigarettes smoked per day by the mother during the second trimester of gestation, maternal age, maternal education, and season of conception. We used an EWAS (environment-wide association study) exposure-by-exposure approach adjusting for multiple hypothesis testing and further applied the deletion-substitution-addition (DSA) algorithm for variable selection. In our EWAS analyses, after correcting for multiple testing, we found statistically significant effects for normalized difference vegetation index (NDVI, a marker of green space land cover), facility density, walkability, facility richness, distance to and size of green spaces, building density, connectivity, NO2 in trimester 3, and PM2.5 for birth weight. In the DSA variable selection model, NDVI and transport lines remained statistically significant. For term low birth weight, NDVI and building density were statistical significant in the EWAS analyses and only building density in the DSA. This is the first large exposome analyses for outdoor exposures and birth weight, systematically quantifying the contribution of multiple outdoor environmental exposures to birth weight using a systematic approach. Birth weight was associated with several factors related to the built environment and green space.

PO2.06.05
Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort: assessing confounding by maternal glomerular filtration rate

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Background: Prenatal exposure to some perfluoroalkyl substances (PFAS) has been associated with low birth weight (LBW) but this association may be confounded by maternal hemodynamics, such as glomerular filtration rate GFR during pregnancy. We evaluated the association between prenatal exposure to PFAS and birth outcomes, and the influence of maternal GFR in 1,206 mother-child pairs from a Spanish birth cohort study.

Methods: We measured perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorononanoate (PFNA) in maternal plasma samples collected in the the 1st-trimester of pregnancy during the years 2003-2008. Birth outcomes included weight, LBW, LBW-at-term, length, head circumference, ponderal index, gestational age, small-for-gestational-age (SGA), and preterm birth. Maternal GFR during pregnancy was estimated using the Cockcroft-Gault formula in 769 mothers.

Results: We detected at least one PFAS in every maternal sample, being PFOS (mean: 5.78 ng/mL) and PFOA (mean: 2.32 ng/mL) the most abundant. Overall, we observed a strengthening of our associations after including GFR in our models. Specifically, all PFAS were associated with higher weight at birth, ranging from 38g (95% CI: 6.52, 68.71) up to 58g (16.86, 99.48) per doubling of PFAS concentrations. Also, higher PFOS concentration was associated with a decrease of 0.30 weeks (-0.53, -0.08) in gestational age, and 2.7 (1.15, 6.40) times higher odds of preterm birth only in boys (p-interactions = 0.06 and 0.07, respectively). Higher PFHxS, PFOS, and PFNA concentrations were associated with higher ponderal index at birth (betas from regression models ranged from 0.02 to 0.04). There was no association between PFAS and birth length, head circumference, LBW, LBW-at-term, and SGA.

Conclusions: In this study, prenatal PFAS exposure was associated with higher weight at birth in both sexes, and reduced gestational age and higher odds of being preterm only in boys. These results were especially strengthened after considering maternal GFR as a confounder. Studies using maternal PFAS concentrations would benefit from adjusting for maternal hemodynamics such as GFR, even if using maternal samples collected early in pregnancy.

PO2.06.06
Exposure to ambient air pollution predicts telomere length in 8-year old children

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Background: Exposure to ambient air pollution predicts telomere length in 8-year old children

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Background: In recent years, studies have emphasized the importance of air pollutants in the formation of reactive oxygen species and inflammation, which can lead to lower telomere length. Telomere length is considered a biomarker of biological aging and shorter telomeres have been associated with age-related diseases such as cardiovascular disease, and type 2 diabetes. In this study we hypothesize that telomere length at 8 years of age is inversely associated with prenatal air pollution exposure.

Methods: In this analysis we used subjects of the HELIX sub-cohort (n = 1223). Prenatal nitrogen dioxide (NO\textsubscript{2}), particulate matter with an aerodynamic diameter < 10 μm (PM\textsubscript{10}), and particulate matter with aerodynamic diameter ≤ 2.5 μm (PM\textsubscript{2.5}) exposure were estimated using the ESCAPE land-use regression models. Relative telomere length was measured using real time polymerase chain reaction (qPCR). Effect estimates were calculated using multiple linear mixed models with a random cohort effect and adjusted for relevant covariates.

Results: Our analyses show that telomere length at 8 years of age (ranging from 5.5-12 years) was negatively associated with prenatal NO\textsubscript{2} exposure, but not with prenatal PM\textsubscript{10} or PM\textsubscript{2.5} exposure. Each SD increment in average pregnancy NO\textsubscript{2} exposure was associated with shorter telomeres of 1.9% (95\% CI: -3.2, -0.6) at age 8 years.

Conclusion: These results show an inverse association between exposure to NO\textsubscript{2} during pregnancy and telomere length at 8 years of age, considered as molecular marker of ageing.

Temporal and spatial variability of personal exposure to radio frequency electromagnetic fields in children in Europe

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Background: Mobile communication technologies represent the main source of exposure to radio frequency electromagnetic fields (RF-EMF) in the general population and little is known about this exposure in children. There is concern that children today are exposed to more RF-EMF than ever before and that this accumulated exposure over a lifetime could lead to adverse health outcomes which have not yet been evaluated. Therefore studies characterizing RF-EMF exposure in children have been identified as high priority by the World Health Organization. This study aims to describe personal RF-EMF exposure levels in European children over a 72 hour period.

Methods: In Denmark, the Netherlands, Slovenia, Switzerland, and five regions of Spain, 559 children and adolescents (ages 8-18 years) were recruited for personal RF-EMF measurements. Measurements were collected for 529 children over a 72-hour period between 2014 and 2016. Measurements of RF-EMF in the 87.5 MHz–6 GHz range were collected using personal portable exposure meters which measured 16 different frequency bands, with a measurement interval of four seconds.

Results: In general, downlink was the largest contributor to total levels of RF-EMF (median 27.20 μW/m\textsuperscript{2}) followed by broadcast transmitters (median 9.89 μW/m\textsuperscript{2}). Exposure from uplink accounted for a median of 4.71 μW/m\textsuperscript{2}. WiFi and DECT contributed very little to exposure levels. Measurements were generally highest while children were traveling and much lower at home or in school. Mean duration of measurements was 62 hours.

Urbanicity of home, parents’ highest level of education, and number of people living in home were all associated (p < 0.05) with measurements in the 90th percentile. One year later, repeatability was low for almost all general frequency bands (Spearman’s ρ = 0.40 for total measurements).
However, measurements of downlink exposures were more consistent (Spearman’s $\rho = 0.70$).

**Conclusion:** This study assesses RF-EMF exposure in a large number of children from different age groups (8-18y) in five European countries. RF-EMF measurements were generally highest while children were traveling, coming mainly from mobile phone base stations. While higher personal exposure levels were associated with several demographic factors, levels were not consistent one year later in a small sample. It would be informative to test repeatability in a larger sample.

Median power densities ($\mu W/m^2$) of RF-EMF over a 72 hour period for 529 children in five European countries, including five regions of Spain.

**PO2.06.08**

**Prenatal particulate air pollution exposure and cord blood homocysteine in newborns; results from the ENVIRONAGE birth cohort**


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**Background:** Particulate air pollution is thought to increase the risk of cardiovascular disease. Plasma homocysteine is an established cardiovascular disease risk factor. Recent studies show that exposure to particulate air pollution is associated with plasma homocysteine levels in adults but no studies on the early life origin of homocysteine levels in association with prenatal air pollution exist.

**Methods:** In 616 newborns of the ENVIRONAGE (ENVIRONMENTAL influence ON AGEing in early life) birth cohort, we investigated the association between prenatal PM$_{2.5}$ exposure and cord plasma homocysteine levels, and in a subset we studied the interaction with 11 single nucleotide polymorphism (SNPs) in oxidative stress-related genes (CAT, COMT, GSTP1, SOD2, NQO1 and HFE), through multiple linear regression. PM$_{2.5}$ levels were obtained using a high resolution spatial temporal interpolation method. Homocysteine levels were measured by the homocysteine enzymatic assay on a Roche/Hitachi cobas c system. SNPs were assessed on the Biotrove OpenArray SNP genotyping platform.

**Results:** In multivariable-adjusted models, cord plasma homocysteine levels was 6.6% higher (95% CI: 1.0 to 12.3%; $p = 0.02$) for each 5 $\mu g/m^3$ increment in average PM$_{2.5}$ exposure during the whole pregnancy. With regard to pregnancy trimesters, there was only a statistically significant association in the 2nd trimester: 3.6% (95% CI: 1.0% to 6.2%; $p = 0.007$). The positive association between PM$_{2.5}$ in the 2nd trimester and homocysteine was modified by the sum score of the 3 studied SNPs in the catalase gene (p interaction = 0.046) but not by any of the other studied polymorphisms.

**Conclusions:** Exposure to particulate air pollution in utero is associated with higher cord blood homocysteine levels. Increased air pollution-induced homocysteine levels in early life might track over life-time and be a risk factor or marker for cardiovascular and other diseases later in life.

**PO2.06.09**

**Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances affects leukocyte telomere length in female newborns**

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**Background:** Evidence has shown that leukocyte telomere length (LTL) at birth is related to the susceptibility to various diseases in later life and is influenced by the intrauterine environment. Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are capable of crossing the maternal-fetal barrier during pregnancy. Few studies have investigated the associations between PFASs exposure and newborn LTL. The aim of our study was to verify the hypothesis that intrauterine exposure to PFASs might affect fetal LTL by increased oxidative stress.

**Methods:** LTL, concentrations of 10 PFASs and reactive oxygen species (ROS) were measured in umbilical cord blood of 581 newborns from a prospective cohort. Generalized linear model adjusted for potential confounders was used to examine the relationships between PFASs concentrations and LTL or ROS levels.

**Results:** Our results showed that LTL was significantly shorter ($\beta = -0.023$, $P = 0.026$; $\beta = -0.026$, $P = 0.011$) and ROS levels were extremely higher ($\beta = 21.62$, $P = 0.031$; $\beta = 25.11$, $P = 0.011$) in the female newborns whose perfluorooctyl sulfonate (PFOS) or perfluorodecanoic acid (PFDA) concentrations fell in the uppermost quartile compared with those in the lowest quartile after taking potential confounders into account.
(Figure 1). Furthermore, ROS levels were inversely associated with LTL in female newborns (Pearson correlation coefficient \(r\) = -0.14; \(P=0.02\)). However, there was no relationship between PFCs and LTL in the males.

**Conclusions:** Our findings suggest a “programming” role of PFASs on fetal telomere biology system in females in intrauterine stage. Oxidative stress may play a role in the process of accelerated LTL attrition influenced by PFASs.

**PO2.06.10**

**Socioeconomic and dietary predictors of BPA, paraben and benzophenone blood levels in a subcohort of EPIC-Spain**

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**Background:** Endocrine disruptors like bishenol-A (BPA) and parabens and benzophenones have been related with several chronic diseases like obesity, diabetes and cancer. The exposure to these compounds in our everyday life can happen via different exposure routes. BPA is widely used in plastic containers of foods and textiles. Benzophenones are also common compounds in plastic and glass bottles. On the other hand, parabens are added as preservatives of different cosmetics and self-care products and foods. The objective of the present study was to analyze the association between socioeconomic, anthropometric and dietary characteristics and BPA, parabens and benzophenone blood levels, identifying predictor variables.

**Methods:** BPA, methylparaben (MP), ethylparaben (EP), propylparaben (PP), butylparabel (BP), benzophenone-1 (BP-1) and benzophenone-3 (BP-3) were analysed in a subcohort of the EPIC-Gipuzkoa cohort (8417 participants) recruited between 1992-1995. Data on age, sex, socioeconomic characteristics, anthropometric measures and living and dietary habits of the participants were recorded. Serum samples of 1503 subjects were collected at recruitment (baseline) and measured by DLLME and a subsequent UHPLC-MS/MS. Associations between the levels of the chemical compounds with the different socioeconomic, anthropometric, living and dietary variables were studied and predictive linear regression models were built.

**Results:** The results showed a low detection percentage for BPA, with 42% of samples below the LOD. This number was particularly low for BP-1 and BP, which were detected in less than 20% of the samples. In opposition, MP could be measured in 80% of the samples. Accordingly, the concentration of MP was the highest, followed by BPA, BP-3, PP, EP, BP, and BP-1 consecutively. The levels of paraben congeners and benzophenones in blood serum were positively correlated. However, BPA showed no correlation with MP or BP-1. Regarding the predictive models for each compound, the explained variance was very low in all cases, being \(R^2 = 0.12\) for MP, and \(R^2 < 0.1\) for the rest of the chemicals. Although predictor variables were different for each compound, sex was a common predictor for all except for BP and BP-3, being the levels of the chemicals higher in women. Among dietary habits, the consumption of vegetables and miscellaneous food was also positively associated with increasing levels of the measured compounds, and appeared to be common predictor variables.

**Conclusions:** The low detection percentage of BPA and some parabens and benzophenones could be probably explained by the period of the study and the much lower use of plastic wrappings, containers and processed food than in the present. The positive association between paraben congeners and benzophenones could indicate a similar origin. Sex was in general a predictor variable for the blood levels of the measured compounds in participants of the study, what could be due to the use by women of cosmetics containing parabens as additives, although further research is needed.

**PO2.06.11**

**Fine particulate air pollution exposure and maternal oxidative stress during pregnancy: the IPANEMA cohort**

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**Background:** Exposure to fine particulate air pollution (PM2.5) is associated with adverse pregnancy outcomes for mothers and babies including low birth weight, intrauterine growth restriction and preterm birth. Epidemiological studies have shown that these adverse birth outcomes are associated
with an amplified risk of chronic diseases later in life. The pathophysiological mechanisms that underlie adverse pregnancy outcomes however, are incompletely understood. One plausible mechanism is oxidative stress induced endothelial dysfunction. Changes in endothelial function may play a significant role in the development of hypertensive pregnancy disorders, which are associated with adverse pregnancy outcomes and a greater cardiovascular risk for mothers in their later life. Geographical variations in the association between maternal PM2.5 exposure and low birth weight have been suggested. Considering the ubiquitous nature of particulate air pollution in Flanders, the associations between maternal PM2.5 exposure and adverse pregnancy outcomes, although relatively small, could be of major public health importance.

Methods: The Flemish institute for technological research VITO and the Antwerp University hospital set up a prospective cohort study (n = 200) among pregnant women living in an urban area in Flanders, the IPANEMA study (Impact of Particulate Matter on Mothers and Babies in Antwerp). We explored the association between PM2.5 exposure and second trimester pregnancy urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) levels, an established oxidative stress biomarker, in 46 pregnant women enrolled in the IPANEMA cohort. Maternal PM2.5 exposure was modelled at the home address. Questionnaires provided information on maternal lifestyle and health. Urinary levels of 8-OHdG were measured using an enzyme-linked immune assay (ELISA). Linear regression analysis was used to assess the association between PM2.5 exposure and 8-OHdG levels; both crude regression analysis as well as analysis adjusted for maternal age were performed.

Results: For all participants, estimated mean annual PM2.5 exposure levels were above the 10 μg/m³ World Health Organization air quality guideline. Estimated PM2.5 exposure one year before urine collection and 8-OHdG concentrations in maternal urine at mid-gestation showed a weak positive correlation (r = 0.301, p = 0.045). In a linear regression model adjusted for maternal age, the association remained significant (p = 0.048; R² = 0.093).

Conclusions: Our preliminary study showed that PM2.5 exposure plays a role in maternal oxidative stress during pregnancy. Analysis of oxidative stress and endothelial dysfunction biomarkers in the full cohort will further explore oxidative stress induced endothelial dysfunction as a plausible pathway underlying adverse pregnancy outcomes.

PO2.06.12
Newborn sex-specific transcriptome signatures and gestational exposure to fine particles: findings from the ENVIRONAGE birth cohort

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Background: Air pollution exposure during pregnancy has been associated with adverse birth outcomes and health problems later in life. We investigated sex-specific transcriptomic responses to gestational long- and short-term exposure to particulate matter with a diameter < 2.5 μm (PM2.5) in order to elucidate potential underlying mechanisms of action.

Methods: Whole genome gene expression was investigated in cord blood of 142 mother-newborn pairs that were enrolled in the ENVIRONAGE birth cohort. Daily PM2.5 exposure levels were calculated for each mother’s home address using a spatial-temporal interpolation model in combination with a dispersion model to estimate both long- (annual average before delivery) and short- (last month of pregnancy) term exposure. We explored the association between gene expression levels and PM2.5 exposure, and identified modulated pathways by over-representation analysis and gene set enrichment analysis.

Results: Some processes were altered in both sexes for long- (e.g. DNA damage) or short-term exposure (e.g. olfactory signaling). For long-term exposure in boys neurodevelopment and RhoA pathways were modulated, while in girls defensin expression was down-regulated. For short-term exposure we identified pathways related to synaptic transmission and mitochondrial function (boys) and immune response (girls).

Conclusions: This is the first whole genome gene expression study in cord blood to identify sex-specific pathways altered by PM2.5. The identified transcriptome pathways could provide new molecular insights as to the interaction pattern of early life PM2.5 exposure with the biological development of the fetus.

PO2.06.13
Nickel boride nanoparticle toxicity and microarray analysis on human pulmonary alveolar epithelial cells

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During the recent years, microarray analysis of gene expression has become an inevitable tool for exploring toxicity of drugs and other chemicals on biological systems. Therefore, toxicogenomics is considered as a fruitful area for searching cellular pathways and mechanisms including cancer, immunological diseases, environmental responses, gene-gene interactions and chemical toxicity. In this study, synthesis, characterization and cytotoxicity evaluation of nickel boride (NiB₂) nanoparticles were performed on human pulmonary alveolar epithelial cells (HPAEpiC) since, main exposure to nanoparticles would generally happen through lung via inhalation. Chemically synthesized Co₂B NPs were characterized by using XRD, TEM, SEM and EDX techniques. MTT, NR and LDH release assays were used to analyse cytotoxicity after NPs exposure. Whole genome microarray analysis was used to find out the effects of NiB₂ NPs on gene expressions of HPAEpiC cells.
Finally, the database for annotation, visualization and integrated discovery (DAVID) analysis was used to reveal relationships between different cellular pathways and NPs exposure. According to cytotoxicity analysis LC20 value for NiB2 NPs was 24.313 mg/L. Microarray results showed that 705 genes expression change (FC ≥ 2) significantly over 40.000 genes analysis. When the gene pathways were analysed, it was seemed that NiB2 NPs mostly affect centrosome organization, microtubule regulation, nucleus regulation and phosphoprotein synthesis.

PO2.06.14

Aflatoxin exposure is correlated with child stunting while distance between water and sanitation infrastructure is correlated with child enteric dysfunction

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Background: Low height-for-age or stunting for children under five years of age has become the primary proxy variable to measure chronic malnutrition among children. Poor health outcomes associated with low child height-for-age include short-term health issues such as increased morbidity and mortality while long-term health issues include increased probability of obesity, non-communicable diseases, lower cognitive function, and premature mortality. Among children in Guatemala under the age of five, 49% have significantly low height-for-age scores which is fifth worst in the world. Therefore, improving our understanding of early human development in regards to physical and cognitive impairments among children is crucial. Two factors that have been hypothesized to be associated with low height-for-age are fungal toxins (specifically aflatoxin) and environmental enteric dysfunction (EED). This study investigates 1) the correlations between aflatoxins, EED, and child height-for-age and 2) potential environmental or geospatial factors correlated with EED.

Methods: 309 mothers of children under five years of age from San Vicente, Totonicapán, Guatemala were surveyed in October of 2016 and February of 2017 by local health staff and anthropometric data was collected on the children. The data was then analyzed utilizing structural equation modeling (SEM) and the Kruskal-Wallis significance tests. SEM was used to test the hypothesized correlations between aflatoxin, enteric dysfunction, and low height-for-age. Kruskal was used to test the hypothesized relationships between the type of water, sanitation, and hygiene (WaSH) infrastructure at the house, the distance between the WaSH infrastructure, and EED among children.

Results: Results from the SEM analysis suggested that symptoms of aflatoxin exposure in February 2017 were correlated with the change in growth between October 2016 and February 2017 (-0.27, p = 0.00). Symptoms of aflatoxin exposure in October 2016 were correlated with symptoms of EED in February 2017 (-0.097, p = 0.06) while symptoms of EED at either time point were not correlated with the change in growth. Results from the Kruskal analysis suggested that at both timepoints the distance between the sanitation facility and the water source was correlated with EED (p = 0.06 and p = 0.05, respectively) while the distance between the kitchen and the hand washing station was correlated with EED in only October 2016 (p = 0.05). Variation on the type of WaSH infrastructure was not correlated to EED.

Conclusion: The data supported the hypothesis that aflatoxins have a negative effect on child height-for-age, but did not support the hypothesis of EED negatively effecting height-for-age. Furthermore, EED was found to be correlated with distance metrics as opposed to quality metrics in regards to WaSH infrastructure.

PO2.06.15

The influence of park features on park satisfaction and park use in a multi-ethnic deprived urban area

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Background: Research has demonstrated green space is associated with improved mental and physical health and well-being. Several studies have also indicated the beneficial impact of green space on pregnancy outcomes, such as higher birth weight. At present there is little information on how to encourage use of green space. There is mixed evidence to show the number of park features can encourage park use, as well as size and proximity to the park. It is suggested that the number of features may be linked to park satisfaction, which is related to use. Little is known about what specific features might influence park satisfaction, and it is not known whether this differs by ethnicity or socioeconomic status. This study aims to
explore the influence of park size, proximity and park features on park satisfaction and use. We also aim to explore whether park satisfaction mediates the relationship between park features and use, and whether ethnicity and socioeconomic status moderate the relationship between park features and park satisfaction.

Methods: A sub-sample (n = 620) of the Born in Bradford cohort completed a survey on park satisfaction and use. The survey was completed by parents on behalf of their child when they were 4 years old. Demographic and socioeconomic data were also collected. Parks were subsequently audited using the Natural Environment Scoring Tool (Gidlow, in preparation). Features were divided into domains: access, recreational facilities, amenities, natural features, significant natural features, non-natural features, incivilities and usability. Park size and proximity were calculated using ArcGIS and participants’ postcodes. Significant predictors of park satisfaction and use were identified using multilevel linear regressions. Multilevel mediation was used to explore the mediating role of park satisfaction in the relationship between park features and park use. Interactions between ethnicity and socioeconomic status and park features were explored.

Results: It was found that higher amenities and usability domain scores were significantly positively associated with park satisfaction (β = 0.7, p = .027; β = 0.11, p = .008), while a higher incivilities domain score was significantly negatively related (β = 0.07, p = .027). The incivilities domain was also found to significantly negatively predict park use (β = 16.02, p = .046). No significant association was identified between individual variables and park satisfaction and park use. Ethnicity and socioeconomic status had no moderating role. No evidence of mediation by park satisfaction in the relationship between park features and park use was found.

Conclusion: This study found the number of amenities, number of activities available and level of incivilities present significantly influenced the degree of park satisfaction. Incivilities also appear to negatively impact on park use. Results suggest it is park quality that influences satisfaction and use, rather than structural factors such as size and proximity. Furthermore, individual level variables did not influence park satisfaction or park use, suggesting environmental interventions to encourage satisfaction and use may be more effective than individual interventions. It is suggested urban planners prioritize adding amenities and eliminating incivilities in parks to encourage use and promote health.

PO2.07 – Neurodevelopment – Pregnancy and growth

PO2.07.01

Influence of intrauterine growth restriction and preterm birth on motor performance in childhood: evidence from a cohort study.

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Background: Intrauterine growth restriction and preterm birth have been associated with child’s neurodevelopment. The objective of this study is to test the association between child’s motor performance and intrauterine growth restriction (IUGR) and preterm birth (PTB).

Methods: This study included children (n = 1003) from the follow-up (2011/13) of convenience prenatal cohort of 1400 mother / child dyads (2010/11). Motor performance was evaluated by means of gross motor and fine motor component of Bayley-III Screening Development Scale. Children were classified as preterm (< 37 weeks) and with IUGR defined by the birth weight ratio (BWR), which is the ratio between the newborn’s weight and the mean weight for gestational age of the sex-specific reference curve. A BWR ≥ 0.85 was defined as no growth restriction, and a BWR < 0.85 was defined as IUGR. Children were classified as preterm-IUGR (PT-IUGR), preterm-non IUGR (PT-NIUGR), term-IUGR (T-IUGR) and term-non IUGR (T-NIUGR). Multiple linear regression analysis was used to evaluate the association between motor scores and birth conditions. Model adjustment included child (sex and age at follow-up) and maternal covariates (alcohol consumption, smoking, schooling, age and type of delivery).

Results: At total, 1.4% of children were classified as PT-IUGR, 7.9% PT-NIUGR, 7.5% T-IUGR and 83% as T-NIUGR. Children from groups T-IUGR and T-NIUGR showed higher adjusted gross motor scores than the PT-IUGR (β-coefficient, β = 1.68, 95% Confidence Interval- 95%CI 0.50-2.87 and β = 1.53, IC95% 0.42-2.64 respectively). Adjusted fine motor scores were higher for groups PT-NIUGR, T-IUGR and T-NIUGR (β = 2.14, IC95% 0.75-3.52; β = 2.33, IC95% 0.92-3.73 and β = 2.36, IC95% 1.04-3.68 respectively) than PT-IUGR group.

Conclusion: For both gross motor and fine motor tasks, children with PT-IUGR showed lower motor performance than their peers. Since PT-NIUGR showed better performance than PT-IUGR for fine motor task, the interaction between preterm birth and IUGR conditions seems to increase difficulties in coordination and fine motor control.

PO2.07.02

Fetal growth and cognitive development in the Born in Bradford (BiB) cohort

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Objective: There is a sizeable literature focussing on the relationship between size at birth and cognitive outcomes in children. There is much less evidence surrounding the association between fetal growth and cognitive outcomes, with one study reporting 'little association between fetal growth measured by ultrasound and cognitive function in childhood' (Walker et al. 2007) and another reporting inconsistent associations between fetal size and growth profiles and a number of cognitive outcomes at 1 and 5 years (von Ehrenstein et al. 2009). Unlike these studies, our objective was to model fetal growth in a multilevel framework and directly relate coefficients of growth to cognitive and academic outcomes, using data from a large prospective cohort study. We hypothesized that a reduced growth rate would be associated with poorer cognitive and academic outcomes.

Methods: Data from the Born in Bradford (BiB) cohort. Individual trajectories of estimated fetal weight (EFW; n = 10921), abdominal circumference (AC; n = 10942), head circumference (HC; n = 12748) and bi-parietal diameter (BPD; n = 10877) were modelled using linear splines in a multilevel framework. The best fitting-linear spline models for (ln)weight, (ln)AC, (ln)HC and ln(BPD) growth had 2 knot points, splitting the fetal period into 3 periods. From these models, random effect coefficients were used to produce individual estimates of rates of change in a particular period, for each of the three fetal parameters (EFW, AC, HC, BPD). These were then standardised (z scores), by sex. These were then related to a range of cognitive and academic outcomes in childhood: (e.g. Early Years foundation (mean age = 63 months); Key Stage 1 scores (mean age = 87 months); British Picture Vocabulary Scale (BPVS) (mean age = 60 months); and letter identification (mean age = 60 months), via secondary linear, logistic and ordinal logistic regression models.

Results: 698 (for weight), 701 (for AC), 1138 (for HC) and 1134 (for BPD) children had all of the exposure, covariate and outcome data. Preliminary analyses did not reveal any consistent associations between growth during fetal life, irrespective of the period of gestation, with any of the outcomes. The inclusion of sex and ethnicity interactions (with growth coefficients) did not reveal any differences between sexes or ethnic groups.

Conclusion: Fetal growth does not appear to be associated with cognitive outcomes in early childhood. For AC and weight, this observation may be unsurprising as these parameters are not closely related to brain development. As such, the lack of an association between HC and BPD growth and cognitive outcomes is more surprising. This may reflect either a true null association between fetal growth and later cognitive outcomes; suggesting that pregnancy does not represent a sensitive period for cognitive development, or, highlights the poor sensitivity of ultrasound for assessing the developing brain. Further analysis will explore associations after adjustment for a number of putative confounding variables.

PO2.07.03
The association of maternal thyroperoxidase antibodies during pregnancy with offspring IQ and brain morphology
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Background: Thyroperoxidase antibody (TPOAb) positivity, which reflects thyroid autoimmunity, occurs in 5-10% of all pregnant women and is a risk factor for thyroid dysfunction and adverse obstetric outcomes. Maternal thyroid hormone (TH) deficiency during early pregnancy is associated with suboptimal neurodevelopmental outcomes of the offspring, including lower IQ and lower grey matter volume. During the same timeframe at which important early brain developmental processes take place, high concentrations of human chorionic gonadotropin (hCG) stimulate the maternal thyroid gland. This leads to an increase in TH concentrations of up to 50%, thereby guaranteeing adequate TH availability for the developing fetus. Recently, we demonstrated that in TPOAb positive women, the thyroidal response to hCG stimulation is severely attenuated. Therefore, we hypothesized that TPOAb positivity influences early fetal brain development. The main aim of this study was to investigate the association of maternal TPOAb positivity during pregnancy with IQ and brain morphology of the offspring.

Methods: This study was embedded in two prospective birth cohorts: Generation R (Rotterdam, the Netherlands) and the Avon Longitudinal Study of Parents and Children (ALSPAC; Avon, England). Mother-child pairs with available data on TPOAbs in early pregnancy (<18 weeks of gestation) and offspring IQ or MRI imaging were included. We used multi-variable linear regression adjusting for potential confounders (i.e. maternal education, smoking, age) to investigate the association of maternal TPOAb positivity (clinical and non-clinical cut-offs) with child IQ (median age 6 years) and brain morphology (median age 8 years) in Generation R (N = 3637 and N = 644, respectively). Subsequently, we aimed to externally replicate the results for child IQ in ALSPAC (at median age 9 years; N = 2396) with two approaches: using the assay cut-off of > 6 IU/L and also Generation R equivalent cut-offs.

Results: In Generation R, TPOAb positivity was associated with a 2.0 ±0.9 points lower mean child IQ (P = 0.03). TPOAb positivity was also associated with a lower cortical grey matter volume (-6189 ±2987 mm³, P = 0.03) but a higher subcortical grey matter volume (1281 ±490 mm³, P = 0.009). Sensitivity analyses showed that these negative effects occurred already from TPOAb concentrations considerably lower than the established cut-off (>20 versus >60 IU/L, respectively). In ALSPAC, neither TPOAb positivity nor other defined cut-offs
were associated with child IQ (TPOAb positivity: 0.72 ±0.97, P=0.45). Adjustment for maternal TH concentrations or urinary iodine/creatinine ratio in a subset (Generation R: N = 753, ALSpac: N = 1065) did not change the results.

**Conclusions:** TPOAb positivity during pregnancy was associated with lower child IQ and lower cortisol, but higher subcortical grey matter volume in Generation R. However, TPOAb positivity was not associated with child IQ in ALSpac. These analyses suggest that thyroid autoimmunity may affect early fetal brain development, presumably neuronal migration which takes place at the same time as thyroidal stimulation by hCG. Further studies are needed to replicate the brain morphology findings and to elucidate if differences between the study populations, such as maternal iodine status, may cause effect modification.

**PO2.07.04**

**Key neurocognitive domains in adults born preterm**

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**Background:** Children born very preterm (<32 weeks) or very low birth weight (<1500 g) perform on average worse at school, attain lower education level, have lower IQ, poorer short term memory and poorer reaction time than their peers born at term. The differences at least partly can be established at adulthood as well. However, over 70% of the preterm births happen between 34 + 0 and 36 + 6 gestational weeks, and little is known about neurocognition of the late preterm group, especially at adult age. Late preterm delivery may be a risk for neurodevelopmental disability. At childhood and school age, late preterm group may perform worse at school and neurocognitive tests than their term born peers, some studies also showing no differences. One cohort study measured neurocognition of the late preterm group, especially at adulthood. The differences at least partly can be established at adulthood as well.

**Methods:** We invited young adults in the ESTER Preterm Birth Cohort Study (born between 1985 and 1989 in Northern Finland) to perform Cogstate® test at the mean age of 23.3 (SD 1.2). Those with severe neurosensory impairment were excluded. 241 late preterm (34 + 0 to 36 + 6 gestational weeks), 133 early preterm (<34 gestational weeks) and 348 full term controls participated. Cogstate® is a computer-based test in which we included the following subtests in multiple exercises: Detection test (measuring psychomotor function), Groton-maze-learning test (executive function), Identification test (attention), One-card-learning test (visual memory), and One-back-test (working memory). We converted the results to standard deviation scores (SDS) standardized within the control group, and compared the results of early and late preterm groups with the control group adjusting for sex and age, and further for birth-weight-SD score, maternal smoking, pre-eclampsia, maternal hypertension, maternal diabetes, parent education, maternal age, and being first-born.

**Results:** The tests we performed showed no differences between either of the preterm groups and controls, with the exception of Groton maze learning test, in which those born late preterm had 0.16 SD and those born early preterm 0.30 SDS less accurate moves compared to full term controls, (Table). Birth-weight-SD did not predict test results.

**Conclusions:** Our results suggest that poorer executive functioning may extend to those born late preterm. Executive functioning may be more sensitive to per- and postnatal environment than single core functions measured by other tests.

**Table.** Effect of being born under 34 gestational weeks at 34+0 to 36+6 gestational weeks on neurocognitive composite test results by linear regression. The simple model included sex and age. The full model also included for birth-weight-SD score, maternal smoking, pre-eclampsia, maternal hypertension, maternal diabetes, parent education, maternal age, and for being first-born. Regression values indicate lower scores as compared to scores of the term born control group (a) lower scores means better performance, (b) higher scores means better performance.

<table>
<thead>
<tr>
<th>Test (a)</th>
<th>34+0-36+6 gestational weeks</th>
<th>Adjusted t value of SDS b</th>
<th>SDS (b)</th>
<th>Adjusted t value of SDS b</th>
<th>SDS (b)</th>
<th>Adjusted t value of SDS b</th>
<th>SDS (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groton maze learning test</td>
<td>-0.04 (-0.08, 0.37)</td>
<td>-1.06 (-2.02, 0.90)</td>
<td>0.11 (0.05, 0.18)</td>
<td>-1.11 (-2.02, 0.89)</td>
<td>0.12 (0.06, 0.20)</td>
<td>0.12 (0.31, 0.20)</td>
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<tr>
<td>Groton maze learning test</td>
<td>-0.12 (-0.26, 0.02)</td>
<td>-0.86 (-1.72, 0.00)</td>
<td>0.16 (0.08, 0.24)</td>
<td>-0.11 (-0.22, 0.00)</td>
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</tr>
<tr>
<td>Groton maze learning test</td>
<td>-0.31 (-0.75, 0.13)</td>
<td>-0.47 (-1.35, 0.42)</td>
<td>0.01 (0.03, 0.08)</td>
<td>-0.30 (-0.62, 0.02)</td>
<td>0.01 (0.16, 0.12)</td>
<td>0.01 (0.31, 0.12)</td>
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</tbody>
</table>

**PO2.07.05**

**Assessing causality in the association between maternal pre-pregnancy obesity and child neurodevelopment: observational and mendelian randomization analyses**

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**Background:** Observational studies have shown that high maternal pre-pregnancy body mass index (BMI) may impair infant neuropsychological development; however, it is unclear whether reported associations are due to intraterine mechanisms or are consequence of residual confounding by socio-economic factors. **Objective:** We aimed to determine whether maternal pre-pregnancy BMI causally influences child neurodevelopment by performing an observational analysis in 24 birth cohorts (>100,000 mother/infant pairs) and a Mendelian randomization analysis in 10 of these cohorts (>10,000 mother/infant pairs). **Methods:** We will use maternal BMI genetic score (30 established single nucleotide polymorphisms) as an instrumental variable for maternal pre-pregnancy BMI. We will also use...
Results: In observational analysis, preliminary results using data from the INMA (Environment and Childhood) Spanish cohort (n = 1402) revealed that each kg/m² increase of maternal pre-pregnancy BMI was associated with a reduction of 0.23 infant cognitive scores (95% CI: -0.42, -0.04) at the age of 1.5 years. In Mendelian randomization analysis, each kg/m² increase of maternal BMI genetic score was associated with a reduction of 1.56 infant cognitive scores (95% CI: -3.06, -0.05) at the same age. Egger analysis showed no bias from pleiotropy.

Conclusions: This study using different population settings and Mendelian randomization approach will serve to disentangle whether there is an intrauterine effect of maternal prepregnancy obesity on offspring neurodevelopment.

PO2.07.06

Seasonality of maternal plasma tryptophan levels in early pregnancy: Implications for fetal brain development

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Background: While the treatment of psychiatric illness has improved incrementally over the decades, our ability to prevent devastating disorders such as schizophrenia, autism, major depression and bipolar disorder is highly limited. In humans, placental serotonin derived from a maternal tryptophan precursor plays a critical role in fetal brain development during the late first/early second trimester. Given that tryptophan and serotonin metabolism are subject to seasonal effects, particularly at northern latitudes, we are examining seasonal differences in maternal plasma tryptophan levels in a normal Canadian pregnancy sample called the Ontario Birth Study (OBS).

Methods: To date, a single maternal plasma tryptophan level collected at 15-18 weeks of pregnancy is available for 20 mothers designated as “highly seasonal” and 35 “non-seasonal” controls. Seasonality was defined based on established cutoffs for the Seasonal Pattern Assessment Questionnaire (SPAQ). Tryptophan is being measured using mass spectrometry. Given the small sample size available for this initial pilot data, only Caucasian women with normal pregnancies were included in this analysis. A 2 group (highly seasonal vs. other) by 4 season-of-sample-collection (spring, summer, fall, winter) ANOVA was used for statistical analysis.

Results: Consistent with our working hypothesis, there was a significant season-by-group interaction for total plasma tryptophan levels (F(3,47) = 4.806; p < 0.01). Tukey’s post hoc analysis further revealed that for highly seasonal women only, plasma levels of tryptophan during early pregnancy were significantly higher for samples collected in winter compared with fall (p < 0.01), in winter compared with summer (p < 0.05) and in spring compared with fall (p < 0.05). The main effect of season was significant while the main effect of seasonal group was not.

Conclusions: Our initial pilot data suggest that pregnant women who meet previously established screening criteria for “high seasonality” based on the SPAQ have a marked seasonal pattern to their plasma tryptophan levels as collected during 15-18 weeks of pregnancy, while non-seasonal women do not show this effect. The overall pattern of results suggests that in highly seasonal pregnant women, plasma tryptophan levels climb from a nadir in the fall to a peak in the winter-spring period. This may reflect a vestigial evolutionary mechanism that protected fetal brain development during seasonal famines in the ice age for example. Future OBS work will include a greatly enhanced sample size, comprehensive measures of other amino acids and tryptophan metabolites such as kynurenine, and careful neuro-behavioural measures of the children over time. Our long term goal is to establish whether maternal plasma tryptophan levels measured at this phase of pregnancy have implications for brain development and thus psychiatric risk. If so, optimizing maternal tryptophan levels using dietary manipulations and/or light therapy, particularly in high risk populations, may be of great interest going forward.

PO2.07.07

Birth weight, gestational age and cognitive functions over the life-course in the Generation Scotland subsample of the Aberdeen Children of the 1950s.

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Background: Factors that influence cognition across the life-course are most likely to be established in early-life but are poorly understood. In this study we examine the relationship between birthweight, gestational age and cognitive functions from childhood to mid-life based on the repeated measures (at ages 7, 9, 11 and 51–61 years) available through the linkage performed between the Aberdeen Children of the 1950s study (ACONF; n = 12,150) and the Generation Scotland: Scottish Family Health Study (GS:SFHS) (ACONF-GS:SFHS;n = 558).

Methods: Childhood cognitive ability was tested within six months of the child’s 7th, 9th and 11th birthdays [Moray House Picture Intelligence; Schonell&Adams Essential Intelligence Test Form; Moray House verbal reasoning tests I/II, Moray House English and Moray House Arithmetic respectively]. Mid-life cognitive functions were assessed with Verbal Fluency, Mill Hill Vocabulary, and Logical Memory Delay. Birthweight (g), gestational age (completed weeks of gestation),
Post-term births did not differ significantly from term births on the mid-life LM (β = −3.91, SE = 3.60, p = 0.015) and DS (β = −9.50, SE = 4.08, p = 0.025) tests compared to term births. Low and high BW performed significantly worse on childhood intelligence tests at ages seven (β = −11.19, SE = 3.91, p = 0.004) and nine (β = −9.50, SE = 4.05, p = 0.020) compared to term births. Also, pre-term births performed worse on the mid-life LM (β = −3.23, SE = 1.32, p = 0.015) and DS (β = −9.17, SE = 4.08, p = 0.025) tests compared to term births. Post-term births did not differ significantly from term births on any of the cognitive functions across the life-course. Low and high BW were negatively associated with childhood cognition at ages seven and nine compared with normal BW but only the high BW were negatively associated with childhood cognition at ages seven and nine compared with normal BW but only the high BW were negatively associated with childhood cognition at ages seven and nine.

Conclusions: In the ACONF-GS:SFHS subsample, the negative effects of pre-term birth on childhood cognitive functions persisted into mid-life. Fluid cognitive abilities, which are more sensitive to ageing processes, were affected the most. Collectively, pre-term birth might constitute a novel risk factor for cognitive ageing.

PO2.07.08
Early postnatal growth and neurodevelopmental outcome in individuals born with moderately low birth weight: a systematic review

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Background: Despite limited evidence, catch-up growth is currently a therapeutic goal for infants born with moderately low birth weight (MLBW) for preserving brain development. However, available evidence shows an association between rapid early postnatal growth and later cardiovascular risk.

The objective was to conduct a systematic review of the relationship between early postnatal growth and neurodevelopmental outcome for individuals born with MLBW, distinguishing between prematurity and size at birth.

Methods: Following PRISMA guidelines, three independent investigators performed a systematic review, searching the Web of Science, EMBASE and PubMed databases for articles published from database inception to March 25, 2017. We selected all studies reporting an association between growth before age 3 years and later neurodevelopmental outcome in individuals born with MLBW. We defined this population as having a birth weight between 1500 and 2500 g, being born at term small for gestational age or born moderately preterm (32 to 36 weeks’ gestational age). A detailed quality scale was used to evaluate articles.

Results: We selected 17 articles relying on 10 distinct population studies and including a median of 341 participants (range 50-5640); seven articles were considered at moderate or high quality. Overall, early postnatal growth was positively associated with neurodevelopmental outcome, especially intellectual quotient (IQ) when available. In this relationship, the first 6 months of life seemed to be a critical period. Analysis of the few articles investigating the shape of the relationships revealed a non-linear association, with a plateau for IQ with higher weight gain, which suggests a possible threshold effect. The lack of standardization of growth analysis methods prevented performing a meta-analysis. Head circumference was not frequently studied. Perinatal complications and early postnatal nutrition, as potential important confounding factors, were rarely considered together.

Conclusions: Although a positive association was generally found between early postnatal growth and neurodevelopmental outcome for individuals born with MLBW, further studies are needed to improve knowledge of a causal link. A better exploration of the role of head circumference and the possibility of a weight-for-length threshold above which there would be no further benefit for neurodevelopment would help guide clinical practice.

PO2.07.09
Perinatal risk factors associated with visual processing dysfunctions at 1 y of age in children born between 26-32 weeks

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Background: Children born preterm are at high risk for neurological damage, including dysfunctions in visual information

Results: The ACONF-GS:SFHS participants comprised 558 individuals (240 males, 318 females; mean age = 57.4; n = 378 with complete covariates) and appeared to be relatively representative of the core population. Overall, 87% of ACONF-GS:SFHS participants had BW within normal range and 73% were term births. Over 70%/56% had a father/mother in manual occupation and 54% completed at least 12 years of education. In the analytical sample, pre-term births were excluded in analyses of the associations of birthweight with cognition.

Conclusions: Early postnatal growth and neurodevelopmental outcome in individuals born with moderately low birth weight might constitute a novel risk factor for cognitive ageing.
processing. Given the long-term adverse effect of visual processing dysfunctions on development in a range of domains (e.g., motor control, social skills, and later cognitive development), early detection is of high importance. With a non-invasive method based on eye tracking, we found evidence for delayed visual processing in children born preterm from 1 year of corrected age (CA) (Pel et al., 2016). However, it is yet unknown what the underlying precursors for these delays are. Our aim was to explore the relation between visual processing delays at 1 year CA and specific perinatal risk factors.

**Methods:** We recruited 109 children born between 26-32 weeks. From each child, the following perinatal risk factors were obtained from the medical record: gestational age (GA), birth weight (BW), 5-minute Apgar score, mild retinopathy of prematurity (ROP < grade 3), intraventricular hemorrhage (IVH), post-hemorrhagic ventricular dilatation (PHVD), bronchopulmonary dysplasia (BPD), infant respiratory distress syndrome (IRDS), and sepsis. At 1 year CA, each child underwent a non-verbal visual processing assessment using a preferential looking paradigm. The paradigm contained stimuli with several types of visual information (color, motion, contrast, form) and was shown on a monitor while simultaneously eye movements were recorded with a remote eye-tracker (Tobii T60XL). For each type of visual information an average viewing reaction time (RT) was calculated and compared to normative reference data from an age-matched control group of 42 children. The prevalence of the perinatal risk factors was compared between children with and without specific visual processing delays.

**Results:** At 1 year CA the number of preterm children with significant delays in RT ranged from 9% (to contrast information) to 24% (to motion information). Compared to the group of children who had RTs within the normative range, the group of children with overall delayed RTs had a significantly higher prevalence of the risk factors IVH (47% vs 15%; $\chi^2 = 3.8, p = .05$), PHVD (21% vs 3%; $\chi^2 = 8.7, p < .05$), and IRDS (95% vs 60%; $\chi^2 = 8.4, p < .05$). The other perinatal risk factors were not related to RT delays.

**Conclusion:** Children born between 26-32 weeks have a modest risk of delayed visual information processing at 1 year CA. Our results show that on a group level, early visual processing delays are more often found in children who had disruptions in cerebral blood flow and oxygen supply shortly after birth. These results provide a basis for screening of visual processing dysfunctions in infants at-risk, which enables referral to visual rehabilitation programs at an earlier age than currently is possible.

**PO2.07.10**

Helicobacter pylori infection and childhood neurodevelopment, the Rhea birth cohort in Crete, Greece.

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**Background:** Emerging evidence in adults suggests an association between Helicobacter pylori infection and neuropsychiatric diseases. Sparse data exists on the association between Helicobacter pylori infection early in life and neurodevelopmental outcomes in childhood. Moreover, Helicobacter pylori infection during pregnancy has been associated with micronutrient deficiencies which are relative resistant to the indicated supplementation. Fetal brain is extremely vulnerable to such micronutrients defects (e.g. folic acid, iron). No study so far has investigated the association between maternal Helicobacter pylori infection and childhood neurodevelopmental outcomes. Thus, in the present study we aim to explore the association of Helicobacter pylori seropositivity in cord blood samples, reflecting maternal status during pregnancy, and four years of age samples, with offspring’s neurodevelopment at four years of age.

**Methods:** We used prospective data on 352 mother-child pairs and cross-sectional data on 674 children to assess the association of maternal and child’s Helicobacter pylori seropositivity corresponding on child’s neurodevelopment at age four in the Rhea birth cohort in Crete, Greece. Blood levels of immunoglobulin G antibodies to twelve Helicobacter pylori proteins (GroEL, UreA, HP0231, NapA, HP0305, HpaA, CagA, HyuA, catalase, VacA, HpC and Omp) were measured using multiplex serology. Child’s neurodevelopment at age four was assessed using the McCarthy Scales of Children’s Abilities. Linear regression models were used to explore the associations after adjusting for child’s age, gender, quality of assessment, examiner, mother’s education, origin, age, child having older sibling and child’s age at day-care entry.

**Results:** Helicobacter pylori seroprevalence (95% CI) in cord blood, representing maternal status, was 41.5% (36.3%, 46.8%) and in four years old children was 6.5% (4.8%, 8.7%). Children of Helicobacter pylori seropositive mothers had lower score in the general cognitive [-3.87 (95% CI: -7.02, -0.72)], verbal [-2.96 (95% CI: -6.08, 0.15)], perceptual performance [-3.37 (95% CI: -6.60, -0.15)], quantitative [-2.85 (95% CI:-6.28, 0.58)] and memory scale [-3.37 (95% CI: -6.67, -0.07)] compared to those of seronegative mothers. Seropositivity in cord blood specifically to GroEL and NapA – two of the twelve Helicobacter pylori proteins investigated and both involved in iron sequestering and storage by the bacterium – was associated with lower scores in almost all scales. At age four, Helicobacter pylori seropositive children performed worst in neurodevelopment assessment compared to their seronegative counterparts although no association reached statistically significant level.
Conclusions Helicobacter pylori infection in early life, including fetal life, may be an important but preventable risk factor for poor neurodevelopment. We speculate that changes in the micronutrient environment following a Helicobacter pylori infection might mediate, at least in part, such an association.

PO2.07.11
Assessing The Impact of Growth Trajectory of Very Low Birth Weight Infants on Executive Functions at 11 Years of Age
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Background and objectives: Several studies on preterm-born children have identified birth weight (BW) as a potent predictor of later cognitive functioning and academic success, with poorer outcomes in those born SGA (small for gestational age) compared with those appropriate for GA (AGA). The objective of the study was to compare SGA and AGA born preterm (< 1500g) children between 10-12 years old (y/o) on growth at 1 and 2 years of life and on the outcomes of the rings subtest (RSubt) of the ENFEN (Evaluación Neuropsicológica de las Funciones Ejecutivas en Niños).

Methods: 92 born preterm (<1500g) children between 10-12 y/o (53 girls, 39 boys) were studied. Children with congenital malformations, genetic syndromes, studied intrauterine infections or cerebral palsy were excluded. Instruments: Growth chart and outcomes on the rings subtest of the ENFEN. This subtest assesses executive functions, especially those related to planning and problem solving. Statistical analysis: RSubt performance scores were divided in 2 categories: 1-4 and 5-10. Low RSubt score was defined as a score less than 4. Normal RSubt score was defined as a score ≥ 5. Categorical data was analyzed using Chi2 or Fisher test. Significance level was set at p < 0.05.

Results: 92 born preterm children (10-12 y/o) were studied. 31.52% were SGA (n = 29) and 68.47% AGA (n = 63). There were 68.96% of girls in SGA group and 52.38% in the AGA group. Table 1. Table 2 shows the Chi2 results of the RSubt scores (Normal RSubt score was defined as a score ≥ 4). IP address: 54.70.40.11, on 26 Jun 2019 at 09:02:26, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms.

Conclusions: Preterm SGA children are at special risk for cognitive impairment. We found that SGA preterm (<1500g) children with growth restriction at 1 and 2 years of life was associated to lower scores in the RSubt of the ENFEN (p < 0.05).

Table 1: Birth weight, gestational age and sex by group.

<table>
<thead>
<tr>
<th></th>
<th>SGA</th>
<th>AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW X (DS)</td>
<td>1214 (237.86)</td>
<td>1220 (368.52)</td>
</tr>
<tr>
<td>GA X (DS)</td>
<td>29 (2.25)</td>
<td>32 (1.94)</td>
</tr>
<tr>
<td>Girls (%)</td>
<td>20 (68.96)</td>
<td>33 (52.38)</td>
</tr>
</tbody>
</table>

Table 2: Results by Rings subtest score, growth at 1 and 2 years and SGA/AGA group.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Growth Z score</th>
<th>RSubt 1-4</th>
<th>RSubt 5-10</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA 1 y/o</td>
<td>&lt; -1</td>
<td>13</td>
<td>2</td>
<td>0.03</td>
</tr>
<tr>
<td>SGA 2 y/o</td>
<td>≥ -1</td>
<td>11</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>AGA 1 y/o</td>
<td>&lt; -1</td>
<td>4</td>
<td>6</td>
<td>0.50</td>
</tr>
<tr>
<td>AGA 2 y/o</td>
<td>≥ -1</td>
<td>19</td>
<td>26</td>
<td>0.50</td>
</tr>
</tbody>
</table>

PO2.07.12
Using phase contrast X-ray computed tomography imaging for valproic acid rat model of autistic brain
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Background: Autism is a neurodevelopmental disorder characterized by impaired social interaction, abnormal communication, and restricted and repetitive behavior. Recently, many researchers have been studied for autism spectrum disorder using autistic rat model, created by exposure of valproic acid (VPA) to rat fetuses on the gestation period. Versatile imaging technique plays an important role in inside studies of autism spectrum disorder. New imaging method phase-contrast X-ray CT, used phase shift, has high spatial resolution and density resolution and it can provide high contrast images. The density resolution for biological soft tissue consisting of low atomic number such as H, C, N, O, is approximately 1,000 times higher than that of traditional X-ray absorption imaging. The purpose of this study was to determine the feasibility of this technique in detailed visualization of morphological structures changes in valproic acid rat model of autistic brain.

Material and Methods: Valproic acid rats model (VPA rats) were created by intraperitoneal injection of VPA (600 mg/kg) into 12.5th day of gestation. Normal Control rats were created by intraperitoneal injection of normal saline at the same condition. 13 weeks old VPA and normal rats brain were used in this study. Rat’s brains were extracted under anesthesia and fixed using 10% formalin for imaging. Two-crystal interferometer based phase-contrast X-ray imaging system was used. The field of view of the detector was 15 × 13 mm² composed of 2560 × 2100 pixels with 6.5 × 6.5 μm². The X-ray energy was set at 17.8 KeV. Experiment was performed at the vertical wiggler beam-line 14C of the Photon Factory, Tsukuba, Japan.
After imaging, all brains were cut 3-mm thick section and stained with Hematoxylin-eosin to examine abnormal histopathological structures.

**Results and Discussion:** Phase-contrast X-ray CT without contrast agent clearly depicted the anatomical structures of rat’s brain including cortex, caudate putamen, thalamus, hippocampus, corpus callosum and lateral ventricle. Especially, high-resolution phase-contrast CT enabled to differentiate the density changes of hippocampus owing to its high sensitivity. Absolute density of hippocampus as CA 1, CA3 regions and dentate gyrus is 1.05 times higher in VPA rats compared to control rats (Fig 1). Corresponding histological section of VPA rat’s brain also showed increased neuronal cell density in the CA1, CA2/CA3 regions and dentate gyrus of hippocampus. It is suggested that neurogenesis in the hippocampus is increased in the VPA rats. In addition, lateral ventricle of VPA rats was mild to moderate dilated compared to that of control rats (Fig 1). It is thought to be caused by axonal decline in periventricular white matter.

**Conclusion:** Phase-contrast X-ray CT clearly depicted the autistic neuronal morphology. Thus, we believe that phase-contrast X-ray CT can be revealed important information about the neurobiological basis of Autism Spectrum Disorder.

![Phase contrast X-ray CT image of Hippocampus; VPA rat (A), Control rat (B).](https://example.com/phase-contrast-hippocampus)

**PO2.07.13**

**Vaccine-preventable childhood disease and adult educational attainment - Evidence from the 1967 measles eradication campaign in the United States**

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Measles is one of the leading causes of death for young children worldwide. We analyze the impact of measles prevention on later-life educational outcomes by taking advantage of a measles eradication campaign implemented in 1967 in the United States. We create a treatment intensity variable with state-level measles incidence data available from Project Tycho and use it with a difference-in-differences design on individual level data from the 2000 US census 5 per cent micro-sample. We provide evidence for the following statistically significant results: the campaign increased completed years of schooling by one week and the probability of completing high school by 0.20 percentage points. Due to the exogenous timing of the eradication campaign, we argue that these results can be interpreted causally. We also perform placebo interventions that support this conclusion. We interpret the point estimates to be at best a lowerbound, due to measurement error, the aggregated nature of the measles incidence data and the limitations of census data. To the best of our knowledge our paper is the first one to document adult educational impacts of early-life measles exposure using a natural experiment.

**PO2.07.14**

**Exploring disorganized attachment: unravelling outcomes and mechanisms/pathways using data mining**

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Infant disorganized attachment is a robust predictor of externalizing behaviour problems in childhood (Fearon et al., 2010), but many other potential health outcomes of attachment disorganization are still unexplored. In the current study we use a data mining approach in a large prospective, population-based cohort study on development and health from foetal life into young adulthood in order to generate new hypotheses and expand developmental theory. An ethnically homogeneous subgroup of $N=900$ infants and their parents was selected for in-depth measurements, including observed attachment, child problem behaviour, motor and cognitive development, and cortisol samples. These detailed measurements were completed at several time points between 0–4 years, at 5 years, and at 9 years. Attachment was assessed when infants were 14 months using the Strange Situation Procedure (Ainsworth, Blehar, Waters, & Wall, 1978). Data for infant-mother attachment is available for more than 700 dyads and little over 20% of children were classified as disorganized (varying somewhat according to the examined correlate). Based on published data so far, infants with disorganized attachment and a fearful temperament displayed more distress during a venipuncture procedure (Wolf et al., 2011), and disorganized infants had lower levels of physiological emotion regulation in the presence of higher levels of maternal postpartum depression (Tharner et al., 2013). Infant disorganized attachment was also associated with a flattened diurnal cortisol pattern (independently of maternal lifetime depression; Luijk et al., 2010). In addition
to these findings, a data mining approach is applied to all available measurements in order to further identify variables consequent to disorganized attachment. The principle of data mining is to search for associations without a priori hypotheses, to let the data speak to evaluate whether associations or patterns exist (Yarkoni & Westfall, 2016). One way to visualize underlying patterns is via decision trees, which display a progressive division of the dataset into homogeneous subsets, based on the features that best distinguish between different values of a certain target variable (e.g., low versus high levels of disorganized attachment). Preliminary decision trees with disorganized attachment (both categorically and continuous disorganization scores) as the target variable showed several levels of decision nodes, i.e., attributes that distinguished between infants with relatively low versus high levels of disorganized attachment, including child empathy and problem behavior (both reported by mother, and therefore controlled for maternal psychopathology). Findings also suggested differential developmental risk for the two groups of children with the highest levels of disorganized attachment. Using the data mining approach we aim to identify mechanisms in the effects of disorganized attachment on later development in a large sample, beyond those predictors and outcomes that may be hypothesized based on existing literature, and thereby generate new hypotheses for future research.

PO2.07.15
Alteration of social behavior and glutamic acid decarboxylase level in the valproic acid-induced autism rat model
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Background: Autism is a complex neurodevelopmental disorders characterized by impaired social communication, social interactions and repetitive behaviors. The etiology of autism remains unknown and its molecular basis is not well understood. In this study, we sought to examine social behaviors, their related gene expressions, inflammatory cytokines and gamma amino butyric acid (GABA) synthetic enzymes in valproic acid (VPA)-induced autism rat model.

Methods: Sprague-Dawley (SD) pregnant rats (Charles River Laboratories Japan, Inc., Japan) were given VPA 600 mg/kg (intraperitoneal injection) on day 12.5 of gestation. Eleven to thirteen week-old male and female offspring were used for 3-chamber social interest test and after behavioral test, the hippocampus was collected from each rat to detect social behavior-related gene and proinflammatory cytokines using real-time RT-PCR method. We also investigated the brain level of rate limiting enzyme, glutamic acid decarboxylase (GAD65 and GAD67), which is responsible for normal conversion of glutamate to GABA in the brain, using Western blot analysis.

Results: We did not find any significant changes of body weight and brain weight of VPA-induced autism model rats compared to the corresponding control of male and female rats. Male and female VPA-induced autism model rats show poor sociability and social novelty preference compared to the corresponding control SD rats. Messenger RNA expression level of social behavior-related genes such as serotonin, brain-derived neurotrophic factor and neuroligin were significantly reduced and proinflammatory cytokines such as interleukin-1 b and tumor necrosis factor-a were significantly increased in the hippocampus of both male and female VPA-induced autism rat models. The protein level of GAD 65 was reduced in male VPA-induced autism rat models compared to the control.

Conclusion: Our results indicate that developmental exposure to VPA affects social behavior by modulating social behavior related genes and inflammatory mediators in the hippocampus and these effects were markedly observed in male than in female rats. We suggest that GAD deficiency may be associated with abnormalities in the levels of glutamate/GABA balance in autistic brain. Our findings show that similarities to autism features were observed in VPA-induced rat models and these animal models are valuable experimental models to study neurodevelopmental alterations induced by environmental risk factors.

PO2.07.16
Understanding mechanistic effects of early life exposures on neurodevelopment: Role of brain structural functional connectivity in DOHaD studies.
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Introduction: An important determinant of health in adulthood is early fetal and childhood growth and development. The concept of Developmental Origins of Health and Disease (DOHaD) suggests that early adverse fetal exposures interact with environment factors over the lifespan of an individual to enhance risk of chronic disease in adult life. The impact on neurocognitive development is a significant outcome of interest due to its potential to impact human capital in adulthood. Besides genetic factors, modifiable epigenetic factors such as maternal nutrition during pregnancy (macro and micronutrients - Vitamin B12, folate, pyridoxine, Iron, Vitamin D, C), childhood nutrition growth & development, and socio-economic factors (poverty, education, life style risk factors and parent child interactions) can influence neurodevelopment. Intelligence Quotient, school achievement, performance on cognitive tests have been traditionally used as markers of neurodevelopment. Assessing functional connectivity in brain networks and integrity of white matter tracts can inform us about neural pathways underlying cognitive
processes. Hence use of brain structural and functional connectivity techniques could provide useful insights into the mechanistic effects of early life exposures on neurodevelopment. The Pune Maternal Nutrition Study (PMNS) birth cohort (n - 700) established in 1994 is considered a unique resource to examine the DOHaD paradigm in a low and middle-income country LMIC. Systematic data on maternal prepregnancy size, nutrition & blood micronutrient levels during pregnancy, neonatal birth parameters, socio-economic factors, child growth and development (nutrition, body size and composition) at 6,12,18 years have been assessed. Cognitive assessments on all offspring were performed at 12 years of age. Biological samples have been collected and stored in a bio-bank and are available for further assessments. The subjects of the cohort are now aged 21-22 years and provide a unique opportunity to study the early life and life course determinants of neurodevelopment using novel brain structural functional connectivity techniques.

**Methods:** Following cross-sectional assessments would be performed on around 700 consenting adult offspring of PMNS (aged 21 years): a) Standardized neuropsychological test battery b)Temperament character inventory c)Information on nutrition, lifestyle factors, socio-economic status, education d) Serum BDNF,IGF-1 from archived serum collected at 6,12,18 years. R resting state brain functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) would be performed on a subset of cohort (selected based on highest and lowest quartile of maternal Vitamin B12 levels during 18 weeks of pregnancy. N = 100 in each group).

**Analysis:** We propose a mediation model, to examine whether the association between early life exposures (maternal nutrition, micronutrient levels – Vitamin B12, folate, homocysteine) and neurodevelopmental outcomes (performance on cognitive tests, temperamental traits) are mediated by brain functional and structural connectivity variables and serum BDNF, IGF1 levels, controlling for moderating and confounding effects of life course factors (childhood nutrition, growth and development, education, lifestyle factors).

**Expected outcomes:** The study could yield a novel brain structural-functional connectivity paradigm with potential applications to understand mechanistic effects of early life exposures on neurodevelopment in DOHaD studies.

Model for understanding mechanistic effects of early life exposures on neurodevelopment

**PO2.07.17**

**Dietary Inflammatory Index of mothers during pregnancy and ADHD symptoms in the child at preschool age: INMA and RHEA cohorts**

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**Background:** Attention deficit/hyperactivity disorder (ADHD) is the most frequent childhood-onset neuropsychiatric condition, with an estimated worldwide prevalence of approximately 5% in school-aged children (Polanczyk et al, 2007). Pregnancy, infancy and childhood are critical periods of development, especially vulnerable to the effects of these risk factors (Tounian, 2011), and growing evidence suggests that exposure to adverse environmental and psychological conditions, especially when occurring in intrauterine life may increase the risk of developing ADHD in childhood (Buss et al, 2011). Previous studies have indicated that maternal dietary patterns during pregnancy are associated with cognitive and behavioural outcomes (Anjos et al, 2013). Given the pro-inflammatory potential of suspected nutrients, and evidence supporting a role of inflammation in the pathogenesis of ADHD, we hypothesise that a pro-inflammatory diet of the mother during pregnancy promotes the development of ADHD in the offspring. Validated dietary inflammatory indexes (DII) have been recently developed to capture the pro-inflammatory potential of diets based on known associations of specific food groups and nutrients with serum inflammatory markers (Cavicchia, 2009). The DII therefore offers a unique tool to assess the overall association of a maternal pro-inflammatory diet with child health outcomes; however this hypothesis has not been previously examined. Thus, the aim of this proposal is to evaluate the association between a validated DII of the mothers during pregnancy and ADHD symptoms in their children at the age of 4 years.

**Methods:** The study population was 3,421 mother–child pairs from four INMA birth cohorts in Spanish regions of Gipuzkoa (N = 544), Sabadell (N = 694), Asturias (N = 589) and Valencia (N = 813) and the RHEA birth cohort in Greece (N = 781) recruited between 2004-2008. A validated (Shivappa, 2013) DII was calculated based on food frequency questionnaire information collected during pregnancy. ADHD symptoms were assessed by ADHD-DSM-IV (18 items) in INMA cohorts and by Attention-Deficit/Hyperactivity Disorder Test (ADHD-T) (36 items) in RHEA cohort at around 4.5 years old of age, with questionnaires filled-out by teachers. Data on sociodemographic and anthropometric characteristics, diet, and lifestyle were collected through questionnaires. Association between maternal DII and ADHD symptoms of
children was evaluated through negative binomial regression models stratified by cohort.

**Results:** Statistically significant differences were observed in maternal DII depending on region (mean(sd)): Gipuzkoa (-1.64 (2.43)), Sabadell (-1.02(2.24)), Asturias (-1.76(2.40)) and Valencia (-1.01(2.44)) and RHEA cohort (2.36(2.01)). In preliminary pooled cohort analyses we found that maternal DII is not significantly associated with the risk of ADHD symptoms in children at 4 years of age. Subsequent analyses will evaluate differences in the association of interest according to region and other potential effect modifiers (eg, maternal overweight).

**Conclusions:** Proinflammatory diets of the mother during pregnancy may have adverse effects on the health of the offspring that are yet not well understood. This study examines the association of a validated maternal DII with and the risk of ADHD symptoms in the offspring at 4 years of age in five birth cohorts with variable dietary patterns, and will provide novel insights for the role of maternal diet in the cognitive development of the child.

**PO2.08 – Nutrition – Growth and cardiovascular health**

**PO2.08.01**

**Nutritional intervention in early life influences by sex the growth velocity during the first 18 months of age**

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**Background:** Growth velocity is a predictor of health in childhood and adulthood. Different studies have explored the effect of type of feeding in early life on infants’ growth during the first 1000 days of life. In the present study we aimed to analyse gender differences on the influence of a nutritional intervention in the early life on the growth velocity of the infants during the first 18 months of life.

**Methods:** 170 healthy term infants between 0-2 months of age were randomized in a double-blind study to receive either standard infant formula (F1: n = 85) or supplemented formula containing LC-PUFAs, milk fat globule membrane components and synbiotics (Nutriexpert® factor) (F2: n = 85). As control, 50 breast-fed infants (BF) were included. Weight, length and head circumference (HC) were performed at birth, 6, 12 and 18 months of age. WHO Child Growth Standards were used with 6-month intervals, and growth velocity was classified as slow (SG: < -1SD), normal (NG: ≥ -1SD and ≤ +1 SD) and rapid (RG: > +1 SD). Statistical analysis: Normal distribution was assumed using Kolmogorov-Smirnov. Differences in weight, height and HC increments by study groups and sex were analysed using Student t-test or Welch test and Chi-Square test for growth velocity were performed using SPSS 22.0.

**Results:** Male children showed higher increments of HC and weight between birth and 6 months of life than girls. According to study group and sex, between 12 and 18 months, male children F2 showed higher increments of length than male children F1; and BF male infants presented weight SG compared to children F2. In relation to girls, the BF group presented higher increments of HC between 6-12 months and 12-18 months than girls fed F1.

**Conclusions:** The growth velocity in head circumference and length according to sex seems to be related to type of feeding during early life. These results shows that sex can influence the nutritional response during early childhood. Further research is needed to elucidate the effect of feeding and sex on growth.

**PO2.08.03**

**Maternal high-fat diet alleviates detrimental impact of early life stress**

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**Background:** Adverse childhood experience is a main risk factor for anxiety disorders and depression later in life. Similarly, obesity, excessive weight gain, metabolic disorders and unhealthy high fat diet (HFD) during pregnancy have been recently hypothesized to increase the incidence of mental health disorders. In rats, maternal separation (MS) is a well characterized animal model of early life stress which leads to emotional and cognitive alterations as well as a hyper-reactivity of the hypothalamic pituitary adrenal axis to stress. Here we examine whether maternal HFD can have similar effects to early stress and/or can exacerbate the effects of MS in the offspring.

**Methods:** To dissociate HFD effect from maternal obesity effects, we used a protocol of maternal HFD exposure (40% from fat, restricted to gestation and lactation periods), which does not produce maternal obesity. From PND2 to PND14, stressed pups underwent daily MS for 180 min. During the separation sessions, dams were placed in new cages with free access to food (according to their respective diet) and water, whereas pups were placed in individual containers in another room under controlled temperature (28±2 °C). Control pups remained undisturbed with the dams. We examine the impact of maternal HFD on MS-induced developmental alterations in the PFC in PND15 pups. Then we studied the long-lasting impact of maternal HFD exposure on MS-induced alterations of emotional and cognitive behaviours, as well as some typical neuroendocrine and neurobiological changes affected by MS.

**Results:** Contrary to our hypotheses, maternal HFD alone has only small impact on gene expression in pups’ prefrontal cortex
(PFC) and on behavior in adulthood. In contrast MS led to changes in the expression of several genes such as Bdnf (brain derived neurotrophic factor), SHT-r1a (serotonin receptor 1a) and Rest4 (neuron-repressive silencer element, repressor element 1, silencing transcription factor (Rest), splicing variant 4) in the mPFC. Maternal HFD alleviates MS-induced mPFC gene expression changes. Furthermore, maternal HFD totally prevented the endophenotypes (anxiety, spatial memory, social behavior, hypothalamic–pituitary–adrenal (HPA) axis response to stress, hippocampal neurogenesis and visceral pain) associated with MS at adulthood. Finally, we also demonstrated that HFD intake reduced anxiety and enhanced maternal care in stressed dams.

**Conclusion:** Overall, our data suggest that a HFD restricted to gestation and lactation, which did not lead to overweight in dams, had limited effects in unstressed offspring, highlighting the role of maternal obesity, rather than fat exposure per se, on brain vulnerability during development. Furthermore our results reveal a protective effect of fat on the immature brain in a context of early life stress, possibly through an anti-stress effect in dams.

**PO2.08.04**

**Maternal protein restriction increases duodenal enteroendocrine cells in young rats.**

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Perinatal malnutrition predisposes to metabolic syndrome in adulthood. Animal studies have shown that maternal protein restriction (MPR) alters the regulation of food intake (FI) increasing the risk of obesity in adult offspring. Gastrointestinal peptides and particularly cholecystokinin (CCK) play a major role in short-term FI. CCK is secreted by a subtype of enteroendocrine cells (EEC) located in the proximal intestine. We hypothesized that MPR may alter the proliferation and/or differentiation of the CCK-producing cells, which could contribute to the programming of a deregulated FI in LP rats. Due to the very low proportion of CCK-producing cells in the gut (0.3-0.5% of total epithelial cells) we developed a ROSA26-eGFP transgenic rat model expressing GFP under the control of the CCK promoter. Low protein transgenic rats were obtained by protein restriction of their dams during gestation and lactation [8% (restricted, LP) vs 20% (Control)]. At 6 weeks old, duodenum was collected and the number and height of the villi were measured. The density of total EEC was determined by immunohistochemistry of chromogranin A a marker of mature EECs and CCK-producing cells stained in green were directly counted. The number of goblet cells was evaluated by hematoxylin-eosin staining. Expression of genes involved in intestinal stem cells fate specification and EEC maturation was measured by qRT-PCR. In the duodenum, the height of the villi was significantly higher in LP rats as compared to control but there was no difference in their number. MPR increased the number of total EEC (2.5 fold) and CCK-producing cells (2 fold) per villi, respectively, whereas the number of goblet cells was not affected. This MPR-induced increase in total EEC and CCK-producing cells was not related to the higher height of the villi since the ratio of EEC number to height of the villi was still higher in LP rats as compared to control. Altogether, these data suggest that MPR seems to specifically increase the density of total EECs and CCK-secreting cells in the duodenal epithelium. The mRNA expression of genes involved in early epithelial cells fate specification (Lgr5, Ath1) or endocrine lineage (Ngn3, Pdx1, Pax6, FoxA1) or CCK-producing cells (NeuroD1 and CCK) were not significantly affected by MPR. In contrast, the mRNA expression of mature EEC gene (Chga) was significantly reduced in LP rats as compared to control. Thus, neither endocrine progenitor proliferation nor CCK-producing cells differentiation appeared to be altered by MPR whereas EEC maturation would be reduced. As intestinal epithelium homeostasis is regulated by a balance between proliferation/differentiation along the crypt-villus axis and constant loss of differentiated cells at the villus tip, further study of proliferative and apoptotic process in EEC lineage of LP rats is in progress. To conclude, MPR induced-modifications of duodenal EEC which secrete CCK could contribute to the deregulated food intake observed in LP rats. Understanding how EEC may be programmed by perinatal malnutrition represents an important issue for preventing diseases of developmental origin such as diabetes and obesity. This work was supported by Region Pays de la Loire, INRA and LCL.

**PO2.08.05**

**Pre-pregnancy dietary patterns and associations with socio-demographic characteristics, maternal gestational weight gain and infant birthweight**

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Few studies have explored diet prior to pregnancy and its relationship with pregnancy outcomes. The objectives of this study were to: (i) derive pre-pregnancy dietary patterns for women enrolled in a prospective cohort (APrON) in the province of Alberta, Canada; (ii) describe associations between dietary patterns and socio-demographic characteristics; and (iii) describe associations between dietary patterns, maternal gestational weight gain (GWG) and infant birthweight. Upon enrollment into the APrON study (median age of gestation, 17 weeks), women aged 16-44 years (n = 1545) completed a
142-item food frequency questionnaire (FFQ) which queried the frequency of foods and beverages consumed ‘in the 12 months prior to pregnancy’. The 142 food items were collapsed into 49 food groups according to nutritional similarity, and frequency of consumption of foods in each group was summed. Dietary patterns were derived using principal components analysis (PCA), with orthogonal varimax rotation. Scores were calculated to represent women’s compliance with each dietary pattern retained. Scores were derived by multiplying the frequency of consumption of each food group by its coefficient for the pattern and then summing. These scores were then expressed as z-scores. Socio-demographic characteristics associated with the diet scores were assessed using linear regression models, adjusted for total energy intake. Associations between diet scores and infant birthweight and women’s GWG guideline concordance (below, met or exceeded the US Institute of Medicine, 2009 guidelines for total GWG) were assessed using linear and logistic regression models, respectively. Four patterns were retained (Table 1) which, combined, accounted for 22.9% of the variation in diet. Higher ‘Healthy Eating’ scores were more likely to be seen in those with higher levels of education (β0.13; P < 0.001), lower household incomes (β-0.07; P = 0.01) or levels of education (β-0.08; P = 0.001). Women with higher ‘Meat and Refined Carbohydrate’ scores were more likely to have lower incomes (β-0.08; P = 0.001) or levels of education (β-0.05; P = 0.035). Women with higher ‘Beans, Cheese and Salad’ scores were more likely to have higher household incomes (β0.11; P < 0.001) or be pregnant with their first child (β-0.13; P = 0.009). Women with higher ‘Tea and Coffee’ pattern scores were more likely to exceed GWG guidelines (RRR 1.17; P = 0.013), independent of pre-pregnancy BMI and education. There were no significant associations between pre-pregnancy dietary patterns and infant birth weight in this cohort of women. This is the first study to explore patterns of diet prior to pregnancy and associations with pregnancy related outcomes in Albertan women. Our observation that women with higher ‘Tea and Coffee’ pattern scores were more likely to exceed GWG guidelines, independent of pre-pregnancy BMI requires further examination. A better understanding of whether this pattern of diet represents a type of lifestyle or behavior which could contribute to excess gestational weight gain is needed in order to identify appropriate strategies for intervention.

The four retained dietary patterns and the food groups associated with each pattern (coefficients >0.2) were as follows:

**PO2.08.06 Early D-cysteine or L-cysteine supplementation prevents later-life hypertension and kidney damage in spontaneously hypertensive rats exposed to high-salt intake**

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**Background:** Nitric oxide (NO), hydrogen sulfide (H₂S), and renin-angiotensin system (RAS) are involved in the development of hypertension and kidney disease. We and others have demonstrated that early renal NO deficiency, a predecessor of hypertension, is a characteristic of the spontaneously hypertensive rat (SHR). Additionally, we found that young SHRs exposed to high-salt (HS) consumption develop accelerated kidney damage and hypertension, which is associated with impaired NO system and increased oxidative stress. Since exogenous H₂S has been reported to protect the SHR against hypertension, we therefore investigated whether supplementation of D- or L-cysteine (the precursor of H₂S) in early life can prevent hypertension and kidney damage is adult SHRs exposed to HS intake and elucidated the interplays between H₂S, NO, and RAS system.

**Methods:** SHRs aged 4 weeks were randomly assigned into four groups (N = 10 for each group): Group 1, SHR without treatment; Group 2, SHR + HS, rats received 1% NaCl in drinking water for 8 weeks; Group 3, SHR + NS + D, rats received HS for 8 weeks and D-cysteine (8 mmol/kg body weight/day) via gastric intubation between 4 and 6 weeks of ages; and SHR + HS + L, rats received HS for 8 weeks and L-cysteine (8 mmol/kg body weight/day) via gastric intubation between 4 and 6 weeks of ages. Blood pressure (BP) was measured in conscious rats by using an indirect tail-cuff method. All rats were sacrificed at 12 weeks of age.

**Results:** The major findings in this study were: (1) HS intake exacerbated hypertension and kidney damage in SHRs, which D- or L-cysteine supplementation prevented; (2) D- or L-cysteine supplementation reduced HS-induced increases of oxidative stress, which were not related to NO pathway; (3) D- or L-cysteine supplementation decreased renal mRNA expression of H₂S-generating enzymes, including Cbs, Cth, and Mps; (4) Renal 3-mercaptopropionate sulfoxtransferase (3MST) protein levels and activity were reduced by D- or L-cysteine supplementation; and (5) D- or L-cysteine therapy protected SHR against hypertension and kidney injury is associated with the decreased mRNA expression of Ren (encoded for renin) and increased protein levels of angiotensin II type 2 receptor (AT2R).

**Conclusions:** Conclusively, HS intake aggravated hypertension and kidney damage in SHRs, which early D- or L-cysteine supplementation prevents later-life hypertension and kidney damage.
therapy prevented. Although early D- or L-cysteine supplementation downregulated renal H₂S-generating enzymes in adult SHRs, their renoprotective and antihypertensive effects might be linked to increases of renal AT2R protein levels, decreases of renal mRNA levels of renin, and reduction of oxidative stress. Our data highlighted that targeting on endogenous hydrogen sulfide pathway before hypertension becomes evident by which the hypertension and kidney damage can be prevented in adult SHRs exposed to HS consumption.

**PO2.08.07**

**Maternal factors associated with antenatal breastfeeding self-efficacy and infant feeding outcomes at 6 weeks postpartum**

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**Background:** Despite national and international recommendations, breastfeeding rates in Ireland remain among the lowest in the world. Breastfeeding is a modifiable early-life behaviour that protects infants against many adverse health outcomes including, but not limited to, gastrointestinal infection, otitis media, and asthma. Breastfeeding also decreases the odds of offspring overweight and obesity. In preparation for a large randomised controlled trial of a breastfeeding-support intervention, we aimed to explore maternal characteristics associated with antenatal breastfeeding self-efficacy and infant feeding mode at 6 weeks postpartum among women giving birth in both a rural and an urban Irish hospital.

**Methods:** This is a prospective breastfeeding-support feasibility study conducted at two sites in Ireland: The National Maternity Hospital (NMH; urban), Dublin and Wexford General Hospital (WGH; rural), Wexford. Participants were nulliparous women over 18 years of age recruited at approx. 32 weeks’ gestation. Participants attended a study-specific breastfeeding class at 36 weeks’ gestation with a support partner, had a one-to-one lactation consultation early postpartum, and had the option to attend a weekly breastfeeding clinic for 6 weeks postpartum. Baseline demographic data and the validated Breastfeeding Self-Efficacy Scale Short Form (score range 14–70) were collected by questionnaire at the antenatal class. At 6 weeks postpartum, mothers completed an online questionnaire about feeding practices. We explored variables associated with antenatal breastfeeding self-efficacy and human-milk feeding (any/exclusive) at 6 weeks postpartum using Chi-square analyses.

**Results:** One hundred mothers participated (77 from The NMH and 23 from WGH) and provided baseline data; 64 mothers (49 from The NMH and 15 from WGH) provided follow-up data. Mothers were an average of 32 years of age, the majority were married or in a relationship, had 3rd-level education, and were Irish, 59% were under/normal-weight and 41% were overweight/obese. Median antenatal breastfeeding self-efficacy score was 42. Three maternal characteristics were associated with antenatal breastfeeding self-efficacy: mothers under 30 years of age, of non-Irish nationality, and who had given up smoking on discovering they were pregnant were significantly more likely to have breastfeeding self-efficacy scores above the group median. Factors associated with infant feeding mode (Figure 1) at 6 weeks postpartum varied depending on the hospital from which mothers were recruited. At The NMH, under/normal-weight mothers were more likely to be exclusively human-milk feeding than overweight/obese mothers (79% vs. 50%, \( P = 0.04 \)). There was a trend for non-Irish mothers to be more likely to be exclusively human-milk feeding than Irish mothers (84% vs. 60%, \( P = 0.07 \)) and for mothers with high antenatal breastfeeding self-efficacy to be more likely to feeding any human milk than those with low self-efficacy (96% vs. 81%, \( P = 0.08 \)). At WGH, mothers with 3rd-level education were more likely to be exclusively human-milk feeding than those with secondary education (71% vs. 0%, \( P = 0.002 \)).

**Conclusions:** Increasing breastfeeding self-efficacy, particularly among older mothers and Irish-born mothers, is a potential mechanism for improving breastfeeding outcomes in future interventions. Populations to target in future interventions include overweight and obese mothers, mothers with lower education, and Irish-born mothers.

**Feeding mode at 6 weeks postpartum (n = 64)**
Effect of maternal low quality protein diet on plasma biochemical parameters in adult male and female offspring

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Background: Sub-optimal nutrition during gestation and lactation may programme the development of chronic diseases later in life. Although several studies showed that exposure to maternal low protein diet may induce detrimental effects on offspring metabolism, the metabolic effects of maternal low quality protein diet on fetal life is largely unknown. This study aimed to determine the effects of low quality protein diet during pregnancy and lactation on plasma glucose, insulin, total cholesterol, triglyceride and leptin concentrations in male and female offspring at 20 weeks of age.

Methods: Virgin female Wistar rats (11 weeks old) were mated and divided into two groups as control (C, 20% casein protein; n = 6) and low quality protein diet (LP, 20% wheat gluten protein; n = 7), randomly. During gestation and lactation both groups were maintained on the same diets. Male and female offspring were weaned onto control diet. Animals were culled and plasma samples were taken at 20 weeks of age. Circulating parameters including glucose, insulin, total cholesterol, triglyceride and leptin were measured. The effect of maternal diet on maternal and fetal outcomes was assessed using a general linear model analysis of variance (ANOVA) (fixed factors, maternal diet and sex).

Results: Plasma glucose, insulin, total cholesterol, triglyceride and leptin concentrations in male and female offspring was shown in Table 1. Plasma glucose (p = 0.249), total cholesterol (p = 0.247) and triglyceride (p = 0.725) concentrations did not differ between groups in both sexes. While maternal low quality protein diet had no effect on plasma leptin levels (p = 0.738), female offspring’s plasma leptin concentrations were lower than male offspring (p = 0.024). Plasma insulin concentrations were significantly decreased in WG group in both sexes. (p = 0.016).

Conclusions: Maternal exposure to a low quality protein diet during gestation and lactation leads to reduced plasma insulin levels in male and female offspring during adult life. Future studies will continue to examine the influence of altered insulin levels on offspring’s phenotype.

Funding: The present study was funded by the Scientific and Technological Research Council of Turkey (TUBITAK), Number 115S538.

Table 1. Plasma glucose, insulin, total cholesterol, triglyceride and leptin concentrations in male and female offspring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Cone %20)</td>
<td>(Wheat g. 20)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>189.3±44.11</td>
<td>142.8±48.32</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>2.20±0.40</td>
<td>3.30±0.44</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>1.10±0.34</td>
<td>1.40±0.37</td>
</tr>
<tr>
<td>Insulin (ng/mL)</td>
<td>8.3±0.50</td>
<td>7.2±0.55</td>
</tr>
</tbody>
</table>

¹ Female offspring’s plasma leptin concentration was significantly lower than male offspring in both groups.

Inadequate Dietary Intake during Complementary Feeding at 12 and 18 Months of Age: PREOBE study

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Background: Nutrient requirements increase dramatically at 6 months of age after birth. Although breastfeeding is the best source of nutrients for infants, other foods are introduced to cover nutrient needs for optimal growth and development during the first 18 months of life. We aimed to analyse if dietary requirement of energy and important nutrients such as protein, sugar, vitamin D, iron, iodine and zinc were covered during complementary feeding in Spanish infants at 12 and 18 months of age.

Methods: 74 infants participating in the PREOBE study (http://www.ClinicalTrials.gov NCT01634464) were selected for the present study. Infant’s dietary assessment was performed using a 3-days 24h dietary record (2 working days and 1 weekend day) which was analysed using the DIAL software version 3.3.8. Nutrient intake was compared to the Dietary Reference Intakes (DRIs) (http://www.nal.usda.gov) and classified in three categories: intake <90% of requirements as low intake, intake between 90-110% as adequate intake and >110% as high intake. Kolmogorov-Smirnov normality test was applied for continuous variables and non-parametric tests (Chi²) was applied for categorical variables using SPSS version 21.0. Values with ±2 standard deviation (SD) of the mean were discarded.

Results: Most of the infants at 12 months of age exceed total energy (79.7%), vitamin D (62.7%) and zinc (87.1%) intake; however, almost 60% of infants were deficient in iron intake (58.6%, p < 0.001). At 18 months of age, 49.3% of infants showed an iron intake over requirements (p = 0.015), as well as 78.3% of them had an intake of energy over DRIs (p < 0.001) and the same for zinc (94.1%, p < 0.001). Only 5.6% of the infants had an adequate intake of vitamin D and the rest...
showed an inadequate intake (47.9% deficient or 46.5% excess, \( p < 0.001 \), respectively) at 18 months of age. 100% of of children, both at 12 and 18 months of age, 100% of infants showed an intake of proteins and sugar higher than recommended (\( p < 0.001 \)), while in the 80.0% of them iodine’ intake resulted insufficient (\( p < 0.001 \)).

**Conclusion:** Our results show an inadequate intake of total energy, proteins, sugar, vitamin D, iron, zinc, and iodine in infants at 12 and 18 months of age. These inadequacies of nutrient intake in infants observed in the present study has been demonstrated to be associated to higher risk of obesity, type 2 diabetes, cardiovascular diseases, and neurodevelopmental disorders. The results suggest the need to optimise the supply of energy, proteins, sugars and micronutrients in infants during the first 1.5 years of life to achieve the nutritional requirements, by improving the quality of complementary feeding during this critical period of life.

**PO2.08.10**

**Effects of maternal coconut oil supplementation during lactation upon their male rat offspring**

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Some oils considered healthy has been commonly used, even in critical periods. We studied the effects of coconut oil supplementation in dams during lactation upon endocrine-metabolic profile of the offspring, and the impact of their continued exposure over a lifetime. At birth, pups were divided into two groups: 1) Soybean oil (SO, \( n = 10 \)); and 2) Coconut Oil (CO, \( n = 10 \)). Dams of each group received the oils through gavage (0.5g/kg of body weight) during lactation. Half of the CO group continued receiving coconut oil in chow throughout life (CO+C). At weaning, milk from CO dams was more caloric than SO due to high cholesterol and triglycerides content, without change of body mass (BM) in dams and pups. At PN180, CO and CO+C groups had higher body mass, but CO group had higher visceral fat mass (VFM) and CO+C group had higher lean mass when compared with SO group. CO group had hyperphagia and CO+C group had hypophagia. CO group showed higher leptinemia when compared with SO and CO+C groups. No changes were found in blood glucose, insulin, corticosterone, cholesterol, triglycerides, liver content of cholesterol and triglycerides. CO group presented higher plasma total T3, TSH and mRNA expression of Dio1 in liver and Dio2 in brown adipose tissue (BAT) in relation to SO, without changes in TRβ1 in liver and UCP-1 in BAT. These parameters in CO + C were similar to SO group. Coconut oil changed breast milk composition, and caused important dysfunctions at long term, characterizing the metabolic programming phenomenon. In adult life CO group developed overweight, hyperleptinemia and thyroid dysfunction. Continuous exposure to coconut oil throughout life prevented most of these dysfunctions. Thus, we suggest that maternal supplementation of coconut oil can be deleterious to their offspring, but if these offspring are continuous supplemented with coconut oil in the diet they had a almost normal profile.

**PO2.08.11**

**The nutrition transition in the rural and urban Free State province, South Africa**

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**Background:** Urbanization is associated with increased risk for chronic diseases, largely due to the nutrition transition, characterised by changes from traditional to westernised diets. This study compared diet, levels of physical activity and anthropometry of rural and urban communities.

**Methods:** Dietary intake and physical activity were measured using 24-hour recalls and food frequency questionnaires in 558 rural (median age 50 years) and 419 urban (median age 45 years) participants. Anthropometric measurements were taken according to WHO guidelines.

**Results:** More than 60% of all participants had an inadequate intake of milk, fruits and vegetables and >50% are more than the requirement for meat and starchy foods. Intake of fats and oils as well as sweets and sugars was significantly higher in rural than urban participants, probably contributing to the significantly higher median energy intake in rural participants compared to urban (8495kJ versus 6463kJ for men and 7705kJ versus 6294kJ for women). 42% of rural men compared to 13% of urban men were classified as very active \( (p < 0.0001) \) and 37% of rural women and only 3% of urban women were very active \( (p < 0.0001) \). Median body mass index (BMI) of both rural and urban men was within the normal range \( (20.2kg/m^2 \) and \( 19.7kg/m^2 \) respectively). In contrast, both rural and urban women were more overweight (median BMI of 28kg/m^2 for both groups).

**Conclusion:** The diet of both urban and rural participants was not prudent, but rural participants were more active. A consequence of poor diet (mostly rural) and low levels of physical activity (mostly urban) are reflected in the high median BMI of women. Interventions aimed at addressing the consequences of the nutrition transition are a priority in both rural and urban areas.

**PO2.08.12**

**Assessment and determinants of compliance to vitamin supplementation in the Pune Rural Intervention in Young Adolescents (PRIYA) trial.**

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Background: One of the important determinants of outcome of any intervention trial is compliance of the study subjects to the intervention. If the compliance is not assessed adequately and controlled for during analysis, it might affect the interpretation of the effects of intervention by introducing a bias. Various methods are employed to estimate the compliance in intervention studies. We report assessment of compliance to vitamin supplementation in the Pune Rural Intervention in Young Adolescents (PRIYA) trial, and analyse the factors influencing compliance.

Methods: The PRIYA trial is a double blind randomized controlled intervention trial in 6 villages near Pune (India) since September 2012. It investigates the effects of pre-conceptional nutritional supplementation on growth and development of their offspring, and will assess the effect on risk of diabesity in the long run. 557 eligible young adolescents of the Pune Maternal Nutrition Study (PMNS) were randomized to receive either Vitamin B12 alone, or Vitamin B12 + multiple micronutrients (UNIMAPP) + milk powder, or placebo. Every month field workers distributed a bottle of investigational product (IP) with labelled instructions to take 2 pills per day. Previous month’s bottle was retrieved to count remaining capsules. Each bottle contained 65 capsules (30 × 2 = 60 capsules and 5 extra capsules to cover any loss or delay in delivery of the next bottle). Percent compliance was calculated for each month by the formula: [(65 − Remaining capsules) / 60] × 100, and average was calculated for each participant over duration of the trial. Compliance ≥ 80% was considered as good; whereas < 50% was considered as unsatisfactory. Multiple logistic regression models were run to determine the predictors associated with good as well as unsatisfactory compliance.

Results: The participants were 16.4 years at randomization (291 boys, 266 girls), mostly school going (average years of schooling: 11.6 yrs ± 1.6). We report compliance for the first 47 rounds of the intervention (Sept. 2012 – Jul. 2016). The median compliance was 81% [0, 108.3], 52% had good and 8% had unsatisfactory compliance. Not unexpectedly, the median compliance was 81% [0, 108.3], 52% had good and 47% had unsatisfactory compliance. Multiple logistic regression models were run to determine the predictors associated with good as well as unsatisfactory compliance.

Conclusion: Pill count is a feasible method to assess compliance in a community based rural intervention trial. Compliance in our trial appears to be higher than other long term community-based trials from different parts of the world. Compliance was better in women and in the lower socio-economic status participants but poorer in less educated.

There was a significant difference between trial groups which will need to be considered in analysis and interpretation.
facilitators to fruit and vegetable consumption: 1) Household dynamics whereby women were the last to eat and had little control over which foods were prepared; 2) Workload and feeling too tired to eat; 3) Likes and dislikes; 4) Time pressures with preparing and eating food a low priority; 5) Environmental Factors such as space and water for kitchen gardens, lack of availability in summer; 6) Social and Cultural Norms including food taboos and gender role expectations; 7) Cost and affordability.

On the supply-side, challenges included destruction of crops by wild animals and unpredictable weather; risk associated with transport.

Conclusions: Most women would like to consume more fruit and vegetables. Several potentially modifiable factors affecting intakes were identified. It is important that the supply chains of fruit and vegetables in these communities are well understood in order to identify opportunities to intervene to increase consumption.

**PO2.08.14**

**Mixed environmental exposures and early childhood nutrition status among children in Bangladesh and rural New Hampshire**

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**Background:** Increasingly, children are exposed to multiple chemicals in the environment, including heavy metals such as lead, arsenic, and manganese. In many countries, these exposures occur concomitantly with over- or under-nutrition, potentially contributing to poor growth and development. We aimed to investigate the associations between mixed environmental exposures and early childhood nutrition status, among cohorts of children in Bangladesh and rural New Hampshire.

**Methods:** Participants from Bangladesh are children aged 2-3 years who are members of a longitudinal birth cohort established to study the health effects of prenatal and early childhood exposures to metals in the environment; New Hampshire participants are members of the New Hampshire Birth Cohort Study, established to explore the effects of fetal exposure to environmental contaminants. In Bangladesh, umbilical cord blood samples were collected at birth, and blood samples were collected via venipuncture at age 20-40 months. Stunting status was determined using the Child Growth Standards developed from the World Health Organization Multicentre Growth Reference Study. Children with height for age < -2 z-scores below the median of the WHO Child Growth Standards were classified as stunted in all analyses. A multi-variable generalized additive model (GAM) was constructed using tensor product smoothing, ti(), to test for interactions between metal mixtures. Similar methods will be applied to our New Hampshire Birth Cohort.

**Results:** In Bangladesh, median (IQR) venous blood lead, manganese and arsenic levels were 5.7 (3.8-8.8), 2.0 (1.5-2.5) and 0.7 (0.3-1.3) μg/dL, respectively. Results of the GAM highlighted a significant main effect of each individual metal on early childhood stunting (p-values: As = 0.02; Mn = 0.004; Pb = 0.04) and a significant As/Mn interaction (p-value = 0.02). Evidence of a significant As/Mn interaction (p-value = 0.02) was found, indicating a manganese-driven reduced effect of arsenic on stunting in our Bangladeshi cohort.

**Conclusions:** Early childhood blood lead and arsenic concentrations were independently associated with an increased risk of stunting at age 20-40 months, whereas manganese exposure was associated with decrease of stunting in rural Bangladesh. Additionally, manganese exposure appeared to decrease the risk associated with arsenic in our Bangladeshi cohort, demonstrating the ability for individual main effects of heavy metals to operate synergistically in a mixture.

**PO2.08.15**

**Understanding the role of cell cycle in the fetal programming response to undernutrition**


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**Background:** The evidence linking early life nutrition to disease in adult life is now accepted as a cornerstone of public health development programmes all over the world. Maternal diet is a key factor affecting fetal development and maternal undernutrition is associated with increased risk of adult disease, involving metabolic syndrome, diabetes, hypertension and cardiovascular disease, alongside the occurrence of obesity in the offspring in the later life. We have previously shown in animal studies, that maternal protein restriction during pregnancy programmes anatomical, physiological and metabolic changes in exposed offspring. Changes in homeostatic regulation and tissue function that follow exposure to maternal undernutrition are closely associated with changes to organ structure. These changes to size and/or numbers of functional units in tissues must be driven by attenuation of cell proliferation and/or differentiation during development. This, and observations from transcriptomics studies in animals, suggest that the cell cycle is a target for nutritional programming. The aim of this study was to determine the progression of cell cycle in response to a challenging nutritional environment in vitro.

**Method:** A series of cell culture experiments were performed using varying amino acid concentrations (0-100% of stock concentrations) and serum replacements. C2C12 cells were cultured in Dulbecco’s modified Eagles medium (DMEM) and...
10% fetal bovine serum. After 24h, cells were treated with Hanks’ Balanced Salt Solution (HBSS) media which was supplemented with different amino acid concentrations and serum replacements for a further 24h. After treatment, cells were harvested, fixed with ethanol and labelled with propidium iodide. Cell cycle arrest was monitored with fluorescence-activated cell sorting, reading on a cytometer at 488nm. The expression of genes in the cell cycle regulatory pathway was determined by quantitative real-time PCR.

Results: Our preliminary result have showed that the culture media has a significant impact on the progression of cell cycle. Insulin Selenium Transferrin (ITS) were used as a serum replacement and showed limited proliferation in the cells compared to Fetal Bovine Serum (FBS) group (P < 0.05). In the FBS supplemented medium, cells grown in medium with 10% amino acids had significantly more cells arrested at G1 compared to cells grown at 100% amino acids (76% G1 arrest vs 67%, P < 0.05).

Conclusion: Limiting the concentration of amino acids in HBSS culture medium decreased the rate of C2C12 cell proliferation in vitro. These findings suggest that effects of protein restriction during development may be due to limiting amino acids altering regulation of the cell cycle. In order to further understand the mechanism that links the fetal environment with later health we will focus on determining the effects of amino acids on gene expression in the cell cycle regulatory pathway.

PO2.08.16
Maternal omega-3 supplementation and endotoxin challenge in late gestation and their effects on piglet health
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Background: Maternal stress, such as a bacterial infection occurring in late gestation, may predispose offspring to a variety of diseases later in life. It may also alter programming of developing systems within the fetus, such as the hypothalamic-pituitary-adrenal (HPA) axis and immune system. Dietary supplementation during the last trimester of pregnancy with immune-modulating compounds may be a means of reducing adverse effects of maternal stress on the developing foetus. Essential omega-3 polyunsaturated fatty acids (n-3 PUFA) such as docosahexanoic acid (DHA) and eicosapentanoic acid (EPA) are well-known for their immune-modulating and anti-inflammatory properties. Sources of these n-3 PUFA include fish products such as fish oil (FO) rich in DHA and EPA, and more sustainable sources such as algae, which is particularly rich in DHA. The aim of this study was to compare a control diet to diets supplemented with algae meal (Unextracted Aurantiochytrium limacinum CCAP 4087/2 algae FORPLUS™, Alltech Inc; AM) or FO, in addition to an immune stress challenge in sows during late gestation, to evaluate the effects of maternal n-3 supplementation on piglet growth, and stress and immune responsiveness.

Methods: Forty-eight sows were fed diets containing 3.12% AM, 3.1% FO or a control diet containing 1.9 corn oil starting during late gestation (gestation day 75; gd75). On gd112, half the sows in each treatment were immune stress challenged with bacterial lipopolysaccharide (LPS) endotoxin (10 ug/kg). After farrowing, the piglets remained with their dams until 21 days of age, and were then weaned. One week after weaning, four piglets per sow were immune stress challenged with LPS (40 ug/kg). At the same time, four piglets per sow were vaccinated with the novel antigens chicken ovalbumin (OVA) and Candida cellular antigen (CAA) at a dose of 1 mg/ml and received booster vaccinations two weeks later. Four weeks after the initial vaccination, a transdermal hypersensitivity immune challenge was performed using the same antigens. Blood samples were also collected to examine immunoglobulin IgG responses to both antigens.

Results: PUFA enrichment in sow blood and piglet brain was detected after 40 days on feed. The sow fever response to LPS challenge was attenuated in FO and AM treatments. Results from piglet performance, piglet stress and fever response to LPS, and piglet immune response to vaccination were affected by both maternal diet and maternal inflammatory status. Results also vary significantly between male and female offspring for parameters including basal cortisol levels, fever response, and skinfold thickness in response to OVA and CAA antigens.

Conclusions: The results from this study show that AM supplementation in sows during late gestation was largely comparable to FO in terms of the piglet stress response and health in the face of an immune stressor, and that FO and AM supplementation may help to prevent the negative effects of maternal stressors on fetal development in this instance.

PO2.08.17
Maternal dietary patterns and associations of having a small-for-gestational-age or a large-for-gestational-age baby
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Background: Maternal diet influences infant growth but associations with food quality are inconsistent. The aim of this study is to assess if maternal dietary patterns affect prevalence of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) in a well-nourished population.

Material/Method: This study is based on the Norwegian Mother and Child Cohort Study and includes 65,904 pregnant women who answered questionnaires in gestational week 15 (general health questionnaire) and 22 (food frequency questionnaire). The food frequency questionnaire covered intakes during the first half of pregnancy. We extracted three data-driven dietary patterns using principal component factor
analyses and categorized participants into four non-overlapping groups “high prudent”, “high Western”, “high traditional” and “mixed”. We obtained information about infant birth size and gestational age from the Norwegian Medical Birth Registry and calculated SGA and LGA according to ultrasound-, population-based and customized based definitions. We estimated odds ratios (OR) with 95% confidence interval (CI), and controlled for confounding with multiple logistic regression.

**Results:** Associations between maternal dietary patterns and SGA and LGA differed with different definitions of the outcome. Women in the high prudent group had increased prevalence of SGA_{ultrasound}, OR 1.25 (95% CI: 1.08, 1.54), compared to women in the high Western group (reference). Furthermore, women in the high prudent group had lower prevalence of LGA_{population}, OR 0.84 (95% CI: 0.75, 0.94) as well as for LGA_{customized}, OR 0.88 (0.78, 0.99). Similar trends were seen in sub-group analyses.

**Conclusion:** Apart from food quantity, food quality might affect birth weight. Adherence to the high prudent dietary pattern was associated with increased prevalence of SGA and decreased prevalence of LGA, compared to high Western diet. High adherence to traditional diet was associated with increased LGA prevalence.

PO2.09 – Embryonic, fetal and placental health

PO2.09.01

First trimester embryonic posture using 4D ultrasonography and Virtual Reality: a pilot study


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**Background:** Neurobehaviour in early life, an expression of the maturational process of the central nervous system, reflects embryonic development. Variations in embryonic development may result in variable pregnancy outcome and hence differences in neonatal health or even health in later life. It is unknown whether neurobehavioral development during embryonic life is associated with pregnancy outcome. Therefore, knowledge on neurobehavioral development during the embryonic period should be expanded. Neurobehavioral development can be reflected by embryonic posture and movement. In order to study embryonic posture it is supportive to image the embryo simultaneously in three dimensions. When studying embryonic movements, a fourth dimension (i.e. time) is needed. The availability of the I-Space Virtual Reality (VR) system allows for instant adjustments of optimal depth perception and therefore facilitates three-dimensional (3D) and four-dimensional (4D) visualization. The aim of this study is to test the reproducibility of embryonic posture measurements performed in the first trimester using 4D ultrasound data and VR. Secondly, we aim to describe the observed anatomic positions of various body parts.

**Methods:** For this observational pilot study 23 pregnant women were included, all participating in an ongoing prospective cohort study (Rotterdam periconceptional cohort (Predict study)). Using a GE Voluson E8 ultrasound machine transvaginal 4D ultrasound examinations were performed for 30 minutes between 9 and 10 weeks’ gestational age (GA). The acquired datasets were evaluated in the I-Space VR system. Datasets with a very low quality (quality score = 0), based on the overall clarity, could not be used for evaluation. For all frames it was determined whether the embryo was at rest or in movement. If distinction between rest or movement could not be made the frame was classified as un-evaluable. Subsequently, embryonic posture was evaluated once during each resting period. To determine posture, we evaluated the position of the head, spine, upper and lower extremities. To analyse the intraobserver and interobserver reproducibility of the distinction between rest and movement all measurements were performed by two investigators separately. To analyse the reproducibility of the embryonic posture we calculated the agreement of designated anatomic position of each body part in percentages.

**Results:** The data of 16 patients had overall good quality. The analysis of the embryonic posture showed a strong (>80%) intraobserver and interobserver reproducibility for the majority of the body parts. Figure 1 shows the anatomic position of embryonic body parts in an embryo between 9 and 10 weeks’ GA. Most body parts are in the same position in each embryo. Variation in anatomic body positions, within and between embryos, was seen in the head, spine, shoulders and wrists.

**Conclusions:** In this study, the posture of the embryo is measured for the first time using 4D and VR datasets. The reproducibility of embryonic posture measurements was high (>80%) in most body parts. Embryonic body parts do show a preference for specific anatomic positions. However, variation already occurred as early as 9 weeks. The current study opens a new era in research of embryonic posture and hence in neurobehavioral development during early life.
PO2.09.02

Fetal fractional thigh volume: a 3D-ultrasound marker of neonatal adiposity

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Background: Obesity in childhood is a major problem, both in the developed and the developing world. The predisposition of obesity is suggested to originate in the prenatal, and even in the periconceptional period. Increasing evidence shows that adiposity in the neonatal period is a better marker for childhood obesity than (birth)weight. If we would be able to identify fetuses at risk for neonatal adiposity during pregnancy, we might have an opportunity to decrease obesity rates in the future. In this study, we assessed the use of a three-dimensional (3D) ultrasound (US) soft-tissue marker of neonatal adiposity. Previous studies showed that this marker, called fetal fractional thigh volume (TVol), can be used shortly before delivery as marker of neonatal adiposity. Measurement earlier in pregnancy might however lead to earlier identification of fetuses at risk for neonatal adiposity, providing a longer timeframe for interventions. Therefore, we investigated the association between neonatal adiposity and fetal TVol from mid-gestation onward, and assessed whether TVol growth during pregnancy - based on serial measurements – would provide a better marker for neonatal adiposity than single TVol measurements.

Methods: Embedded in the Rotterdam Periconception cohort, this prospective perinatal cohort study was conducted between September 2014 and September 2016. Singleton pregnancies with term born neonates were selected for the analyses. Fetal TVol was measured on 3D-US scans performed at 22, 26 and 32 weeks of gestation. Neonatal adiposity measurement (percentage body fat, %BF) was planned between 42 weeks postmenstrual age using air-displacement plethysmography (PEAPOD®). Associations between neonatal %BF and TVol (single measurements and TVol growth) were analyzed using linear regression analysis, taking into account the following covariates: gender, gestational age at 3D-US and at body composition measurement, maternal age, smoking and BMI and parity.

Results: Seventy-nine mother-child pairs with 192 prenatal 3D-scans were included in the analyses. Median (interquartile range) TVol increased from 7.6 (7.1;8.5) cm³ at 22 weeks to 36.5 (33.8;40.9) cm³ at 32 weeks. Median neonatal %BF was 14.3% (11.7;17.0). TVol at 22 weeks (β = -1.58, 95%CI -2.49; -0.67, explained variance 0.31) and to lesser extend TVol growth between 22 and 32 weeks were negatively associated with %BF (explained variance 0.18). TVols at 26 and 32 weeks were not significantly associated with %BF.

Conclusions: This prospective periconception birth cohort shows that fetal TVol in mid-gestation is an easily applicable 3D-US marker, potentially useful for the prediction of neonatal adiposity, and for monitoring the effects of prenatal prevention strategies for childhood obesity. Serial assessment for TVol growth between 22 and 32 weeks of gestation showed little additional value for prediction of neonatal adiposity when compared to the single TVol measurement at 22 weeks.

PO2.09.03

Prenatal salivary hormone levels and the risk of small-for-gestational age

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Introduction: Small-for-gestational age (SGA) infants are at higher risk for short- and long-term adverse health outcomes. There is evidence in animals that maternal sex hormones such as testosterone can affect fetal growth as well as postnatal catch-up growth. The extent to which maternal hormones affect fetal growth in humans is not known.

Methods: We analyzed 2⁷th trimester saliva samples (3 samples per participant from one day) from 481 pregnant women in a Mexico City birth cohort (PROGRESS). Progesterone, testosterone, estradiol, dehydroepiandrosterone and cortisone were analyzed using LC-MS/MS and log-transformed. We used modified Poisson regression models to calculate risk ratios of SGA versus appropriate-for-gestational age (AGA) according to maternal hormonal status. We also analyzed associations between hormones and Fenton birth weight-for-gestational age z-scores using linear regression models. We adjusted all models for maternal age, sex, BMI, parity, smoking, education and socioeconomic position. We also performed stratified analyses by sex.

Results: There were 72 (15.0%) SGA infants. Median (IQR) testosterone was 14.6 (15.7), estradiol was 31.0 (37.7), and testosterone/estradiol ratio was 0.5 (0.4). Higher testosterone/estradiol ratio was associated with a higher risk of SGA versus AGA (RR = 1.50 [95% CI: 1.13, 1.99]) per IQR increment in log ratio. Higher testosterone/estradiol ratios were also associated with lower birth weight z-scores (β = -0.15 [95% CI: -0.27, -0.02]). Stratified analyses revealed similar effect estimates among boys and girls (β = -0.14 [95% CI: -0.33, 0.05] and β = -0.15 [95% CI: -0.31,0.02], respectively). There were
Background: Young maternal age is associated with an increased risk of adverse fetal and birth outcomes. We used data from a prospective cohort of pregnant women living in Mumbai slums, India, to examine associations of maternal age with fetal ultrasound measures and newborn anthropometry, and whether associations could be explained by maternal parity, BMI, height, lifestyle and socio-demographic factors.

Methods: The data were collected between 2006 and 2012 as part of the Mumbai Maternal Nutrition Project, a randomised controlled trial investigating the effect of newborn measures of a food-based micronutrient-rich supplement taken by the mother from before pregnancy until delivery. At recruitment, maternal weight and height were measured, and information about the women’s socio-economic status, parity, BMI, height, lifestyle and socio-demographic factors.

Results: The sample comprised of 1,653 singleton fetuses from a prospective cohort of pregnant women living in Mumbai slums, India, to examine associations of maternal age with fetal ultrasound measures and newborn anthropometry, and whether associations could be explained by maternal parity, BMI, height, lifestyle and socio-demographic factors.

Conclusion: Fetuses of younger mothers were smaller from the first to the third trimesters. Maternal parity, BMI, height, lifestyle and socio-demographic factors did not influence the associations between maternal age and fetal size suggesting the possible effect of other factors not captured by these variables.

PO2.09.05

Antenatal fetal size, birth weight and maternal deprivation - not so straight forward after all?

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Introduction: Deprivation is associated with increased risk for low birth weight (LBW) and also for many non-communicable diseases (NCD). What is not understood is the gestation at which deprivation is first associated with reduced fetal size. Our hypothesis was that deprivation would be related to reduced fetal size at birth and also in the first, second and third trimesters.

Methods: Routinely acquired fetal ultrasound scan data were linked to neonatal and maternal details held in the Aberdeen Maternity and Neonatal Databank. Maternal details included the Carstairs index of deprivation (1 = least deprived, 6 = most deprived), maternal height, age, parity, self-reported smoking status. Neonatal details included sex, gestation and birth weight. Fetal and neonatal measurements were expressed as z score standardised for gestation.

Results: Birth weight and occipito frontal circumference (OFC) were available in 56,967 infants. The mean birth weight and OFC was lowest in infants whose mothers came from the most deprived communities, and measurements were relatively increased in deprivation categories 5, 4 and 3 but were similar across categories 1, 2 and 3, p < 0.001 for trend (see figure). This trend was also seen for the subset where fetal scan data were also available. The mean z score difference in birth weight and OFC between infants whose mothers were from the most and least deprived communities were 0.09 [95% CI 0.06, 0.12] and 0.13 [95% CI 0.10, 0.16] respectively. Fetal measurements were available in the third trimester from 5,974 pregnancies; here there was no difference in estimated fetal weight (EFW) across deprivation categories, and there was increased biparietal diameter (BPD) in category 2 compared to category 6 (mean difference 0.10 [95% CI 0.01, 0.19]). In the second trimester, data from 15,896 scans were available and EFW was
highest in the most deprived communities and lowest among categories 1-3, \( p = 0.007 \) for trend (see figure); the mean difference between categories 1 and 6 was 0.11 [95% CI 0.04, 0.19]. The relative increase in weight between second trimester and birth differed across deprivation categories (\( p < 0.001 \)), and was on average 0.18 z scores greater [95% CI 0.09, 0.27] for those in the least deprived compared to those in the most deprived category. There was no relationship between first trimester size and deprivation among the 13,533 pregnancies studied.

**Conclusion:** There are relatively minor associations between deprivation and fetal size and growth, but the nature of the relationship may not be straightforward. These findings need replication on other populations.

**PO2.09.06**

**Maternal PI GF is positively correlated to cord blood leptin concentrations in infants born small-for-gestational-age**

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**Background:** Circulating placenta growth factor (PI GF) is a biomarker of placental function. Mothers with low circulating PI GF levels are more likely to deliver small-for-gestational-age (SGA) infants who are at increased risk of metabolic syndrome related disorders in later life. Leptin and adiponectin are important hormones in regulating insulin sensitivity. We sought to assess whether maternal circulating PI GF levels are associated with leptin and adiponectin concentrations in infants born SGA.

**Methods:** This was a nested case-control study in a prospective pregnancy cohort - the Integrated Research Network of Perinatology in Quebec (\( n = 2366 \)). Maternal plasma PI GF at the 3rd trimester (32-35 weeks) of gestation and cord plasma leptin and adiponectin were measured. The study included 162 SGA (birth weight \(<10^{th}\) percentile) and 162 AGA (25\(^{th}\) -75\(^{th}\) percentiles) singleton infants matched for ethnicity, smoking status and gestational age.

**Results:** SGA newborns had significantly lower maternal PI GF and cord plasma leptin concentrations than AGA infants. Maternal plasma PI GF concentrations were positively correlated to birth weight (\( r = 0.35, P < 0.0001 \)) and cord plasma leptin (\( r = 0.14, P = 0.03 \)) concentrations, but not correlated with adiponectin concentrations. Interestingly, there were differential correlations between maternal PI GF and cord leptin concentrations in SGA (\( r = 0.20, P = 0.03 \)) and AGA (\( r = -0.08, P = 0.35 \)) infants. Among SGA neonates, those with low maternal PI GF concentrations (<25th percentile) had lower cord blood leptin concentrations (median: 6128.00 vs. 8355.00 pg/ml, \( P = 0.01 \)).

**Conclusions:** Our study is the first to reveal that maternal PI GF is positively correlated to cord blood leptin in SGA infants. Maternal PI GF may be a biomarker partly reflecting adiposity in fetuses/infants.

**PO2.09.07**

**Gender-specific differences in the association between first-trimester HbA1c and placental volume**

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**Background:** Hyperglycemia during pregnancy has been linked to detrimental outcomes for both the mother and the unborn child beyond the manifestation of gestational diabetes mellitus (GDM). The placenta has a central function in fetal glucose supply and placental volume has been related to the risk for both small- and large-for-gestational age neonates. As the first trimester is of particular importance for fetal development, we aimed to assess the association between HbA1c, as a marker for glycemic control, and placental volume in the first trimester of pregnancy. We further wanted to examine potential interactions by fetal gender, as recent studies suggest an effect of fetal gender on maternal risk for GDM.

**Methods:** Analyses were based on data from the PRINCE (Prenatal Identification of Children Health) cohort, a population-based low-risk prospective cohort study from Hamburg, Germany. To be included in the present study sample, data on first trimester-HbA1c and placental volume had to be available, leading to a study sample of 100 women (\( n = 50 \) women carrying a female and male fetus each). To test for differences according to fetal gender, Student’s t-test and Mann-Whitney-U test were used according to variable distribution. A test for interaction was conducted, to assess possible sex-specific effects. Multivariate linear regression models were performed to cross-sectionally examine the association between HbA1c and placental volume. We included maternal age, first-trimester BMI and estimated first-trimester fetal weight as possible confounding factors.
Results: The mean HbA1c value in our cohort was 4.86% (SD: 0.28), with no significant statistical difference regarding fetal gender (4.89% and 4.84% for mothers carrying a female or a male fetus, respectively; \( p \) for difference = 0.4). Likewise, first-trimester placental volume did not differ between fetal gender (\( p \) for difference = 0.4). The association between HbA1c and placental volume may depend on fetal gender with a positive association observed for women carrying a male fetus and a negative relation for those with a female fetus (test for interaction, \( p = 0.06 \)). In a combined multivariate regression model including an interaction term for HbA1c and fetal gender, for each percent increase in HbA1c, placental volume increased by 44.8 mm\(^3\) in women carrying a male fetus as compared to those carrying a female fetus (\( p = 0.02 \)).

Conclusions: Despite similar HbA1c values in the normal range, our results indicate a gender-specific effect of HbA1c on placental volume. While this supports available evidence of an effect of fetal gender on the risk of GDM and might indicate a possible mechanistic link, further, preferably prospective investigations are required to examine the clinical relevance of our findings.

PO2.09.08

Sex-specific changes in placental glucocorticoid barrier at term after a single course of antenatal betamethasone in preterm pregnancies

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Background: We have previously shown that antenatal betamethasone (BET) exposure in preterm singleton and twin pregnancies reduces fetal weight gain in a dose-dependent manner without improving neonatal morbidity or mortality. In both animal and human studies, sex-specific strategies for adapting to changes in the uterine environment such as glucocorticoid treatment have shown poorer outcomes in males. Whilst the mediators of these strategies are unknown, it is likely that differences in placental glucocorticoid metabolizing enzymes (11-\( \beta \) hydroxysteroid dehydrogenase type 1 & 2; HSD11B1 & 2), could contribute to the observed sex-dependent responses to antenatal glucocorticoids.

Methods: Pregnant women treated with a single course of BET (n = 86, 2 x 12 mg intramuscular, 24hrs apart) between 23 5/7 to 34 0/7 weeks of gestation (wks) were compared to gestational-age-matched controls (n = 92; range: 31 4/7–41 4/7 wks) without BET treatment. Maternal venous blood samples, umbilical venous blood samples as well as placental samples were collected. Sex-specific BET effects on neonatal anthropometrics, neonatal outcome parameters, umbilical and maternal cortisol and ACTH levels, HSD11B1 and HSD11B2 protein levels and HSD11B2 activity levels in preterm and term gestations were analyzed. Data were analyzed using a Mann-Whitney U test or an independent-samples t-test, then further split into subgroups by gestational age (< 37 0/7 and ≥ 37 0/7 wks) and analyzed with a Kruskal-Wallis test or one-way ANOVA. Data were controlled by ANCOVA for possible confounders such as sex, gestational age, maternal weight gain, placental signs of amnion infection and onset of labor. Significance was accepted at \( p < 0.05 \).

Results: In females born ≥ 37 0/7 wks, a single course of antenatal BET treatment significantly reduced head circumference compared to controls (34.5 ±0.21 cm vs. 33.7 ±0.23 cm, \( p < 0.05 \)). Although no significant changes in maternal and fetal cortisol levels could be detected in females, antenatal BET exposure resulted in lower placental HSD11B2 protein levels and lower HSD11B2 activity levels in females when born ≥37 0/7 wks (\( p < 0.05 \)). Antenatal BET treatment in males reduced body length compared to controls (49.8 ± 0.39 cm vs. 46.0 ± 0.76 cm, \( p < 0.05 \)), independent of gestational age at delivery. Maternal and fetal cortisol levels in males were not significantly changed after BET exposure, but placental HSD11B2 protein levels were increased compared to controls (\( p < 0.05 \)).

Conclusions: BET exposure significantly decreased HSD11B2 protein levels and activity in term-born females suggesting that the female fetus is exposed to higher levels of maternally derived cortisol late in gestation, which may facilitate autonomous development of fetal hypothalamic-pituitary-adrenal (HPA) function. This may be a strategy to survive any potential maternal insults, but could contribute to an altered HPA-axis later in life. Further research is needed to conclude the significance of increased HSD11B2 levels in males. However, studies in newborns have reported higher free cortisol responses in males compared to females after a mildly stressful behavioral assessment procedure (Neonatal Behavior Assessment Scale) and psychological stress studies revealed higher cortisol responses in young men than in young women after exposure to acute real-life psychological stress.

PO2.09.09

Occupational exposure to cosmetics is associated with excessive fetal growth and preterm birth. Results from the Elfé and Epipage2 cohorts

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Background: The cosmetic sector employs a large proportion of women of childbearing age as hairdresser, beautician, man-icure, perfume sellers… Cosmetics contain many different compounds such as aromatic amine derivatives, solvents, alde-hydes, phthalates and parabens. Some of these compounds have teratogenic, foetotoxic or endocrine disrupting activity in animals. Previous studies have suggested an excess risk of small for gestational age (SGA) infants and premature births in this sector. Large for gestational age (LGA) has not been examined as an outcome. We used the data of two large French birth cohorts to study associations between occupational exposure to cosmetics and birth weight and prematurity.
Methods: Both cohorts, Elfe and Epipage2, recruited children at birth in 2011. Infants born after 33 weeks of gestation (GW) were enrolled in Elfe (N = 18329) from a random sample of 340 French maternity units (oversampling large units) whereas Epipage 2 targeted those below 34 GW in all maternity units of 340 French maternity units (oversampling large units) whereas

Occupational exposure to perfumes (N = 424) was associated with an excess risk of preterm birth. Compared to non-exposed, adjusted OR associated with exposure of 1-5%, 5-50%, ≥ 50% of work time were respectively 0.95 (0.70-1.30), 2.13 (1.13-4.02), 2.37 (0.99-5.68). This was not observed for exposure to other cosmetics. No excess risk of SGA was observed whatever the prematurity strata. In contrast, occupations in the cosmetics sector were associated with an OR for LGA of 1.20 (1.00-1.44) and 1.42 (1.14-1.77) in term and moderately preterm Elfe children respectively. Although none of the analyses related to frequency of exposure to specific subgroups of cosmetics was significant, the highest OR for LGA were observed for skin products.

Results: Occupational exposure to perfumes (N = 424) was associated with an excess risk of preterm birth. Compared to non-exposed, adjusted OR associated with exposure of 1-5%, 5-50%, ≥ 50% of work time were respectively 0.95 (0.70-1.30), 2.13 (1.13-4.02), 2.37 (0.99-5.68). This was not observed for exposure to other cosmetics. No excess risk of SGA was observed whatever the prematurity strata. In contrast, occupations in the cosmetics sector were associated with an OR for LGA of 1.20 (1.00-1.44) and 1.42 (1.14-1.77) in term and moderately preterm Elfe children respectively. Although none of the analyses related to frequency of exposure to specific subgroups of cosmetics was significant, the highest OR for LGA were observed for skin products.

Conclusions: Our results suggest that LGA is an outcome that deserves attention in the analysis of potential adverse effect of occupations exposed to endocrine disruptors. The excess prematurity risk for occupational exposure to perfume products may reflect specific exposures or working conditions that were not accounted for.

PO2.09.11
The effects of glucocorticoid exposure on the preimplantation human embryo
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Insults during the 1st week post-fertilization may affect the developmental trajectory and long-term health outcome of the human embryo. During this window, the embryo divides to form the trophectoderm (TE), primitive endoderm (PE) and epiblast (EPI). Subfertility affects 1 in 6 couples, but the current success of assisted reproductive medicine (ART) is ~ 40%. Glucocorticoids (GCs) are commonly used as an adjuvant therapy to improve success; however, prenatal GC exposure has been associated with adverse effects on offspring outcome. Further, the effects of GCs have been shown to persist long after withdrawal, thus preimplantation GC exposure may impact the first lineages and initiate a cascade of reprogramming events ultimately impacting offspring outcome. Studies examining the immediate and long-term potential for

PO2.09.10
Erasmus MC, ROTTERDAM, The Netherlands

Current knowledge on embryonic growth and development in the general population is derived from previous studies assessing fetal growth using conventional ultrasound, or in vivo studies on developmental stages of the embryo after miscarriage. Also, although strong evidence suggesting differences in first trimester growth exists, pregnancy dating using one crown-rump length measurement at 12 weeks of gestation is still routine care. This approach assumes no variation in first trimester growth. However, recent studies suggest that impaired growth at 12 weeks of gestation is associated with adverse health outcomes, for example adverse cardiovascular risk profiles in school age children. These findings suggest embryonic and fetal growth and development in the weeks after conception play a critical role in a human life, and could be an important predictor for health in later life. Modern methods to assess embryonic and fetal growth before 12 weeks include transvagal 3D ultrasound and analysis using Virtual Reality, facilitating precise estimation of crown-rump length and estimation of more advanced parameters, such as embryonic volumes, brain development and assessment of Carnegie stages. Currently, such data is available in a hospital based population; data on embryonic and early fetal growth and development measured using 3D ultrasound in a large healthy population is lacking. We will discuss approaches for assessing embryonic growth in a large population-based prospective cohort study. We invite women in the first weeks after conception. Serial ultrasound volumes at 7, 9, and 11 weeks will be acquired and embryonic growth and development will be measured offline, using V-scope software in a BARCO I-Space or desktop Virtual Reality system.

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reprogramming following preimplantation GC exposure in the human are lacking. The aim of this study was to investigate the impact of preimplantation GC exposure on the initial lineages of the human embryo and identify key genes modified during this insult. Using single-cell RNA-sequencing, we have now have preliminary data from GC exposed (n = 7 embryos, 271 cells) and control (n = 18 embryos, 531 cells) human embryos on embryonic day 7. On average 9366 ENSEMBL genes were detected per cell. Using MAST, 1922 genes were significantly (FDR < 0.001) differentially expressed between the GC treated embryos and controls including metabolic genes such as INSIR, IGF2, MTHFD1 and CYPI9A1, immunological genes ILK and IL6, pluripotency genes HAND1 and IFITM1, steroidogenic genes POOMC, HSD17B12 and CYPI1A1, and epigenetic genes DNMT3L, DNMT1, TET1 and TET2. This data now demonstrates that the human embryo is susceptible to preimplantation GC exposure and that genes important in development, metabolism and the epigenome are altered. Computational approaches will determine the timing of events, transcriptome/methylome signatures and signaling components underlying these modifications. Delineating key genes and pathways modified will provide crucial information pertaining to the comprehension of mechanism(s) underlying embryo reprogramming and potential for disease/disorder onset later in life. Data from these studies may aid with the therapeutic use of GCs during ART.

PO2.09.12
Measurement of pulmonary vascular volume using virtual reality three-dimensional ultrasound in fetus with an increased risk of chronic lung disease
Erasmus MC, ROTTERDAM, The Netherlands

Background: To study the pulmonary vascular volume (PVV) using three-dimensional (3D) virtual reality (VR) ultrasound in fetus at risk of chronic lung disease (CLD).

Methods: 3D power Doppler volumes of the pulmonary vasculature were obtained in fetus at risk of developing CLD between April 2012-December 2014. Sixty-eight fetus were included, of which 37 with a congenital diaphragmatic hernia (CDH), 9 with an omphalocele, 18 with a congenital vascular anomaly (CPAM) and 4 with congenital anomalies resulting in an oligohydramnios. The PVV was measured using a 3D-VR ultrasound technique in the BARCO I-space and correlated with postnatal outcome (postnatal mortality).

Results: The survival rate was 75% (51/68). The median [interquartile range] of the PVV in mm³ at 20, 26 and 30 weeks gestational age (GA) for neonates who survived versus those who died was 172 [57.8-452.3] vs 32 [0.3-28.3], 487.6 [164.3-972.5] vs 88.3 [24.5-225.2] and 271.5 [139.3-720.5] vs 263.8 [12.1-713.6], respectively. The PVV in all fetus at risk for CLD who survived, was significantly larger at 20 (<p,0.001) and 26 (p,0.003) weeks GA.

Conclusions: The PVV is significantly larger in surviving fetus at risk for CLD at 20 and 26 weeks GA and can be used as a valuable measurement in the prediction of postnatal outcome. Part of the data described in this abstract were previously presented at the ISUOG world congress in 2014 (OC18.01).

PO2.09.13
Intrauterine growth restriction alters gene expression in white adipose tissue in aged female mice
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Background: White adipose tissue (WAT) is a major endocrine organ. The factors produced by WAT, including tumor necrosis factor α, interleukin-6, leptin, adiponectin and angiotensinogen, are involved in regulation of satiety, lipid metabolism, glucose metabolism, inflammation and cardiovascular health. The origin of WAT and its progenitors takes place in early life, which makes it a potent target for developmental programming. Intrauterine growth restriction (IUGR), which complicates around 10% of all pregnancies, is known to compromise metabolic health later in life. The aim of this study is to examine the long-term consequences of IUGR on WAT physiology in aged mice.

Methods: IUGR was induced by conditional knocking out of Tjαp2c⋅, which encodes the transcription factor AP-2 gamma protein, from embryonic day 8.5 onwards in TBPBA⁺ progenitor cells. This leads to growth arrest of the placental junctional zone. Both male and female offspring were followed until 9 to 12 months of age. Gene expression and DNA methylation of several adipogenic, lipogenic and inflammatory genes were analyzed in gonadal WAT.

Results: Both males and females in the Tjαp2c-/- group show a decreased body weight at birth and later in life compared to the wild types. In gonadal WAT, which is part of the visceral WAT, gene expression of Lipoprotein Lipase (Lpl), Fatty Acid Synthase (Fasn) and CCAAT-enhancer-binding protein α (Cebpα) is significantly increased in females and there is a trend for increased glucocorticoid receptor (Nrr3c1) gene expression. Free fatty acids in serum are increased in IUGR females at later life. Remarkably, none of these changes is seen in males.

Conclusion: IUGR leads to disturbed lipid signaling of the WAT in female mice. Adipogenic and lipogenic genes, which promote adipocyte differentiation and hypertrophy and are associated with obesity, are increased. Plasma free fatty acids are increased, which is also seen in obesity, while body weight is not increased. Increased free fatty acids are a major link between obesity and its consequences, including metabolic syndrome and atherosclerotic vascular disease. These results
PO2.09.14

The different response of male and female fetuses to Vibratory Acoustic Stimulation test

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Introduction: One of the most common test used to assess the health of fetus is Non Stress Test (NST); Vibratory Acoustic Stimulation (VAS) is applied to reduce non-reactive cases and the time of NST. Sleeping of fetus in the uterus starts from 24th week in third trimester of pregnancy; even can dreams during this time. The vibratory and acoustic waves are produced by an electric device with specific frequency and intensity in vibratory acoustic stimulation test; Therefore VAS can be used to wake the fetus up while sleeping and NST with improved acoustic stimulation is a convenient, fast, safe, and effective method on detecting false non-reactive NST and it can increase the specificity of NST.

Aim: This is an analytical and prospective study aims to investigate the different response of male and female fetuses to VAS test in the Specialized Clinic of Gynecology and Obstetrics of Rajaie Hospital in Tonekabon, Iran, in 2016.

Methods and Materials: One hundred women (56 male and 44 female fetuses) with gestational age of 32-40 weeks were included in this study through random sampling. The pregnant women lay on the flank and NST was carried out before the VAS, then fetus’s head was stimulated for 3 seconds from over the uterus by using an electric toothbrush and NST was performed again. The result of NST and the time required to achieve the result of NST was recorded in the prepared checklist. Diabetic mothers, malformed fetus, cigarette smokers, drug abusers and CNS-drug consumers were removed from the study. The data obtained were analyzed by paired T-test, one way ANOVA and Pearson correlation in SPSS19 software.

Results: Paired T-test indicated that there was statistically significant difference between the mean reaction time of NST before and after VAS in women with female fetuses with 95% confidence and less than 5% margin of error. However, in women with male fetuses there was no statistically significant difference between the mean reaction time of NST before and after VAS. The difference of average reaction time of NST before and after VAS in pregnant women with female fetuses was more than women with male fetuses; it means that there was more decrease in average reaction time of NST in female fetuses (108.2 seconds↓) than male fetuses (50.26 seconds↓). Pearson correlation test showed no correlation between difference of reaction time of NST before and after VAS with gestational age, mother’s age and gravidity; this means that increase or decrease in difference of reaction time of NST before and after VAS have no correlation with increase or decrease of mentioned variables.

Conclusion: The results of this primary research suggest use of VAS for decrease of non-reactive cases and time of NST. Considering the fact that the primary auditory cortex in the brain of fetus is formed at 26-28 weeks of pregnancy and due to that VAS increase the reactive cases of NST significantly after 26th week of pregnancy, therefore VAS’s response confirms the health of brain stem and the auditory nerves in the fetus indirectly.

PO2.09.15

Maternal high-fat diet programs sex-specific alterations of the endocannabinoid system and antioxidant activity in liver of adult rats


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Background: Maternal high-fat diet consumption during perinatal period programs obesity and liver metabolism changes in adulthood. Obesity is related to over activation of the endocannabinoid system (ECS) in humans and rodents. ECS activation in liver increases lipogenesis and contributes to steatosis development. However, the relationship between the ECS and metabolic programming is poorly known. We hypothesized that maternal high-fat diet would alter liver metabolism in parallel to sex-specific changes in the ECS of male and female adult offspring. The aim of this study was to evaluate the effect of maternal HF diet on liver content of the main components of the ECS, cannabinoid receptors (CB1 and CB2) and metabolizing enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). In addition, we aimed to evaluate liver antioxidant system and plasma lipid profile of the offspring at adulthood.

Methods: Female progenitor rats received control (C; 9% fat) or high-fat diet (HFD; 29% fat) for 8 weeks before mating and during pregnancy and lactation. Male and female offspring were fed control diet from postnatal day 21 until 180-day-old, when they were killed for blood and liver harvest.

Results: Maternal HF diet programed increased food intake, body weight and white adipose tissue mass in both male and female adult offspring. However, we observed higher plasma and liver content of triglycerides only in male HF offspring (+67%, p < 0.05), without effect on total cholesterol or non-esterified fatty acid content. Maternal HF diet also increased the protein content of CB1 (+68%, p < 0.05), CB2 (+60%, p < 0.001), FAAH (+65%, p < 0.01) and MAGL (2 fold, p < 0.001) in liver of adult male rats, while it did not affect liver ECS of female offspring. In addition, maternal HF diet decreased the activity of the antioxidant enzymes glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase.
(CAT) in liver of male offspring (-20%, -12%, -30%, p < 0.05, respectively). In female HF offspring, we observed reduced activity of SOD and CAT enzymes (-20%, -56%, p < 0.001 respectively). However, the effect of maternal HF diet on oxidative stress markers was observed only in male HF offspring, which presented decreased liver content of Thiol (-31%, p < 0.001) and increased content of protein carbonyl groups (+30%, p < 0.01).

**Conclusions:** Maternal HF diet during prenatal period induced sex-specific modifications in the liver ECS and antioxidant system of rat offspring at adulthood, with male rats being more affected. This profile suggests that ECS may be involved in the sex-dependent early origins of metabolic programming.

**PO2.09.16**

**Sex-specific alterations in materno-fetal endocrinological/metabolic state after a single course of BET**

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**Background:** Even a single course of antenatal betamethasone (BET) exposure (2 × 12 mg, 24 hrs apart) has been associated with impaired fetal growth and development. Since the fetus depends heavily on transplacental glucose supply via glucose transporters (Glut), and given the importance of insulin, leptin and insulin like growth factors (IGF) as key regulators of human fetal growth, we examined the impacts of a single course of antenatal BET on these factors as potential associations for fetal nutrient deficiency and low birth weight.

**Methods:** Pregnant women treated with a single course of BET (n = 86, 2 × 12 mg intramuscular, 24 hrs apart) between 23 5/7 to 34 0/7 weeks of gestation (wks) were compared to gestational-age-matched controls (CON n = 92; range: 31 4/7 – 41 4/7 wks) without BET treatment. Maternal venous blood samples, umbilical venous blood samples as well as placental samples were collected. Sex-specific BET effects on Glut-1 and Glut-3, umbilical and maternal glucose, insulin, IGF-1, IGF-2, IGFBP-1, IGFBP-3 and leptin levels in preterm and term gestations were analyzed. Placental efficiency, parameters of fetal glucose consumption and transplacental glucose transfer were calculated. Data were analyzed using a Mann-Whitney U test or an independent-samples t-test, then further split into subgroups by gestational age (< 37 0/7 and ≥ 37 0/7 wks) and analyzed with a Kruskal-Wallis test or one-way ANOVA. Data were controlled by ANCOVA for possible confounders such as sex, gestational age, maternal weight gain, placental signs of amniotic infection and onset of labor. Significance was accepted at p < 0.05.

**Results:** In female fetuses born ≥ 37 0/7 wks, a single course of antenatal BET treatment significantly reduced fetal head circumference compared to CON. BET treatment resulted in elevated umbilical cord glucose levels. In mothers, BET treatment increased maternal HOMAIR compared to CON. Maternal IGFBP-1 levels were decreased after BET treatment, but IGFBP-3, IGF-1/2 and leptin levels were similar between groups. No significant BET effects were found in placental GLUT-1 and -3 protein levels. In contrast to females, BET decreased body length in males without affecting the maternal/fetal metabolic parameters.

**Conclusion:** We show a sex-specific impact of BET treatment on maternal insulin resistance levels, where female fetuses are more vulnerable to BET than male fetuses. These data may be indicative of sex-specific mechanisms to deal with metabolic changes or stressors in mothers treated with BET. Whether these metabolic changes will persist requires further investigation.

**PO2.09.17**

**Sex-specific associations between parental factors and fetal growth and body proportions from mid pregnancy until birth; a multi-ethnic cohort study.**

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**Background:** Differences in size and body composition between males and females may be observed from early fetal stages. Fetal growth and development are regulated by complex mechanisms and are linked, not only to perinatal-, but also long term health, and with various environmental exposures, including parental height and maternal ethnicity, socio-economic status, age, parity, BMI, gestational weight gain and glucose levels during pregnancy. Our aim was to explore associations between these parental factors and fetal size, body proportions and growth rate during the second half of pregnancy in an ethnically and socioeconomically diverse cohort of pregnant mothers, fathers and offspring, and to determine if these associations differ by offspring sex.

**Methods:** The sample is parent/offspring triplets with either South Asian (n = 191), Middle East/North-African (n = 153) or European (n = 359) ethnic origin, from a population-based, prospective cohort in Oslo, Norway. Outcomes were mean z-scores of estimated weight (EFW), head circumference (HC), abdominal circumference (AC) and length (measured as femur length in pregnancy), in gestational week 24, 32 and 37 and at birth (size) or change in z-scores during this time period (growth). Associations between parental factors and the fetal/neonatal outcomes were explored using general linear models and linear mixed models, adjusting for covariates. Interactions with sex were explored entering one interaction term at the time, and further analyses were performed stratified by sex.
Results: We found four significant interactions (all p < 0.01) between parental factors and offspring sex, indicating that the effect of these variables differed depending on whether the fetus was a boy or a girl. Maternal glucose levels during pregnancy, South Asian ethnic origin and paternal height were all more strongly associated with fetal/neonatal outcomes in girls than in boys, while maternal socioeconomic status was more strongly related to fetal/neonatal outcomes in boys. The effects of paternal height and maternal socioeconomic status mainly represented effects on fetal size in mid-gestation, while maternal glucose levels and South Asian ethnic origin were associated with growth rates from mid gestation and size at birth. Further, socioeconomic status had the strongest impact on fetal length, while South Asian origin was mainly affecting fetal AC.

Conclusion: Our results indicate that fetal growth may express gender-, gestational age- and organ-specific sensitivity to parental influence. Gender differences in the response to maternal and paternal environmental or genetic factors could be under-appreciated sources of variation in fetal growth, and may reflect differential growth strategies between male and female fetuses.

PO2.10 – Endocrine health
PO2.10.01

Genome-wide association meta-analysis identifies eight novel loci influencing the 2D:4D digit ratio, a presumptive marker of prenatal androgen exposure.

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Objective: During the prenatal period sex steroids influence several systems of the body, including the musculoskeletal system. Yet, prenatal androgen (pA) exposure is extremely difficult to measure. The ratio of the lengths of an individual’s second to fourth digit (2D:4D) is a sexually dimorphic trait that has been postulated as a retrospective non-invasive biomarker of testosterone exposure in utero. Our objective was to identify the genetic determinants underlying variation in 2D:4D.

Methods: Genome-wide association study (GWAS) meta-analysis of 2D:4D adjusted for sex and genetic principal components was applied to 15,597 individuals from seven cohorts: ALSPAC (n = 5,337), Generation R (n = 3,059), Rotterdam Study (n = 2,091), Twins UK (n = 1,109), QIMR (n = 1,602), QIMR2 (n = 1,109) and Raine (n = 1,003). Genotype data of all participants were imputed to the 1000 GP reference panel (~30 million variants). Genome-wide significance (GWS) was set at P = 5 x 10^-8. The 2D:4D was measured across cohorts on X-rays and DXA scans of the hands.

Results: This, the largest GWA meta-analysis of 2D:4D to date, identified ten GWS signals, of which eight were novel, mapping to the 1p32.3 (GLIS1), 1q22 (EFNA1/EFNA3), 2p24.1 (LDAH), 2q31.1 (OLAI), 2q31.1 (HOXD12), 11q24.3 (FLI1-A51), 16q12.1 (C16orf97) and 18q23 (SALL3) regions; and two already established, mapping to the 14q24.1 (SMOCH1) and 6q21 (LIN28B) regions. No variant known to be robustly associated with androgen/testosterone levels was associated with 2D:4D in our study.

Summary/Conclusions: These findings suggest that 2D:4D ratio is a heritable skeletal trait. We found no evidence that levels of prenatal testosterone contribute to the variation in 2D:4D at the population level. Any effect of prenatal testosterone exposure on the 2D:4D may be small relative to the combined influence of other sources of variation and should be considered when examining associations of 2D:4D with other (skeletal) traits.

PO2.10.02

Early-life stress permanently alters the adult neuro-immune phenotype within the HPA axis in female Japanese quail.

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Background: Activation of the hypothalamic pituitary adrenal (HPA) axis during development can have persistent and often dysfunctional effects on several physiological systems, including long-term immune function, reducing the individual’s ability to combat infection. Within the CNS microglia, macrophages resident throughout the brain and spinal cord provide the main form of active immune defence and react to a range of insults including localised infections, injury, inflammation, ischaemia and as well as playing a role in regulating neurogenesis. This response is inextricably linked to the action of the HPA axis as cytokine release can activate the HPA axis, and glucocorticoids can in turn regulate cytokine release from microglia, having an anti-inflammatory effect. The close links between these two physiological systems, coupled with potential for long-term alterations of the HPA axis following developmental adversity suggest the neuro-immune response as another target for developmental programming. However, little is known about the potential programming effects of early life stress on the functioning of this neuro-immune response. Here,
we aimed to test if pre- and/or post-natal stress permanently altered basal immunity within the hypothalamic-pituitary-adrenal (HPA) axis in a precocial bird, the Japanese quail (Coturnix japonica).

**Methods:** We obtained whole brain and pituitary gland tissue from adult female quail that were pre-natally exposed to elevated corticosterone in ovo (embryonic day 5) and/or post-natally exposed to unpredictable food availability (post-natal day 4-20). Using quantitative polymerase chain reaction (qPCR), we measured mRNA levels of pro (IL-1β) and anti-inflammatory (IL-10) cytokines and a microglia-specific gene (CSF1R) in the hippocampus, hypothalamus, amygdala and pituitary gland. These genes are all known to be associated with the regulation of the neuro immune response in several brain regions and the pituitary.

**Results:** We found that post-natal stress induced increases in IL-1β in the pituitary gland and decreased levels of IL-10 within the amygdala and hypothalamus. We also observed that post-natal stress induced an imbalance in the IL-1β: IL-10 ratio within the hippocampus and hypothalamus. Post-natal stress also impacted on microglia abundance where a decline in CSF1R expression was observed within the hypothalamus and the pituitary gland. We found no evidence for an interaction across life stages in altering immune function.

**Conclusions:** Our results provide the first evidence that stress during post-natal development permanently alters basal immunity in specific brain regions associated with the HPA axis. Such alterations in cytokine homeostasis and microglia abundance may create a shift towards an immune-reactive phenotype. This can lead to the dysfunction of both adaptive immune responses and the HPA axis, which can lead to the onset of anxiety and depressive-like behaviours as well as cognitive impairments in adulthood.

**Background:** Cortisol, as a marker of stress, has been primarily measured in blood, saliva and urine in clinical practice and health research. However, these cortisol levels reflect acute stress, and vary markedly due the diurnal rhythm and pulsatile secretion. Cortisol in scalp hair has been used in recent research to assess chronic stress exposure from one to three months. Two small pilot studies have shown that fingernail cortisol levels may have potential as an alternative or additional marker of chronic stress, as it takes an average of three months to grow from the nail matrix to become a free nail. We report the initial results from a life course study examining the correlation between concentrations of cortisol in fingernails and hair, as well as perceived stress levels and experiences of stressful life events in young adults.

**Methods:** The Life Course Program, based in the Northern Territory, Australia, encompasses two distinct but complementary cohorts: Aboriginal Birth Cohort (Indigenous) and Top End Cohort (non-Indigenous). Participants of both studies were examined in young adulthood aged 21-27 years (2013-2015) with 459 Indigenous and 117 non-Indigenous participants seen. Fingernail samples were clipped directly into a plastic bag (196 Indigenous and 72 non-Indigenous) and scalp hair samples were cut from the posterior vertex area (360 Indigenous and 101 non-Indigenous). The hair and fingernails were fragmented and then extracted with 1.5ml methanol twice as reported by Sharpley et al 2009. The methanol was evaporated under vacuum and then the residue redisolved in 100ul of methanol and analysed by LC/MS/MS using a Shimadzu UPLC and 8050 Mass Spectrometer. Questions covering experiences of 13 stressful life events in past 6 months and Perceived Stress Scale (PSS-4) encompassing the last four weeks were obtained on 301 Indigenous and 101 non-Indigenous.

**Results:** Rates of collection were lower for fingernail (47%) than hair (80%), largely due to no free nail being available. Initial results of the first 40 fingernail and hair samples (Indigenous only) showed the capacity for cortisol extraction on very small amounts of fingernail and hair (median weight 5.8mg & 8.1mg respectively). One participant had hair cortisol concentrations that were considerably higher than the average (121nmol), and considered as an outlier. Cortisol levels were lower in fingernails than hair (Geometric mean 1.2 vs 2.5 nmolr respectively). Spearman’s correlation of 0.6 was seen between fingernail and hair. Indigenous participants reported a significantly higher number of stressful life events (mean 6 & 1 respectively). However, similar levels of perceived stress were reported (mean 4.6 Indigenous & 4.9 non-Indigenous).

**Conclusions:** These initial results demonstrate the feasibility of measuring fingernail cortisol from a very small quantity in a population at increased risk of stressful life events. Further examination, currently in progress, will provide data on whether fingernail is a useful alternative or additional biomarker to hair cortisol in those most at risk in a population experiencing chronic stress levels which may be detrimental to their health and wellbeing.
**PO2.10.04**

**Prevalence and experiences of food insecurity among migrant women connected to a community-based organization in Edmonton, Canada**

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**Background:** Inadequate or excessive gestational weight gain and poor dietary intake can increase the risk of pregnancy complications in both mother and baby, and long-term risk of chronic disease. Low socioeconomic status can negatively affect many aspects of a healthy pregnancy, including women’s ability to access and consume healthy foods. In Canada, the prevalence of household food insecurity – defined as “inadequate or insecure access to food because of financial constraints” – is greater (19.6%) among families that recently immigrated to Canada (< 5 years) than the national Canadian average of 12.6%. A large proportion of migrants are women of childbearing age who might experience pregnancy and childbirth in Canada while being at an increased risk for food insecurity. In Edmonton, these women might receive additional support from a Community-Based Organization (CBO), the Multicultural Health Brokers (MCHB) Cooperative. MCHB is a collective of health brokers from diverse backgrounds who serve migrant women and families in difficult life circumstances, including food crisis situations where families lack immediate access to food. The objectives of our research were to investigate the prevalence of household food insecurity among women connected to MCHB perinatal programs, and explore their life circumstances and experiences with food insecurity.

**Methods:** We used an exploratory sequential mixed method research design. Women were asked to complete the 18-question Household Food Security Survey Module (HFSSM) from the Canadian Community Health Survey with help of a health broker. Fisher’s exact test was used to examine differences in food insecurity by family origin (e.g., Africa and Middle East vs. Asia and Pacific). Semi-structured interviews were then conducted with a sample of Northeast African women. Qualitative data were analyzed using qualitative content analysis to inductively derive codes and categories. Data were collected sequentially, analyzed separately, and then integrated.

**Results:** A sample of 213 women connected to MCHB programming (reporting on behalf of their household) completed the HFSSM. Of these 94% (n = 199) were food insecure, and 53% (n = 112) were severely food insecure. Food insecurity differed by family origin (p < 0.001), with families from Africa and the Middle East being more likely to experience food insecurity. In the past year, 85% (n = 182) of families did not have enough money to eat balanced meals, and 39% (n = 79) cut meal sizes or skipped meals because there wasn’t enough money for food. In semi-structured interviews, Northeast African women (n = 20), commonly described not having enough money to buy vegetables, fruit and meat, and eating mostly rice, bread and pasta throughout the month. Moreover, their perceived sense of control over foods available at home was low since they could not afford to buy what they want for themselves and their families.

**Conclusion:** Improving migrant women’s diets will require addressing migration as a determinant of health. CBOs, such as MCHB, can foster opportunities for social and economic integration of women and families into Canada. Policies that support CBOs, and ensure adequate funding, will enable continuing services that can assist migrant women in being healthier during pregnancy and postpartum.

**PO2.10.05**

**Principal component-derived pediatric bone density phenotypes and genetic regulation of the developing skeleton**

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**Background:** Osteoporosis is a classic complex disease that can have its developmental origins in childhood if bone accretion is insufficient. Large-scale genomic studies have discovered common and low frequency variants that associate with adult and pediatric areal bone mineral density (aBMD), and most of the variants discovered are skeletal site specific. The skeletal site-specific phenotyping approaches used thus far have considered each site in isolation, but an integrative approach that combines information from individual skeletal sites, but with greater resolution than total body phenotypes, could advance our understanding of the genetic regulation of the skeleton. We therefore aimed to determine if genetic variants associated with principal component-derived pediatric aBMD loading scores that integrate information across four skeletal sites.

**Methods:** Our sample comprised 1,293 children of European ancestry enrolled in the longitudinal Bone Mineral Density in Childhood Study (52% female). The participants completed up to 7 annual study visits. From dual energy X-ray absorptiometry scans, sex and age-specific aBMD Z-scores, adjusted for height, were calculated for total hip, femoral neck, spine and distal radius. Principal components analysis, applied to the four Z-scores, generated new integrated aBMD phenotypes. Linear mixed effects models, adjusted for age, Tanner, BMI-Z, dietary calcium and physical activity, were used to test associations between a genetic score (percentage aBMD-lowering alleles
carried at 63 GWAS-implicated loci) and the loading scores. We also performed a GWAS, using the baseline data, to identify loci associated with the loading scores.

**Results:** Four principal components (PC1-PC4) were identified that explained 68.1%, 18.6%, 10.5%, and 2.8% of the variance, respectively (Figure 1). A higher PC1 loading score indicated higher bone Z-scores across all four sites. The genetic score was associated with lower PC1 loading score (beta = -0.05, P = 3.9 × 10^{-11}); from the GWAS, rs114260199 (LMO2/CAPRIN1, P = 3.9 × 10^{-9}) and rs75321045 (ZMAT4, P = 2.5 × 10^{-8}, females) were associated with PC1 loading score. A higher PC2 loading score indicated higher distal radius Z-score only. The genetic score was not associated with PC2; from the GWAS rs67991850 (CPEDI1, P = 2.5 × 10^{-11}) was associated with PC2 loading score. A higher PC3 loading score indicated higher spine Z-score only. The genetic score was not associated with PC3; from the GWAS rs58649746 (RAB11FIP5, P = 4.8 × 10^{-10}, females) was associated with PC3 loading score. A higher PC4 loading score indicated lower total hip Z-score, but higher femoral neck Z-score. No genetic associations were observed for PC4.

**Conclusion:** We identified four integrated pediatric aBMD phenotypes, including non-site-specific (PC1), distal radius-specific (PC2) and spine-specific phenotypes (PC3). An established genetic bone fragility score associated with the non-site-specific phenotype, but not the site-specific phenotypes. Novel variants near LMO2/CAPRIN1, ZMAT4, and RAB11FIP5 associated with non-site specific or spine specific phenotypes. These results highlight the utility of an integrated skeletal site phenotyping approach, which may help identify additional genetic loci associated with skeletal development that will aid in the prevention of osteoporosis in later life.

**PO2.10.06**

**Common adult height variants influence pediatric bone mineral density: a longitudinal candidate gene analysis**


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**Background:** Osteoporosis is a complex disease that may have origins in childhood, necessitating the need to understand the genetics of bone accretion. The strongest pediatric areal bone mineral density (aBMD) genetic locus resides at 7q31.31 (CPEDI1-WNT16). Interestingly, variants near CPEDI1-WNT16 also influence adult height, and linear growth is an important dimension of bone accretion. Over 700 known genetic variants for adult height have been reported. We therefore aimed to determine the associations of height variants that are common (>5%), low frequency (1-5%), and rare (<1%) with pediatric aBMD.

**Methods:** We analyzed data from the Bone Mineral Density in Childhood Study, restricted to participants of European ancestry (N = 1,298; 52% female). Dual energy X-ray absorptiometry was used to calculate spine, total hip, femoral neck and distal radius aBMD Z-scores, and total body less head bone mineral content (TBLH-BMC) Z-scores, adjusted for height. Genetic risk scores (GRS) for taller stature were calculated using: 1) 683 common height variants and 2) 83 low frequency or rare (LFR) variants. Both scores were standardized and weighted based on their effect size with adult height. Linear mixed models were used to test for association between each standardized GRS (beta = bone Z-score change per 1 SD increase in the GRS), as well as the individual variants (with Bonferroni correction for multiple comparisons), and the bone Z-scores. Age and sex interactions were tested.

**Results:** As expected, the common-GRS and LFR-GRS were positively associated with height Z-score (beta = 0.26, P = 3.6 × 10^{-29}); and beta = 0.10, P = 1.1 × 10^{-6}, respectively); and the associations were stronger among older children (P-age interactions < 0.05; Figure 1). No sex differences were observed with respect to the common-GRS, LFR-GRS and the height Z-score outcome. In contrast, the common-GRS was negatively associated with bone Z-scores (e.g. TBLH-BMC: beta = -0.08, P = 1.2 × 10^{-4}); and these negative associations were stronger among older children (P-age interactions < 0.05; TBLH-BMC example). No sex differences were observed with respect to the common-GRS and bone Z-score outcomes. The LFR-GRS was not associated with bone Z-scores, and no age or sex interactions were observed with respect to the LFR-GRS and bone Z-score outcomes. At the individual variant level, a common height increasing allele near CPEDI1 (rs6952113-G) associated with higher distal radius aBMD (beta = 0.21, P = 4.9 × 10^{-6}); this association was stronger in females (P-sex interaction = 7.9 × 10^{-5}; beta = 0.39, P = 4.2 × 10^{-12}); and only observed among younger male children (P-age interaction = 1.4 × 10^{-5}). In contrast, a common height increasing allele near PDE3A (rs4326884-A) associated with lower spine
aBMD (beta = -0.14, P = 0.002); no sex or age differences were observed for this variant with respect to spine aBMD.

**Conclusion:** Overall genetic predisposition to taller stature associated with lower aBMD in childhood. Our observations therefore provide insight into the genetic regulation of the growing skeleton and could aid in developing more effective therapies for preventing and treating osteoporosis. However, since bone accretion continues into young adulthood, after peak height is attained, follow-up studies are needed to determine if our observations translate into risk of osteoporosis and fracture in later adulthood, and if our associations remain once peak bone mass has been attained.

**PO2.10.07**

**Finger dermatoglyphics and reproductive success in women**

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Finger ridge counts characteristics are under genetic and environmental (including sex hormones) influence and developed before the 19th week of pregnancy. Dermatoglyphics are biomarkers of early environmental conditions and are related to many diseases, including reproductive cancers (breast, cervix) in women. Here we analyze, for the first time, the association between two dermatoglyphic biomarkers and women’s reproduction (First Birth Interval, number of children, age at first and last birth, mean interbirth interval and reproductive span).

The participants were 237 women aged 45-92 (mean = 61.6; SD = 11.18) from rural population with natural fertility at the Mogielica Human Ecology Study Site in Poland. Two dermatoglyphic indices: AFRC (absolute finger ridge count, total amount of ridge counts in both hands) and Md15 (difference between mean number of ridge counts on thumbs and little fingers between hands) were calculated according to standard procedures. Age, education, age at marriage, age at first birth, mean interbirth interval, husband’s age at marriage and age difference between spouses were included as covariates, depending on the analysis.

AFRC was negatively related to First Birth Interval (borderline significance p = 0.06), number of children (p = 0.02), age at last birth (p = 0.03) and reproductive span (p = 0.02). Md15 was negatively related to reproductive span (p = 0.02). No statistically significant associations were observed for age at first birth and mean interbirth interval.

Our results suggest that more favourable early developmental conditions, reflected in lower values of AFRC and Md15 indices, are related to women’s higher reproductive success. This study adds to the growing body of evidence that early developmental conditions are important for shaping later life.

**PO2.10.08**

**Stress early in life and child stress responses at age 6**

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**Background:** In stressful situations individuals respond behaviorally and physiologically. Physiologically, the Hypothalamic-Pituitary-Adrenal (HPA) axis becomes activated producing its primary hormonal end product cortisol (e.g., Dickerson & Kemeny, 2004; Nicolson, 2007). Behaviorally, people often change their behavior, for example their gazing behavior by avoiding or increasing looking time at the threatening stimulus (Wilson & MacLeod, 2003). Efficient stress responses are needed to deal with day-to-day stressors. However, there are individual differences in physiological and behavioral responses (e.g., Kudielka, Hellhammer, & Wüst, 2009; Wilson & MacLeod, 2003) and alterations in these responses have been associated with (mental) health (e.g., McEwen, 2008; Wilson & MacLeod, 2003). Therefore, it is important to understand predictors of these stress responses during childhood. Stress early in life may be an important predictor of those stress responses. Prenatal maternal distress has been found to be associated with infant cortisol stress responses (e.g., Leung et al., 2010) as well as with gazing during a peek-a-boo task (e.g., Lin, Cmic, Luecken, & Gonzales, 2014). Moreover, postnatal early life stress has also been associated with children’s cortisol stress responses (Loman & Gunnar, 2010). To determine if these associations persist over time, we examined whether stress early in life, in the form of maternal prenatal and early postnatal distress, is associated with behavioral and physiological stress responses of typically developing six-year-old children. Moreover, because stress responses might facilitate or inhibit each other, associations between the physiological and behavioral stress responses were explored.

**Methods:** A total of 149 six-year-old children (Mage = 6.09; 70 girls) participated in a standardized stress paradigm in which they had to perform in front of a judge. During the test their cortisol as well as their behavioral stress response, in the form of
gazing behavior were recorded. Physiological stress responses were operationalized by collecting six cortisol saliva samples and calculating total stress cortisol and cortisol stress reactivity. Gazing behavior was operationalized by interval recording of gazing behavior during the stressor. To operationalize stress early in life maternal distress both prenatally (week 37 of pregnancy) as well as postnatally (at child age 3 and 6 months) was measured. Child gender, maternal educational level, and maternal feelings of anxiety at child age six were taken into account as confounders.

**Results:** Hierarchical regression analyses indicated that more maternal fear of giving birth was associated with lower total stress cortisol at child age six. Moreover, higher prenatal maternal evening cortisol concentrations as well as more maternal feelings of anxiety in the first six months of the child’s life were associated with higher total stress cortisol concentrations of the children at age six (see Table 1). Regarding associations between the physiological and behavioral stress responses, higher cortisol stress reactivity was associated with less gazing in the direction of the judge (Spearman’s $Rho = -1.7$, $p < .05$).

**Conclusions:** These results suggest that maternal distress early in the child’s life may program children’s later HPA-axis functioning. Also, in six-year-olds confronted with a stressful social evaluative situation, gazing may be used to deal with stress.

**PO2.10.09**

**Birth weight is associated with lean and bone mass in healthy young adults from the Nutritionists’ Health Study - NutriHS**

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**Background:** Osteosarcopenia has been associated with accelerated functional decline and disability in elderly. Its determinants have been more commonly investigated at advanced age, although early-life factors may be already influencing bone and muscle mass peaks and rates of decline. This study examined whether birth weight (BW) was associated with parameters of muscle and bone compartments in healthy young adults from the NutriHS which is a cohort study of undergraduates and graduates from Nutrition courses in São Paulo, Brazil.

**Methods:** This cross-sectional analysis was performed in 121 healthy participants of the NutriHS, aged 20-40yrs, who answered a questionnaire about early-life events, and had anthropometric data, muscle performance parameters, body composition and bone densitometry (DXA Lunar Ge$^2$ and blood sample collected. Appendicular skeletal muscle mass index (ASMI) was calculated. BW was categorized in quartiles and variables compared by ANOVA + post-hoc Bonferroni. Associations between BW quartiles (exposure) and calf circumference, handgrip, chair-stand test, ASMI, bone mineral density and content (BMD and BMC) and concentrations of 25-hydroxyvitamin D, lipids, glucose and insulin (outcomes) were tested using multiple linear regression.

**Results:** Ninety percent of the sample were women; mean values of age, BMI and BW were 24.4 ± 5.2yrs, 23.5 ± 4.3kg/m$^2$ and 3227.9 ± 440.0g, respectively. Pre-pregnancy BMI of their mothers was 22.1 ± 3.5kg/m$^2$. Comparing means values among BW quartiles, direct associations in calf circumference ($p = 0.007$), handgrip ($p = 0.017$), ASMI ($p = 0.009$) and BMC of total body ($p = 0.024$), femoral neck ($p = 0.037$) and total femoral ($p = 0.021$) were observed. In linear regression models, after adjustments for confounders, direct associations of BW quartiles with calf circumference ($r^2 = 0.09$; $p = 0.006$), handgrip ($r^2 = 0.48$; $p < 0.001$) and ASMI ($r^2 = 0.35$; $p < 0.001$) but not with chair-stand test were detected. Also, BW quartiles were associated with total body BMC ($r^2 = 0.04$; $p = 0.019$), femoral neck ($r^2 = 0.06$; $p = 0.035$) and total femoral ($r^2 = 0.07$; $p = 0.013$). Laboratory variables, including 25-hydroxyvitamin D (24.2 ± 10.4ng/mL) were within the normal ranges and not associated with BW.

**Conclusions:** The associations of BW with structural and functional parameters suggest that may be a predictor of muscle and skeletal health in young adults. Since BW is considered a
marker of quality of the intrauterine environment, our findings reinforce the importance of nutrition in the early stages of development also for the prevention of skeletal muscle loss.

PO2.10.10

Basal cortisol concentrations and growth in children of Mexico City

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Background: Cortisol plays an important role in processes of bone, muscle and fat mobilization. This could influence body composition, affecting anthropometric indicators like weight and height. Children’s growth is clinically monitored with the World Health Organization growth indexes (WHO). In Mexico, children’s growth problems have shown changes over time: a negative trend for stunting and undernutrition, and a positive trend for overweight and obesity between 1988 and 2012. Studies of children’s cortisol and their growth are scarce. The aim of the study is to explore the association between basal cortisol levels, growth indexes, and undernutrition or obesity in Mexican children of 12 to 48 months of age.

Methods: 404 Participants from the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) birth cohort were included. Salivary cortisol was measured at 12, 18 or 24 months of age 4 times per day over 2 days. Total diurnal cortisol level was calculated averaging the area under the curve (AUC) for both days and quartiles were used for analyses. Height and weight were analyzed longitudinally from the saliva collection time-point to 48 months of age. Z-scores for growth indexes: weight for age (WFA), height/length for age (HFA), weight for height/length (WFH) and body mass index (BMI) for age (ZBMI), were constructed according to the WHO standards. We used mixed models to analyze the association between total daily cortisol levels and growth indexes, and longitudinal ordered logistic regression to explore the odds to develop obesity (>2SD in growth indexes).

Results: A similar non-linear relationship was found between cortisol AUC and the 4 growth indexes: weight for age (WFA), height/length for age (HFA), weight for height/length (WFH) and body mass index (BMI) for age (ZBMI), were constructed according to the WHO standards. We used mixed models to analyze the association between total daily cortisol levels and growth indexes, and longitudinal ordered logistic regression to explore the odds to develop obesity (>2SD in growth indexes). Longitudinal models for z-scores at 12, 18, 24 and 48 monthsc with quartiles of cortisol AUC.

PO2.10.11

Fetal protection from maternal cortisol: How early is 11-beta hydroxysteroid dehydrogenase type 2 (11β-HSD2) expressed in the human placenta

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Maternal physiologic stress during gestation has been associated with negative developmental outcomes, including intra-uterine growth restriction and reduced birth weight, which can impact postnatal development, behaviour and health. The human fetus is partially protected from elevated cortisol exposure by placental 11β-HSD2, an enzyme which oxidizes bioactive cortisol into bio-inactive cortisone. In humans, placental 11β-HSD2 has been shown to be present from as early as the middle of the first trimester until parturition. However, the onset of placental 11β-HSD2 expression has yet to be clearly established. Given the protective role this enzyme is hypothesized to have during gestation, we predicted that placental 11β-HSD2 expression should begin during the earliest stages of the placentation.

Conclusion: Total diurnal cortisol levels are associated with children growth. Hypothalamic pituitary adrenal axis development could influence weight and length/height gain in early infancy. Analysis using longitudinal cortisol measurement can improve knowledge about this association.
process, the critical peri-conceptional period. Specifically, we predicted that this enzyme’s expression should be most conspicuous in cells that are in intimate contact with the mother’s circulatory system. We performed immunocytochemical analysis of placentas collected 3 to 6 weeks post-conception. Consistent with our predictions, 11β-HSD2 was present as early as 3 weeks post-conception in syncytiotrophoblasts, where most maternal-fetal exchange occurs, and in columnar epithelial cells encircling uterine endometrial glands, which provide early histiopathic nutrition to the embryo. 11β-HSD2 expression in these critical maternal-fetal exchange areas is consistent with its hypothesized role as a protective barrier to modulate embryonic/fetal exposure to cortisol of maternal origin. Further research is necessary to investigate which mechanisms, if any, protect the conceptus before the onset of placentation.

PO2.10.12

Neonatal TSH: A controversial biomarker of iodine and selenium status
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Background: Neonatal TSH has traditionally been used as indicator for monitoring iodine deficiency in a population. Nevertheless, the neonatal TSH measurement may be affected by potential confounding factors which should be identified. The current study was designed to determine the relationship between thyroid function, iodine status and selenoproteins in healthy mothers and their newborns at the time of birth.

Methods: A cross-sectional study included 83 healthy mother-baby couples. TSH, FT4, FT3 and anti-thyroid peroxidase antibodies were measured in maternal serum and cord blood. Neonatal TSH from heel-stick blood specimens were compared to TSH from cord blood. Iodine concentration was determined in maternal urine and amniotic fluid. Total selenium and selenoproteins were measured in maternal serum and cord blood through a coupling based on in series two-dimensional size exclusion and affinity high-performance liquid chromatography (2D/SE-AF-HPLC). GPx activity and Selenoprotein P1 (by ELISA) were also measured.

Results: The median maternal urinary iodine concentration was 145.6 μg/L. TSH in cord blood correlated positively with amniotic fluid iodine concentration ($r=0.45$, $p<0.01$) and maternal urinary iodine concentration ($r=0.24$, $p<0.05$). The heel blood TSH only correlated with cord blood TSH ($r=0.37$, $p<0.01$). Total selenium was significantly higher in maternal serum compared to cord blood (68.9 ±15.2 and 56.1 ±14.6 μg/L respectively; $p<0.01$). Selenoproteins significantly correlated between mothers and newborns. The cord blood TSH correlated positively with neonatal Selenoprotein P1 measured by ELISA ($r=0.37$, $p<0.01$). This association remained significant after adjusting for maternal Selenoprotein P1 and heel blood TSH ($R^2=0.28$, $p<0.05$)

Conclusions: The heel blood TSH does not show correlation with iodine status nor selenium status in mothers and newborns at the time of birth. However, our results seem to indicate an association between cord blood TSH and the antioxidant protein Selenoprotein P1 in neonatal serum.

PO2.10.13

Cortisol concentrations in breast milk: associations with infant crying
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Background: Breastfeeding is beneficial for infant health and development. For example, breastfeeding has been related to fewer illnesses in the infant, and better child cognitive development, even beyond infancy and childhood. Less research has been devoted to the hypothesis that biological constituents of breast milk influence offspring phenotype, also known as the lactational programming hypothesis. Breast milk contains, next to water, protein, carbohydrates, and immune factors, several hormones, including glucocorticoids (in humans: cortisol). Evidence from animal research shows that these glucocorticoids are related to offspring behavior. For example, higher glucocorticoid levels in maternal breast milk are related to reduced anxiety and improved learning in rat offspring (Catalani et al.
Conclusions: Small sample size.

Both the female and the male curves, which might be due to a homeostasis leading to metabolic and pancreatic-function dysfunction and the high risk to metabolic disease aggravation. In the present study, we assessed the short- and long-term effects of low-protein diet on the glucose homeostasis, pancreatic-islet function and hypothalamic-pituitary-testicular (HPT) axis in male rats.

Methods: When the infant was 2, 6, and 12 weeks old, breastfeeding mothers (N = 70) collected one morning sample (approximately 20 ml) of their breast milk. At the same ages, the mothers kept a 3-day infant cry diary. Crying and fussing behavior were summed up and operationalized as 1) Crying total duration (mean crying duration in minutes per 24 hours), 2) Crying frequency (the mean number of episodes of crying per 24 hours), and 3) Crying bout (mean bout length of crying episodes). Cortisol was extracted from breast milk samples with methyl tertiary butyl ether, and quantified by Liquid chromatography-tandem mass spectrometry (LC-MS/MS). A mixed model approach (multilevel) was used to investigate the association of breast milk cortisol and the three infant crying variables. Infant sex and interactions between infant sex and breast milk cortisol were included to explore sex differences.

Results: Breast milk cortisol was unrelated to infant crying total duration, crying frequency, and crying bout. However, there was a significant interaction effect between infant sex and milk cortisol on infant crying bout. More cortisol in breast milk was related to longer crying bouts in female infants, and to shorter crying bouts in male infants. Simple slope analyses showed that the individual curves did not reach significance (p = .08 for both the female and the male curves), which might be due to a small sample size.

Conclusions: Breast milk cortisol is differently related to crying bout length in male and female infants. This may be pointing at differential lactational programming effects of cortisol depending on infant sex. Replication of the study with a larger sample size is needed.

PO2.10.14

Adolescence-malnutrition in rats disrupts testosterone homeostasis leading to metabolic and pancreatic-function impairment at adulthood


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Background: Protein-calorie restriction in critical stages of life development, as well as changes in the homeostasis of testosterone among other hormones involved in metabolism control are great contributing factors to the worldwide epidemic of metabolic disorders like obesity and type 2 diabetes mellitus. In the present study, we assessed the short- and long-term effects of low-protein diet on the glucose homeostasis, pancreatic-islet function and hypothalamic-pituitary-testicular (HPT) axis in male rats.

Methods: At 30-days-old, Wistar male rats were fed a low-protein diet (4% of protein, LP group) until 60-days-old and then, to dietary rehabilitation, were fed with normal-protein diet (20.5% of protein) from 60- to 120-days-old. At the same time, control rats (NP group) were fed a normal-protein diet throughout life. A batch of rats was euthanized at 60-days-old, while another at 120-days-old. Food intake, body weight, mesenteric-fat pad, lipid profile, plasma glucose, insulin and testosterone were evaluated in rats at both ages (60- and 120-days-old). In addition, the pancreatic-islet insulinotropic response, testosterone production as well as androgen receptor (AR) protein expression in hypothalamus were assessed.

Results: At 60-days-old, LP rats were leaner, hypophagic, hypoglycemic, hypoinsulinemic and hypotestosteronemic (P < 0.05). Indeed, a weak insulinotropic response (P < 0.01), as well as reduced testosterone production and hypothalamic-AR down regulation were found. In addition, the cholinergic and glucose pancreatic-islet’s response were smaller in 60-days-old rats. Contrarily, at 120-days-old, LP rats were hyperphagic and displayed higher accumulation of mesenteric fat-pad, dyslipidemia, hyperglycemia, hyperinsulinemia and peripheral insulin resistance (P < 0.01). The blood levels of testosterone, testosterone release and hypothalamic expression of AR were reduced (P < 0.05). Both, the glucose and acetylcholine response of pancreatic-islet were drastically increased either in baseline and high concentrations (P < 0.05).

Conclusions: Protein-calorie restriction at adolescence disrupt hypothalamic-pituitary-testicular axis, malprogramming adult rats to glucose-insulin impairment associated with pancreatic-islet dysfunction and the high risk to metabolic disease aggravation.

PO2.10.15

Cortisol/cortisone ratio in early childhood in very-low-birth-weight infants and term born infants

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Background: Programming of the hypothalamic-pituitary-adrenal axis, resulting in increased activity in later life, probably plays an important role in the later metabolic and cardiovascular consequences of intra-uterine growth restriction (IUGR) and/or preterm birth. In IUGR born children, changes in the activity of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) probably contribute to the metabolic and cardiovascular
consequences in later life. 11ß-HSD2 converts cortisol into inactive cortisone and is mainly active in the kidney; cortisol/cortisone ratio is used as a marker for 11ß-HSD2 activity. We hypothesize that changes in 11ß-HSD2 activity could also contribute to the later consequences of preterm birth. The aim of the present study was to compare serum cortisol, cortisone and cortisol/cortisone ratio and it relationships to metabolic syndrome components in infancy and early childhood in very-low-birth-weight infants (birth weight < 1500 g) and term appropriate for gestational age born infants (birth weight above the 10th percentile).

Methods: We included 41 very-low-birth-weight infants and 64 term infants. Cortisol and cortisone were measured in blood samples taken at 6 months and 2 years corrected age (very-low-birth-weight children) and at 3 months, 1 and 2 years of age (term children). At 1 year and 2 years of (corrected) age total cholesterol, HDL cholesterol, triglycerides, glucose and insulin were also measured. Linear mixed model analyses were used to analyse the longitudinal differences in serum cortisol, cortisone and cortisol/cortisone ratio between the very-low-birth-weight children and term born children and were also used to analyse the longitudinal relationship between the cortisol/cortisone ratio and several components of the metabolic syndrome.

Results: During the first 2 years of life cortisol/cortisone ratio is significantly higher in very-low-birth-weight children compared to term children. Serum cortisol and cortisone alone do not differ significantly between the very-low-birth-weight children and term children over time. In the term children there is a significant longitudinal relationship between cortisol/cortisone ratio and total cholesterol, glucose and insulin over the first 2 years of life. In the subgroups of very-low-birth-weight children with high glucose levels or low HDL cholesterol levels, cortisol/cortisone ratio is correlated to triglycerides and glucose respectively.

Conclusions: Very-low-birth-weight infants have higher cortisol/cortisone ratio during early childhood compared to term born children and cortisol/cortisone ratio is related to several metabolic syndrome components in early childhood. These results suggest that in very-low-birth-weight infants lower 11ß-HSD2 activity could contribute to the long-term metabolic and cardiovascular risks. The negative effect of cortisol on insulin sensitivity probably plays a crucial role in the association between high cortisol/cortisone ratio and metabolic and cardiovascular consequences later in life.

PO2.10.16
Stress and Inflammation in Children
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Background: Research findings from diverse studies indicate that adult health outcomes can be predicted from early stress exposures. It is less clear if early stress exposures have detectable effects on health outcomes in children. The current study examined the association between early stress exposures and inflammation in pre-adolescent children. We focused on inflammation because it is established mechanism of disease and may mediate the effects of stress on diverse health outcomes.

Method: The study is based on the Family Life Project, a prospective longitudinal study of 1,292 families who have been assessed since the target child was 2 months of age. The FLP oversampled rural poor families living in Pennsylvania and North Carolina in the US. Families were visited when the child was 2, 6, 15, 24, 35, 48, 58 months of age and 1st grade. The current study, based on an in-person assessment conducted when the children were age 11 years, included a subset of children in the FLP study; selected children (n = 461) were stratified by poverty and race. At the age 11 home visit, a phlebotomist collected a blood sample from venipuncture; children’s physical health and anthropometrics were also assessed. Detailed measures of psychological and sociodemographic stress and caregiving were also collected from questionnaire, interview, and observational methods. We focus in this report on the innate immune system, measured from circulating levels of the pro-inflammatory cytokines IL-6 and TNF-alpha and the acute phase protein CRP using enzyme-linked immunoassay (ELISA) high sensitivity kits.

Results: IL-6, TNF-alpha, and C-RE were moderately inter-correlated (r = .23-.49), and each was reliably associated with BMI (r = .17-.38). There were sizable and consistent differences in immune markers by race [e.g., for IL-6, means were 1.52 pg/ml [1.4] in African-Americans and 1.11 pg/ml [0.92] in Caucasian children, p<.001]. Socioeconomic status was reliably associated with IL-6; however, the association was significant in Caucasian (r = .19, p < .01) but not African-American children (r = .03, ns); differences in effects were not explained by race differences in BMI. Further analyses will examine birth and growth parameters and early stress exposures as predictors of immune data at age 11 years.

Conclusions: The findings extend research on early stress exposure, and suggest that inflammation may be one mechanism underlying social gradients of illness from childhood.

Wednesday October 18th Abstracts oral presentations

PA3.01 - Early origins of aging
PA3.01.01
Life-course paths to metabolic health
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There is an increasing awareness that the process of premature ageing starts in early life via psycho-social adversities acting on human physiology. The recent large meta-analyses based on adult populations show that low socioeconomic position
increases premature mortality, and it should be targeted by global health strategies. Most of the research in this respect has focused on adult life information. However, childhood and adolescent overweight and obesity, and consequent metabolic adversities have become major public health concerns in both westernized and, more recently, in developing countries. Traditional approaches for the management of these disorders have had poor long term efficacy. Therefore prevention, from early life, is currently the most promising strategy for controlling the metabolic disease epidemic. Consequently, it is important to understand the life-course paths and trajectories leading to metabolic ill-health that impact the risk of premature ageing. Longitudinal birth cohort studies have already produced a vast amount of evidence and shown a strong association between prenatal factors, early infancy weight gain, adiposity and childhood and adult body mass index and other metabolic outcomes e.g. In Northern Finland Birth Cohort studies and other longitudinal data we have aimed to build predictive algorithms for the early identification of individuals at an increased risk for childhood and adolescent overweight/obesity and other metabolic adversities. These analyses show that there are key markers in pregnancy and early life with high prediction ability. We have also shown that early life stress may modify the association between genetic variants and early growth. Ongoing research provides insight into the mechanisms linking early growth patterns with healthy metabolic ageing. To take these works forward, in the context of the DynaHEALTH H2020 program (http://www.dynahealth.eu/), we have set out to explore a composite of biological and psycho-social factors (gluco-psychosocial axis) that may predict premature ageing associated with metabolic adversities from early life onward, using a population of over 1 million subjects across Europe. The analyses support a strong interplay of metabolic and psychosocial factors in establishing risk of premature ageing. Although the bio-psycho-social model was introduced 40 years ago by Engel and acclaimed by the scientific community, it has yet to be successfully operationalized into research approaches and routine practice. The methodological challenge is to explore in-depth the life-long psycho-social wellbeing by taking into account metabolic measures, heritability, temporal relationships, interactions and causality, and how direct biological markers such as epigenetic modifications maybe used as a more “objective measures” of the impact of the environment on health and as a mechanistic instrument.


PA3.01.03

Developmental origins of “aging”: an epidemiological perspective

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In this presentation I will argue (1) that “there is no such thing as ageing”, and (2) that the etiologic factors that are responsible for the occurrence of diseases late in life are generally likely to act throughout the life span. I will use data from two Erasmus cohorts, i.e. the Rotterdam Study and Generation R, to exemplify these points, and I will stress the potential of using these cohorts in joint analyses.

PA3.01.05

Child maltreatment as a predictor of adult physical functioning in a prospective British birth cohort

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Background: Child maltreatment (abuse and neglect) has established associations with mental health; however, little is known about its relationship with physical functioning. Physical functioning in adulthood is an important outcome to consider, as it is strongly associated with an individual’s ability to work, and future disability, dependency, and mortality. We aimed to establish whether maltreatment was associated with physical functioning, independent from other early-life adversities.

Methods: Using data from the 1958 British birth cohort (n = 8150), we examined associations between child neglect and physical, psychological, witnessing and sexual abuse with physical functioning at age 50. Poor physical functioning was defined by those scoring ≤65 on the Short-Form 36 (SF-36) Physical Functioning sub-scale. Two secondary outcomes were examined: mental and self-reported health at age 50. Associations between each maltreatment and outcome were assessed using logistic regression with and without adjustment for covariates, e.g. childhood social class, birthweight, and parental and childhood health. Missing data was handled using multiple imputation.

Results: 23% of participants reported at least one type of maltreatment; 12% were identified with poor physical functioning. Neglect, psychological, and sexual abuse were associated with poor physical functioning independent of all covariates and other maltreatments: ORadj 1.55 (95% CI 1.24-1.93), 1.49 (1.17-1.88) and 2.56 (1.66-3.96), respectively. Odds of poor physical functioning increased with multiple types of maltreatment (p_trend < 0.001); ORadj ranged from 1.49 (1.23-1.82) for a single type of maltreatment to 2.09 (1.53-2.87) for those reporting ≥3 types of maltreatment, compared to those with none. Associations of comparable magnitude were observed for mental and self-reported health outcomes.

Conclusion: Child neglect, psychological, and sexual abuse were associated with poor physical functioning at 50yrs, with accumulating risk for those with multiple types of
maltreatment. To our knowledge, we are the first to demonstrate that these associations are independent of numerous early-life adversities, and comparable in magnitude to those observed for mental health and self-rated health. The prevention of maltreatment and the alleviation of its ill-effects could be an effective policy intervention to promote healthy ageing.

Conclusions: Small skin biopsies represent a powerful method of studying molecular mechanisms of developmental programming. Phenotypes are retained ex vivo in primary cultures. Our data show that multiple pathways associated with cellular aging are affected by IUGR.

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PA3.01.06
Skin fibroblasts enable study of life course developmental programming mechanisms in a baboon model of intrauterine growth restriction (IUGR)
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Background: Age-related diseases are modified by developmental programming, defined as programming of later life phenotypes following challenges in utero or in neonatal life. Methods based on small, minimally invasive, easily obtained biopsies that can be repeated across the life course are needed to study emergence and life course progression of developmental programming mechanisms. We have developed a cohort of baboon offspring of mothers fed ad libitum (control, CTR) or a 30% global caloric reduced diet whose offspring were IUGR (birthweight ~ 12% less than offspring of ad libitum fed mothers, PMID 23482706). IUGR offspring show early emergence and accelerated development of aging-related phenotypes such as aging of left (PMID 27988927) and right (PMID 28439937) ventricular function and premature brain aging (PMID 28443017). We have derived primary skin fibroblast lines from adult CTR and IUGR baboons (ages 7-11 years; human equivalent ~ 32-50 years) to test molecular pathways changed during programming.

Methods: A 2 mm sterile post-aural punch biopsy was obtained (n = 9 CTR, 7 IUGR). Following enzymatic dissociation, isolated fibroblasts were subcultured using standard techniques to generate sufficient numbers for further testing.

Results: From explant and isolation, fibroblasts isolated from IUGR baboons required ~ 50% greater time to reach confluence in culture. Cell numbers at confluence were reduced 25% in IUGR lines compared to CTR. This delay in growth appeared linked to reduced mitochondrial respiration, suggesting potential functional defects in oxidative phosphorylation that might drive delayed growth. IUGR lines showed 15-20% reduction in oxygen consumption as measured by Seahorse Bioanalyzer (Figure). In addition, IUGR-derived fibroblasts displayed reduced cellular resilience to mitochondrial stress in response to the mitochondrial uncoupler FCCP, suggesting reduced energetic reserve in these cell lines (40% reduction in IUGR). IUGR was also associated with reduced resiliency to cellular senescence with earlier and increased levels of senescence-associated β-galactosidase and p16 expression.

Conclusions: Fibroblasts for IUGR offspring (open, n = 7) showed decreased maximum respiration and energetic reserve compared to CTR (closed, n = 9). M ± SEM.

PA3.01.07
Accelerated age-related life-course changes in plasma lipids in offspring of poorly nourished baboons: biological (programmed) versus chronological age
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Background: Female but not male offspring of the Dutch Hunger Winter had elevated total cholesterol and low-density lipoprotein (LDL) cholesterol (PMID: 19386743). Total and HDL cholesterol levels in children are associated with metabolic programming, potentially predisposing to later life cardiovascular diseases (PMID: 25840838). We hypothesized that globally reduced maternal nutrition in a nonhuman primate model would accelerate offspring life-course lipid changes.

Methods: Pregnant baboons (Papio hamadryas) ate Purina Monkey Diet 5038 ad libitum (CTL) or 70% ad lib diet in pregnancy and lactation, which produced intrauterine growth restriction (IUGR; ~ 12% decrease in body weight) in offspring. We studied IUGR females (N = 8, 8.6 years; human equivalent ~ 34 years) and age matched CTL (N = 9, 8.9 years)....
as well as 25 females from 7-22 years. The normal baboon life course in captivity is ~25 years. Serum lipids were measured on an Alfa Wassermann ACE Clinical Chemistry Analyzer. Data analyzed by linear regression and Student’s t-test.

Results: The figure shows that (A) across the life-course total cholesterol was unchanged but (B) LDL rose (slope = 2.8 mg\textper坊 dl\textper坊 year\textper坊\textsuperscript{1}) and (C) HDL:LDL ratio fell (slope = -0.067). In IUGR baboons compared with age-matched controls, LDL was increased (Fig E) and HDL:LDL decreased (Fig F) by amounts equivalent to advancing of aging by 4 and 6 years, respectively.

Conclusions: In female baboons, serum LDL rises by 2.8 mg\textper坊 dl\textper坊 year\textper坊\textsuperscript{1} and HDL:LDL falls 0.67 units per year across the life-course from 7 to 22 years. Programming by a reduced maternal diet accelerates this process by ~4-6 years of life. These data demonstrate the importance of knowing the developmental background of subjects in both human and animal studies when addressing issues of biological and chronological age.

Total cholesterol, LDL, and HDL:LDL ratio (A-C) across the life course and (D-F) at ages 8.6-8.9 years in CTR and IUGR offspring. Mean ± SEM; *P < 0.05.

PA3.01.08

Caloric restriction at adulthood reverses hepatic dysfunction induced by transient postnatal overfeeding in mice. A possible role of SIRT-1

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Background: An altered nutritional environment during critical periods of development can lead to metabolic disorders later in life. The liver, involved in lipid/glucose homeostasis, is particularly vulnerable to nutritional programming during the perinatal period. Oxidative stress (OS) has been associated with stress-induced premature senescence (SIPS) and involved in metabolic and liver dysfunctions. Sirtuin (SIRT)-1, an anti-aging protein, plays a major role in metabolism regulation as well as in SIPS, and its expression can be modulated by caloric restriction (CR). In this study, we investigated in a murine model whether transient postnatal overfeeding (OF) can lead thereafter to metabolic and hepatic disorders associated with OS and SIPS, and if CR at adulthood can reverse these dysfunctions.

Methods: C57BL/6 male pups were maintained, during the lactation period, in litters adjusted to 9 pups for normal feeding (NF) or reduced to 3 pups to induce transient postnatal OF. After weaning at postnatal day (PND) 24, all mice had free access to a standard diet. At 6 months of age, mice from NF and OF groups were randomly assigned to either the ad libitum (AL) diet or the caloric restriction diet (CR, daily food supply reduced by 20%) for one month. The following parameters were studied at PND 24 and 7 months of life: i) body weight; ii) markers of OS (reactive oxygen species, antioxidant defenses); iii) markers of SIPS (factors involved in cell cycle arrest (p21, p53, Acp53 and p16, pRb/Rb), SIRT-1); iv) liver structure/function (histological analysis, insulin signaling pathways and glucose transporters expression).

Results: At PND 24, the body weight of OF pups was 63% higher to normal fed pups, but no difference in hepatic structure and function were observed between both groups. At 6 months of life, OF mice displayed an increased area under curve of blood glucose concentration after glucose challenge as well as a higher blood glucose concentration after insulin injection (p < 0.05) compared to NF animals. At 7 months, body weight of OF group mice was 11.7% higher compared to NF animals. Moreover, in the liver from 7 months old OF mice we observed, compared to NF mice: i) higher levels of superoxide anion, and decreased catalase and superoxide dismutase expression (p < 0.01); ii) increased expression of p21, p53, Acp53 and p16, but decreased pRb/Rb and SIRT-1 expression (p < 0.01); iii) microvesicular steatosis and hepatic fibrosis; iv) decreased IRS-1/2, pIRS-1/2, PI3K, pAkt/Akt expression (p < 0.01), decreased GLUT-2, but increased GLUT-4 expression (p < 0.05). CR at adulthood decreased body weight, reversed OS, SIPS, microvesicular steatosis, improved insulin signaling pathway and normalized glucose transporter expression, but did not reverse hepatic fibrosis.

Conclusions: A transient postnatal OF leads to glucose intolerance, insulin resistance, and impaired hepatic structure and function at adulthood, associated with decreased SIRT-1 expression. Caloric restriction at adulthood reverses liver alterations induced by transient postnatal OF, including decreased SIRT-1 expression.

PA3.01.09

Influence of nutritional intervention in early life behaviour in healthy children at 2.5 years

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Background: Mental health is the basis for achieving all the other skills of human development. During childhood many clinically significant behaviour problems may occur (conduct problems, hyperactivity, emotional problems). These problems are often being identified first in early childhood, which then show considerable stability across older ages. Nutrition is the most important environmental factor that will influence in the development of the brain, conditioning mental health during childhood. Aim: To analyse the influence of a new infant formula supplemented with Nutriexpert® factor on behaviour in healthy children up to 2.5 years of age.

Methods: 170 healthy term infants with adequate birth weight for gestational age and aged between 0-2 months were enrolled in a randomized double-blind study to receive a standard infant formula (F1: n = 85) or a new one supplemented with long chain polyunsaturated fatty acids (LC-PUFAs), milk fat globule membrane components and symbiotics (Nutriexpert® factor) (F2: n = 85). As a control group, 50 breastfed infants (BF) were included. Mothers rated behavior problems using the Child Behavior Checklist (CBCL) when their children were 2.5 years of age. Normal distribution was assumed using Shapiro-Wilk test. Differences in CBCL scores by study groups were analysed using ANOVA and ANCOVA adjusted for confounding factors (maternal cultural level, area of residence and lactation time). Bonferroni corrected post hoc comparisons were used to identify significant pairwise group differences. Associations between categorical variables were estimated by Chi-Square Test, performed using SPSS version 22.0.

Results: At 2.5 years, 103 children attended the follow-up call (F1: n = 29/F2: n = 41/BF: n = 33). CBCL scores were obtained and children fed F1 presented higher scores in anxious/depressed (p = 0.041), withdrawn (p = 0.017), attention problems (p = 0.026), aggressive behaviour (p = 0.045), attention deficit/hyperactivity problems (p = 0.039), oppositional defiant problems (p = 0.029) and total problems (p = 0.017), compared to BF children. Also, children fed F2 and BF showed lower scores in externalizing problems (p = 0.005) than children fed F1. However, in adjusted analysis by maternal cultural level, area of residence and lactation time, these results disappeared. Also after adjustment, children fed F2 showed lower scores in affective problems (p = 0.038) compared to children fed F1 and BF. Additionally, the scores in each scale were divided in three variables: normal, borderline and clinical (pathological), and children fed F1 presented more clinical affective problems (p = 0.026) compared to children fed F2; and more borderline internalizing problems than children fed BF (p = 0.042).

Conclusions: Early nutritional intervention with Nutriexpert® factor and breastfeeding promotes long-term effects by determining less development of child’s psycho-behaviour problems at 2.5 years of age in children. These results suggest the need to follow-up of these children in order to demonstrate the maintenance of these pre-neuropsychiatric disorders.

PA3.02 - Specific nutrients

PA3.02.01

Gestational vitamin D supplementation and offspring bone development: translation from observation to intervention

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Although the effects may be transient, the accrual of bone mass during childhood is influenced by a range of factors such as calcium and vitamin D nutrition, physical activity, body composition and illness. Additionally, there is increasing evidence that factors acting during intrauterine life may have a long-term influence on postnatal bone development of the offspring. Maternal characteristics such as diet, adiposity, smoking, physical activity and 25-hydroxyvitamin D [25(OH)D] status during pregnancy have all been associated with offspring bone development, most recently to the age of 20 years. Several, but not all, studies have demonstrated positive associations between maternal 25-hydroxyvitamin D status during pregnancy and offspring bone mass. Recently the role of maternal gestational vitamin D supplementation to improve offspring bone mass was tested in a UK multicentre, randomised, placebo-controlled, double-blind trial of 1000IU/day vitamin D3 (cholecalciferol) versus placebo from 14 weeks gestation till delivery of the offspring. In this MAVIDOS trial, although there was no difference in offspring neonatal whole body BMC between babies born to treatment versus placebo mothers overall, in a pre-specified analysis, amongst winter births maternal vitamin D supplementation led to a marked increase in offspring BMC. Further analyses have identified environmental and genetic predictors of 25(OH)D response to supplementation, and mechanistic inferences relating to perinatal epigenetic marks.

In this session, I will give an overview of early factors which may alter bone development, focusing on vitamin D exposure during intrauterine life, and will consider implications for public health approaches aimed at optimising bone development.

PA3.02.03

Influence of maternal fatty acids status on offspring cardio-metabolic health

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Obesity is a major public health problem among women of reproductive age, with obesity prevalences up to 30% in Western countries. An even higher percentage of women gain...
an excessive amount of gestational weight according to the US Institute of Medicine Criteria. Accumulating evidence suggests that maternal obesity during pregnancy leads to adverse cardio-metabolic health outcomes in offspring, but the underlying mechanisms remain to be explored. The fetal overnutrition hypothesis suggests that increased placental transfer of nutrients to the developing fetus in obese mothers and mothers with high levels of gestational weight gain, may subsequently affect fetal development, fetal fat deposition and the development of the hypothalamic-endocrine system that controls appetite and energy metabolism. These adaptations may predispose individuals to a greater risk of adverse health outcomes in later life. Fatty acids are one of the nutrients that may play a key role in these developmental adaptations. The fetus depends on maternal transfer of essential fatty acids, which are an important source of metabolic energy, and their structural and signaling properties are crucial for fetal growth and development. Among overweight and obese pregnant women, there is a suboptimal fatty acid profile, characterized by higher saturated fatty acids, lower N3-PUFAs and increased N6/N3 PUFAs ratio. Observational studies have shown that lower N3-PUFA levels and higher N6 PUFA levels are associated with a higher childhood BMI, adverse body fat distribution, a higher systolic blood pressure and adverse metabolic profile. However, thus far, intervention studies focused on increasing maternal N3-PUFA levels do not show a strong effect on offspring BMI and obesity risk. Further studies are needed to explore the causality of these observed associations, underlying mechanisms and the potential for development of preventive strategies focused on optimizing maternal fatty acids status during pregnancy to improve long-term health outcomes of offspring.

**Background:** There is accumulating evidence of associations between perinatal epigenetic markers and offspring bone mass. We have previously demonstrated associations between perinatal DNA methylation at the retinoid-X-receptor-alpha (RXRA) locus and offspring bone mass in the Southampton Women’s Survey mother-offspring cohort, and shown that this may be mediated by maternal vitamin D status. This may be of functional relevance as RXRA is known to play a key role in the nuclear action of 1,25(OH)2-vitamin D.

We tested the hypothesis that maternal supplementation with vitamin D during pregnancy in a randomised controlled trial setting would lead to altered perinatal DNA methylation at the RXRA locus.

**Methods:** The Maternal Vitamin D Osteoporosis Study (MAVIDOS) is a multicentre, double-blind, randomised, placebo-controlled trial of 1000iu/day cholecalciferol or matched placebo from 14 weeks gestation until delivery. Umbilical cord tissue from the fetal side was collected at birth and frozen at -80°C (n = 436). Pyrosequencing was used to perform in-depth DNA methylation analysis at 10 CpG sites within the RXRA promoter. These CpG sites were selected on the basis of the sites previously analysed in the observational Southampton Women’s Survey mother-offspring cohort. Independent t-tests were used to assess the differences in methylation between the treatment groups.

**Results:** We observed statistically significant (p ≤ 0.05) differences in methylation at the RXRA region of interest between the cholecalciferol supplemented and placebo group at 4 of 10 CpG sites. Overall, RXRA methylation levels were significantly lower in the umbilical cord from offspring of cholecalciferol supplemented mothers: e.g. at RXRA CpG 5, mean difference in % methylation between the supplemented and placebo groups was -2.1% (n = 433, 95% CI -3.7 to -0.3, p = 0.02). We have previously demonstrated in vitro, using electrophoretic mobility shift assays, that methylation in this region leads to reduced transcription factor binding. Therefore, the reduced methylation observed in the cholecalciferol supplemented group may be associated with an upregulation of 1,25(OH)2-vitamin D signalling.

**Conclusions:** Our findings from the MAVIDOS trial support previous observational results and provide new evidence that maternal gestational supplementation with cholecalciferol leads to altered perinatal epigenetic marking. Such results inform potential mechanistic pathways linking maternal 25(OH)-vitamin D status to offspring bone mass, and may yield novel biomarkers of future bone development.

**PA3.02.06**

**Placental uptake and metabolism of vitamin D: a potential mediator of fetal growth?**

J.K. Cleal, C.L. Simner, B. Ashley, C. Cooper, R.M. Lewis, N.C. Harvey

University of Southampton, SOUTHAMPTON, United Kingdom

**Background:** There is accumulating evidence of associations between perinatal epigenetic markers and offspring bone mass. We have previously demonstrated associations between perinatal DNA methylation at the retinoid-X-receptor-alpha (RXRA) locus and offspring bone mass in the Southampton Women’s Survey mother-offspring cohort, and shown that this may be mediated by maternal vitamin D status. This may be of functional relevance as RXRA is known to play a key role in the nuclear action of 1,25(OH)2-vitamin D.

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**Conclusions:** Our findings from the MAVIDOS trial support previous observational results and provide new evidence that maternal gestational supplementation with cholecalciferol leads to altered perinatal epigenetic marking. Such results inform potential mechanistic pathways linking maternal 25(OH)-vitamin D status to offspring bone mass, and may yield novel biomarkers of future bone development.
Background: Low 25-hydroxyvitamin D (25(OH)D) levels are common in pregnancy and are linked to suboptimal fetal growth and increased risk of adulthood obesity and poor bone health. 25(OH)D was thought to diffuse across the placenta to be hydroxylated into the active-1,25-dihydroxyvitamin D (1,25(OH)2D) by the fetus. However we have shown that expression of megalin and cubulin, which can mediate vitamin-D uptake (alone or bound to albumin) are associated with measures of fetal growth. We investigated whether 25(OH)D uptake (alone or bound to albumin) are associated with expression of megalin and cubulin, which can mediate vitamin-D dependent gene expression, implying the placenta converts vitamin D to active form.

Methods: Placental villous fragments were dissected from term human placentas cultured for 8 h in Tyrodes buffer containing 20 μM 25(OH)D (n = 6), 25(OH)D + 0.7 mM albumin (n = 6), 50 nM 1,25(OH)2D (n = 11) or 1,25(OH)2D + 0.7 mM albumin (n = 11). Endocytic mechanisms of 25(OH)D uptake were blocked by adding 5 mM amiloride (n = 5) or 1 μM cytochalasin D (n = 5). mRNA expression of CYP24A1, a vitamin D responsive gene, was measured by qRT-PCR. Data were analysed by one- and two-way ANOVA.

Results: 25(OH)D induced CYP24A1 mRNA expression (p < 0.001) compared to controls and expression was further increased by the addition of albumin (p < 0.001). 1,25(OH)2D increased CYP24A1 mRNA expression (p < 0.001) compared to controls, but was not increased further with albumin. Both amiloride and cytochalasin D reduced CYP24A1 mRNA expression compared to 25(OH)D with and without albumin (p < 0.001).

Conclusion: These data suggest that both 25(OH)D and 1,25(OH)2D are taken up into the placenta and can induce vitamin D dependent gene expression, implying the placenta converts 25(OH)D to 1,25(OH)2D. Cubulin and megalin mediated endocytosis has previously been demonstrated in the kidney and our data now support a role for endocytic uptake of vitamin D by the placenta. Furthermore, uptake of 25(OH)D may be enhanced by albumin. Relationships between placental genes involved in vitamin D handling and neonatal size support the idea of the placenta actively mediating the amount of vitamin D transferred to the fetus.

This work was supported by the Gerald Kerkut Charitable Trust.

PA3.02.07
Improving nutritional status in pregnant teenagers: The Babies, Eating and Lifestyle in Adolescence Study (BELLA)
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Background: Worldwide, approximately 17 million girls under 19 give birth every year. Though the majority of these births are to adolescents in low and middle income countries, the UK continues to have the highest teenage pregnancy rate in Europe. Teenage pregnancy has a high risk of poor outcomes for mother and baby. Teenage girls have the poorest diets of any population group in the UK, a recognised determinant of poor pregnancy outcome. Pregnant teenagers trust advice from their midwives, but midwives feel they do not have time or opportunity to discuss diet and nutrition or the confidence and knowledge to do so. An intervention that increases midwives confidence to address diet in pregnancy and teenagers’ capacity to improve their quality of diet has the potential to improve outcomes for both themselves and their babies. This study aimed to develop a complex intervention that uses the relationship between pregnant teenagers and their midwives to deliver support to improve diet quality in pregnant teenagers.

Methods: This research was conducted across three study sites in the UK: Manchester, Doncaster and Southampton. The study used an innovative Person-Based Approach to intervention development in conjunction with Social Cognitive Theory to design format and content of the intervention. Interviews were conducted at each site with pregnant teenagers and their health and social care practitioners regarding diet and lifestyle, and what form of support they might find helpful. Experts’ insights on implementation were also sought from stakeholder groups responsible for the provision and commissioning of maternity care. Content analysis was then used to identify guiding principles for the design of the intervention, which were mapped onto appropriate behaviour change techniques to produce an outline intervention design.

Results: A total of 113 young women and 49 practitioners were interviewed. Findings suggest that pregnant teenagers have low awareness of the importance of a healthy diet for themselves and their baby; they often feel socially isolated, judged and not in control of their own lives. Pregnant teenagers and their midwives lack a reliable resource for immediate support with eating healthily. Midwives felt that it was their role to support young mothers with diet in pregnancy, but were anxious about initiating conversations and felt they lacked clear guidance. Stakeholders felt the interview findings were congruent with their experiences and that the proposed intervention format was necessary and acceptable for implementation.

Conclusions: An effective intervention to improve pregnant teenagers’ dietary quality must empower and motivate teenage mothers and their midwives, provide an engaging and easy to

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use 24-hour source of information and support, and enable connections with other young mothers. The proposed intervention therefore comprises training in skills to support behaviour change for midwives and a digital support tool that is relevant to improving dietary quality and appropriate for the needs of the pregnant teenagers. The digital support resource will incorporate clear information on healthy diet choices, peer-modelling of real-life solutions to diet problems, goal-setting, and feedback. The resource will be introduced by the midwife to support pregnant teenagers between appointments.

PA3.02.08

Maternal protein restriction around conception increases foetal neuronal differentiation and is associated with adult memory deficits.

J. Willaime-Morawek, P. Fleming, M. Gould

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Background: Maternal malnutrition during pregnancy is detrimental to foetal development and increases the risk of many chronic diseases in later life i.e. increased risk of schizophrenia. Previous studies have shown maternal protein malnutrition during pregnancy and lactation compromises brain development in late gestation and after birth, affecting structural, biochemical and pathway dynamics with lasting consequences for motor and cognitive function. However, the importance of nutrition during embryogenesis for early brain development is unknown. We have previously shown maternal low protein diet confined to the preimplantation period (Emb-LPD) in mice is sufficient to induce cardiometabolic and behavioural abnormalities in adult offspring.

Methods: Using the same diet model, female mice were fed different diets from conception to the end of pregnancy: normal protein diet (NPD), low protein diet (LPD) or embryonic LPD (Emb-LPD: LPD for 3.5 days, NPD thereafter). Foetal brains were analysed during gestation with in vivo analysis using FACS and immunofluorescence for neurogenesis markers, and in vitro techniques using the neurosphere assay. Follow up behavioural tests in the offspring were performed, including the short-term memory novel object recognition.

Results: We have shown that Emb-LPD and sustained LPD reduce neural stem and progenitor cell numbers through decreased proliferation in both ganglionic eminences and cortex of the foetal brain at E12.5, E14.5 & E17.5 (p < 0.001). Moreover, Emb-LPD causes remaining neural stem cells to upregulate the neuronal differentiation rate in compensation beyond control levels during gestation, independently of sex (p < 0.001). When analysing the adult offspring behaviour, the Emb-LPD males and females show a clear deficit in short-term memory (p = 0.00001).

Conclusions: Our data are the first to demonstrate clearly that poor maternal nutrition around conception has adverse effects on early brain development and is associated with adult memory deficits.

Funding: BBSRC, Wessex Medical Trust, Rosetrees Trust, University of Southampton.

PA3.03 - Innovative DOHaD Experiments

PA3.03.01

New animal models of placental dysfunction in DOHaD research

T. Plösch

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Classical rodent models used in DOHaD research are based on dietary interventions during pregnancy. Simulation of human hunger periods by caloric or protein restriction are examples. Similarly, placental dysfunction is often simulated by clamping of the uterine artery, which requires surgical procedures. I will here compare several novel mouse models of placental dysfunction and their benefits for DOHaD research. These models are based on the genetic deletion of the transcription factor TFAP2C in the placenta (Sharma et al., Development 2016 Mar 1;143(5):787-98), or on a combination of adenosinergic receptor expression of sFlt1, with or without low-grade inflammation (Stojanovska et al., this conference, #278). The former model leads to growth restriction in the offspring, whereas the latter model is furthermore accompanied by signs of preeclampsia. Interestingly, in both cases also the sex of the offspring matters for the outcome. These new models, especially when compared to each other, will in future allow us to specifically differentiate between different forms of placental dysfunction and their long-term consequences.

PA3.03.03

Early life impacts on reproductive programming: effects in female ovarian development and function

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Disease risk is established well before birth. Lifestyle associated diseases, including obesity and Type 2 diabetes, are known to be influenced by fetal adaptations to in utero conditions and critically, these disease effects span multiple generations. Reproductive maturation and function is similarly influenced by early life events. This should not be surprising, since the primordial germ cell pool is established during embryonic life and is thus vulnerable to early life events. Epidemiological studies of populations born low birth weight (LBW) due to intrauterine growth restriction (IUGR) and/or small for gestational age (SGA) show significant associations between growth, birth weight, and postnatal reproductive function. In males, prenatal events have been shown to modify sperm counts and fertility, and in females modify ovarian function. In females, a
multitude of “modifying” cues inducing nutritional insults have been identified, that result in a decline in ovarian follicular reserve, changes in ovulation rates and altered age at onset of puberty. In both males and females, early life nutritional adversity accelerates pubertal onset. We have shown in humans and in animal models, that fetal growth restriction results in early pubertal onset, and results in a premature loss of adult ovarian follicles, underpinned by an increase in apoptosis and increased ovarian oxidative stress levels. Critically, low birth weight offspring show impaired ovarian follicle function already as neonates, and demonstrate reproductive impairment early in young adulthood, well before full adult reproductive maturity. Similarly, maternal obesity and nutrient excess, modifies reproductive maturation and results in impaired female ovarian development that impacts on long term function. Many pathways have been suggested to underpin these associations, where studies have investigated the maternal-fetal-placental relationship as well as events occurring in the early postnatal environment. But the underlying ovarian mechanisms regulating the relationship between the early life developmental environment and postnatal reproductive dysfunction remain unclear.

PA3.03.05
Time-dependent evolution of non-alcoholic fatty liver disease in young-to-adult MSG-obese mice
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Federal University of Maranhão, SÃO LUÍS - MA, Brazil

Background: Monosodium L-glutamate (MSG)-induced obese rodents have been largely used in pre-clinical tests investigating drugs, plant extracts or probiotics effects on non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) onset and progression. However, literature is controversial on the underlying mechanisms, as well as disease triggering timing for this model. Thus, this study sought to characterize metabolic and histopathological features of NAFLD-to-NASH progression in MSG obese mice.

Methods: Newborn Swiss male mice (Mus musculus) were injected with MSG (4g/Kg/day, s.c.) or saline solution (0,1mL/10 g/day, s.c., CTR) on alternate days, from postnatal day (pnd) 2 through 10. Animals from both groups were weighed twice a week and euthanized at pnd 60, 120 or 180 (MSG/CTR60,120,180). Liver as well as peripididymal and retroperitoneal fat pads were collected for morphometric assessment. Blood was taken for fasting glucose, triglycerides, total cholesterol and cytokines (IL-6, TNF-α, IL-10 and IL-4) measurement. TyG Index was calculated as a surrogate method to estimate hepatic insulin sensitivity. Liver samples were further used to measure hepatic lipid profile and histopathological analysis by hematoxylin-eosin and Mason’s trichrome stains, followed by NAFLD activity score (NAS) evaluation. Ultimately, multivariate analysis was performed for identification of variables independently correlating to total NAS value. Statistical analysis was made by Student’s t test for age-mated groups and one-way ANOVA followed by Newman-Keuls post-test for MSG or CTR multi-age comparison, for p < 0.05.

Results: MSG mice presented higher body mass and hypertriglyceridemia at all ages, as compared to their age-mated CTR, which were followed by higher total fat and triglycerides in the liver. However, hyperglycemia and impaired hepatic insulin sensitivity was observed only after pnd 120. Histopathological analysis showed that MSG60 developed NAFLD with microvesicular steatosis and rare ballooning, which evolved to additional presence of centrolobular polymorphonuclear cells foci and increased ballooning in MSG120. MSG180 maintained these features, but presented larger steatosis resulting in higher NAS value (see abstract image). No fibrosis was observed. Assessment of serum cytokines levels showed no difference among groups. Multivariate analysis showed that retroperitoneal fat pad accumulation was the only variable independently associated with total NAS value, R² > 70%.

Conclusion: Our data show that MSG obese mice precociously presented NAFLD, which promptly evolved to NASH in parallel with increased serum triglyceride accumulation. These features anticipated ulceration impairment of glucose homeostasis. Finally, our data support the appliance of MSG obese model for studies focusing on underlying mechanisms of NAFLD-to-NASH progression in young obese subjects.

Arrows: inflammatory foci. N = 5-7, mean ±SEM, *p < 0.05 vs. CTR (age-mated), #p < 0.05 vs. pnd 60 (same group), §p < 0.05 pnd 120 (same group).

PA3.03.06
Maternal undernutrition increases fibrosis in heart of the late gestation sheep fetus
R. Darby, C. Lock, C. Mcmillen, L. Morrison
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Epidemiological studies have consistently shown that poor in utero conditions influence adult cardiac health. Previously,
models of placental insufficiency that restrict both oxygen and glucose delivery to the fetus have shown increased hypertrophic signalling in the heart of the growth restricted fetus. We aimed to determine the effect of decreased fetal nutrient supply in late gestation in normoxic fetuses. At 115 days (d) gestation (term = 150 d), ewes were randomly divided into either a control or an undernutrition (UN) group that received a 50% reduction in nutrient intake until 145 d gestation. Fetal blood samples were collected across late gestation for blood gas and glucose analysis. Right ventricle tissue was collected at post mortem. Histological analysis and quantitative real-time RT-PCR were performed to determine the presence of myocardial fibrosis and the expression of factors which promote fibrosis. Maternal undernutrition decreased fetal glucose concentrations across late gestation and increased the mRNA expression of factors which increase fibrosis, COL1A, TIMP-1 and TIMP3 in fetal cardiac tissue. In addition, there was an inverse relationship between fetal glucose concentrations and COL1A mRNA expression (Figure). Increased interstitial fibrosis in fetal UN right ventricle tissue was observed through unbiased quantification of picrosirius red stained fixed tissue sections. We have shown that decreased glucose supply may drive the onset of myocardial fibrosis in the late gestation fetal heart. This may have negative implications for cardiac health in adulthood.

Maternal UN increased fetal cardiac mRNA expression of COL1A (A), but not COL3A1 (B).

**PA3.03.07**

Maternal low intensity physical exercise changes insulin milk composition and prevents obesity in offspring rats exposed to early overnutrition.

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**Background:** Low intensity exercise during pregnancy and lactation may create a protective effect against the development of obesity in offspring exposed to overnutrition in early life.

**Methods:** To test these hypotheses, pregnant rats were randomly assigned into 2 groups: Exercised mothers (EM) and sedentary mothers (SM). The exercise was performed throughout pregnancy and lactation on a rodent treadmill at 30% VO2Max /30-minute/session/3x/week. At lactational day 3 (LD3), mothers were distributed into 4 groups: Exercised mothers with normal litter (EM-NL), Exercised mothers with small litter, (EM-SL), sedentary mothers with normal litter (SM-NL), and, sedentary mothers with small litter (SM-SL). At postnatal day 3 (P3) males offspring were distributed into 4 groups: Normal litter of exercised mothers (NL-EM), small litter of exercised mothers (SL-EM), normal litter of sedentary mothers (NL-SM) and small litter of sedentary mothers (SM-SM). Results were reported as means SEM. The data sets were analyzed using Two-way analysis of variance (ANOVA) followed by Tukey’s post hoc test. *p < 0.05* was considered significantly different when considering the main effect of exercise (E), litter size (L), their interaction (LxE; litter size vs exercise) and the differences between groups.

**Results:** Exercised mothers showed low mesenteric fat stores and fasting glucose and improved glucose-insulin tolerance, VO2max during. Moreover, the breast milk contained elevated levels of insulin. In addition, SL of sedentary mothers presented metabolic dysfunction and glucose and insulin intolerance and were hyperglycemic and hyperinsulinemic in adulthood. SL of exercised mothers showed lower fat tissue accretion and improvements in glucose tolerance, insulin sensitivity, insulinemia and glyceremia.

**Conclusions:** The results suggest that low maternal physical exercise during the perinatal period life improve maternal health, as well as, increase milk insulin concentration, which may be associated with a possible reprogramming effect to prevent metabolic dysfunction in adult rat offspring exposed to early overnutrition.

![Table 1](image-url)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Markers Parameters</th>
<th>SM-NL</th>
<th>SM-SL</th>
<th>EM-NL</th>
<th>EM-SL</th>
<th>Source of variation</th>
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<tr>
<td>Fasting Insulin (LDL g/mL)</td>
<td>0.51 ± 0.05</td>
<td>0.56 ± 0.04</td>
<td>0.51 ± 0.07</td>
<td>0.57 ± 0.06</td>
<td>LDL: F1-E1</td>
<td>&lt;</td>
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<tr>
<td>Fasting Glucose (LDL g/mL)</td>
<td>92.6 ± 2.6</td>
<td>97.1 ± 2.8</td>
<td>98.3 ± 1.7</td>
<td>82.8 ± 3.6</td>
<td>LDL: F1-E1</td>
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<tr>
<td>TMAO-B (LDL)</td>
<td>3.1 ± 0.6</td>
<td>3.8 ± 0.2</td>
<td>3.8 ± 0.0</td>
<td>3.8 ± 0.0</td>
<td>LDL: F1-E1</td>
<td>&lt;</td>
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<tr>
<td>Mean serum (µg/dL)</td>
<td>1137.0 ± 350.0</td>
<td>1034.0 ± 320.0</td>
<td>1034.0 ± 320.0</td>
<td>1034.0 ± 320.0</td>
<td>LDL: F1-E1</td>
<td>&lt;</td>
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</tbody>
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**PA3.03.08**

The impact of altered IL-1 signalling on metabolic dysfunction during pregnancy


University of Auckland, AUCKLAND, New Zealand
Background: Over the last two decades, maternal obesity has been exposed as a major driving force in the predisposition to adult onset cardio-metabolic disease in offspring. These conditions are strongly associated with a state of persistent low-grade inflammation. IL-1R1 is a key signalling mediator which bridges metabolic and inflammatory systems. Previous work has demonstrated that male IL-1R1 knockout mice (IL-1R1^-/-) are partially protected from metabolic dysfunction. This study aimed to investigate the role of this receptor on metabolic health during pregnancy.

Methods: C57BL/6 mice and IL-1R1^-/- were assigned to either a purified control (CD) or high fat diet (HFD; 45% kcal from fat) for a 10 day acclimatisation period and throughout gestation (n = 12-18/group). Glucose tolerance was assessed at gestational day (GD) 16.5 by oral glucose tolerance test (2g/kg). Mice were culled at GD18.5 by cervical dislocation. Maternal tissues, fetuses and placentas were weighed and either snap frozen or fixed in neutral buffered formalin. Plasma was analysed by ELISA and adipose tissue morphology and gene expression was determined. Data was analysed by 2-way ANOVA with maternal genotype and diet as factors. OGTT was analysed by repeated measures ANOVA.

Results: IL-1R1^-/- mice consumed less calories and gained less weight over pregnancy. Despite this, HFD induced glucose intolerance irrespective of genotype. Furthermore, IL-1R1^-/- HFD mice had significantly reduced adipose tissue gene expression of the glucose transporter GLUT4 and the insulin signalling mediator IRS1. Adipocyte size was significantly increased and PPARγ expression significantly decreased in C57BL/6HFD, IL-1R1^-/-CD and IL-1R1^-/-HFD groups compared to C57BL/6CD. Male but not female fetuses of IL-1R1^-/- genotype exhibited increased placental and body weight compared to C57BL/6 groups. Expression of placental glucose transporters GLUT3 (female) and GLUT4 (male) were increased in IL-1R1^-/- compared to C57BL/6 groups.

Conclusion: Despite a reduction in pregnancy weight gain and caloric intake, IL-1R1^-/- mice displayed significant adipocyte hypertrophy, reduced adipogenic potential and a reduction in the expression of adipose tissue insulin sensitive markers during pregnancy. However, irrespective of these adverse effects, IL-1R1^-/- did not result in adverse hepatic outcomes and appears to have beneficial effects on fetal growth, perhaps through increased expression of placental glucose transporters. It is clear that IL-1R1 signalling plays an important role in adipogenic processes during pregnancy and disruption of adipose tissue expandability promotes metabolic dysfunction associated with HFD.

PA3.03.09

Resveratrol prevents the development of hypertension programmed by maternal plus post-weaning high-fat consumption in male offspring

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Background: Hypertension can originate from early life. Our previous study showed that maternal plus post-weaning weaning high-fat (HF) induced programmed hypertension in adult offspring. Foods can activate several nutrient sensing mechanisms to maintain energy homeostasis and regulate autophagy. These nutrient sensing signals include SIRT (Silent information regulator transcript), AMP-activated protein kinase (AMPK), and PPAR pathway. Additionally, HF consumption can induce changes in gut microbiota that results in dysbiosis, which is related to hypertension. Hence, we intend to examine whether resveratrol (a SIRT activator) can reprogram two-hit induced programmed hypertension via regulating nutrient sensing pathway, autophagy, and gut microbiota.

Methods: Female Sprague-Dawley rats were assigned to receive either a normal diet (ND) or HF diet (D12331, Research Diets) for 5 weeks before mating and during gestation and lactation. The male offspring were onto either the ND or HF diet from weaning to 4 months of age, resulting in four experimental groups (maternal diet/post-weaning diet; n = 8-10/group): ND/ND, ND/HF, HF/ND, and HF/HF. Rats were killed at 4 months of age. Another group of HF/HF rats (n = 10) were treated with 0.05% resveratrol in drinking water during pregnancy and lactation (HF/HF + R). Rat fecal samples were collected for 16s ribosomal DNA sequencing.

Results: Maternal plus post-weaning HF induced increases of BPs in adult offspring, which resveratrol prevented. Post-weaning diet increased BW of both ND/HF and HF/HF animals at 4 months of age, which was prevented by maternal resveratrol treatment. We observed that higher plasma Ang I level and lower renal Ang (1-7) level in the HF/HF group compared to those in controls. HF diet significantly reduced renal mRNA expression of Sirt1, Sirt4, Pparg1a, Ppara, and Pparg in the HF/HF group vs. control. Resveratrol therapy increased SIRT1, pAMPKα2, and PGC1α protein levels in the HF/HF + R group. Additionally, HF diet inhibited renal mRNA expression of Ulk1 and Atg5, which resveratrol prevented. Resveratrol increased LC3-II/LC3-I ratio. Maternal and post-weaning HF both increased the Firmicutes/Bacteroidetes ratio, a signature of gut dysbiosis. Also, maternal and post-weaning HF increased the relative abundance of Tenericutes (~6-fold) and Verrucomicrobia (~40-fold), respectively. Butyrate-producing bacteria Coprococcus was in lower quantities in the HF/HF group compared to control. In contrast, lactate-producing bacteria Lactococcus was in higher quantities in the HF/HF group compared to control.

Conclusions: In conclusion, maternal plus post-weaning HF consumption induced programmed hypertension, which was related to the activation of RAS, nutrient sensing pathway, inhibition of autophagy, and gut dysbiosis. Resveratrol prevents HF-induced programmed hypertension in adult male offspring, which is associated with increases of SIRT1, pAMPKα2, and PGC1α protein levels in the kidney, induction of autophagy, and restoration of the RAS and gut microbiota. It is thought that by exploring the underlying mechanisms to HF-induced programmed hypertension, we might develop novel
reprogramming strategy for the prevention of programmed hypertension in children exposed to high-fat intake in early life.

PA3.04 – Maternal gestational disorders

PA3.04.01
Maternal gestational exposures and offspring cardio-metabolic health
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Over the last 10 years in high income countries interest in in utero exposures that might influence future cardio-metabolic health has shifted from factors related to fetal undernutrition to factors related to overnutrition. Concern that exposure to higher maternal pregnancy adiposity and its associated metabolic disruptions will influence future offspring body composition and cardio-metabolic health are beginning to influence obstetric practice but the evidence for this is unclear. These issues also have relevance in low- and middle-income countries, where population health is increasing affected by the joint extremes of under- and over-nutrition. In this talk I will summarise current evidence regarding: (i) the impact of maternal gestational disorders on future offspring cardio-metabolic health; (ii) the impact of maternal pregnancy adiposity and associated traits on offspring birth size and (iii) the impact of maternal pregnancy adiposity and associated traits on future offspring adiposity and cardio-metabolic health. I will end by suggestions (that hopefully will continued to be discussed after the talk) for future research that is required to fill current knowledge gaps.

PA3.04.04
Association of pre-pregnancy body mass index with future offspring metabolic profile: findings from three independent European cohorts
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Background: It is unknown whether maternal pregnancy adiposity is associated with long-term risk of adverse metabolic profiles in offspring, and if so, whether this association is causal, via intrauterine mechanisms, or explained by shared familial (genetic, lifestyle, socioeconomic) characteristics.

Methods: We used one and two-stage individual participant data (IPD) meta-analysis, and a negative-control (paternal BMI) to assess associations in three European cohorts (offspring age at metabolic assessment 16, 17 and 31 years). A comprehensive profiling of offspring circulating lipids and metabolites was done by a high-throughput Nuclear Magnetic Resonance (NMR) metabolomics platform.

Results: One-stage IPD meta-analysis (N=5327 to 5377 mother-offspring trios) showed that increasing maternal and paternal BMI was associated with an adverse cardio-metabolic profile in offspring. We observed strong positive associations with VLDL-lipoproteins, VLDL-C, VLDL-triglycerides, HDL-diameter, branched/aromatic amino acids, glycoprotein acetyllys, and triglycerides, and strong negative associations with HDL-lipoprotein, HDL-diameter, HDL-C, HDL2-C and HDL3-C (all P<0.003). Stronger magnitudes of associations were present for maternal compared with paternal BMI across these associations, however there was no strong statistical evidence for heterogeneity between them (all bootstrap P>0.003, equivalent to 0.05 after accounting for multiple testing). Results were similar in each individual cohort, and in the two-stage analysis. Offspring BMI showed similar patterns of cross-sectional association with metabolic profiles as for parental pre-pregnancy BMI associations, but with greater magnitudes. Adjustment of the parent BMI-offspring metabolite associations for offspring BMI suggested the parental associations were largely due to the association of parental BMI measures with offspring BMI.

Conclusion: Our findings suggest that maternal BMI-offspring metabolome associations are likely to be largely due to shared genetic or familial lifestyle confounding, rather than intrauterine programming mechanisms. They do not support the introduction of antenatal measures to reduce maternal pregnancy BMI in order to prevent disruption of offspring cardio-metabolism in later life. Interventions to reduce BMI in all family members may be more beneficial.
PA3.04.05

The role of maternal obesity in the associations of pregnancy complications with childhood overweight and obesity. Individual participant data meta-analysis.

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Background: Gestational diabetes and hypertensive disorders of pregnancy have been shown to be associated with greater offspring adiposity. Whether these associations are confounded by maternal adiposity, which influences these pregnancy complications and offspring adiposity, remains unclear. We aimed to assess the associations of gestational diabetes and hypertensive disorders of pregnancy with offspring body mass index (BMI) throughout childhood, and to explore the role of maternal BMI during pregnancy in these associations.

Methods: In this individual participant data meta-analysis of 161,184 mothers and their children from 34 pregnancy and birth cohorts from Europe and North-America, we assessed the association of gestational diabetes, gestational hypertension and pre-eclampsia with sex and age-adjusted standard deviation scores (SDS) of childhood BMI and the risk of overweight and obesity in early (2.0-4.9 years), mid (5.0-9.9 years), and late childhood (10.0-17.9 years).

Results: Gestational diabetes was associated with a higher early childhood BMI SDS and higher risk of overweight and obesity (Odds Ratio (OR) 1.57 (95% Confidence Intervals (CI) 1.34, 1.84)) as compared to an uncomplicated pregnancy. Similar associations were observed in mid- and late childhood. These effect estimates attenuated by 45-100% after adjustment for maternal pre/early-pregnancy BMI and were no longer significant in mid and late childhood. Likewise, gestational hypertension was associated with a higher BMI SDS and a higher risk of overweight and obesity throughout childhood, with the strongest effect in late childhood (OR 1.48 (95% CI 1.29, 1.69), as compared to an uncomplicated pregnancy). Additional adjustment for maternal pre/early-pregnancy BMI attenuated these associations by 79-100% into non-significance. Children born to mothers with pre-eclampsia had a lower early childhood BMI SDS as compared to children born to mothers with an uncomplicated pregnancy (p-value < 0.05). This association reversed in mid and late childhood, but was fully attenuated after adjustment for maternal pre/early-pregnancy BMI.

Conclusions: The positive associations of gestational diabetes and hypertensive disorders of pregnancy with offspring greater overweight and obesity across childhood are largely due to confounding by maternal pre/early-pregnancy BMI.

PA3.04.06

Influence of maternal vomiting during early pregnancy on lung function and asthma at school-age.


PA3.04.07

Maternal obesity influences offspring obesogenic adipogenesis but not developmental adipogenesis in mice

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Background: Obesity is an escalating threat of pandemic proportions. Its effect on the economy is crippling, costing the UK government over £15 billion per year. An inevitable consequence of rising obesity levels is an increased prevalence of obesity during pregnancy. This is particularly bothersome as numerous animal models have documented that maternal obesity predisposes offspring to obesity in later life. How maternal obesity during pregnancy promotes obesity in offspring remains to be fully established. One possible mechanism behind the causal relationship between maternal obesity during pregnancy and offspring obesity in later life is the programming of offspring adipogenesis in white adipose tissue (WAT). In recent years, studies have reported enhanced adipogenic capacity of mouse embryonic fibroblasts and stromal vascular fractions (SVF) cells isolated from gonadal white adipose tissue (gWAT) of offspring of obese dams. While these studies demonstrate that maternal obesity may promote adipogenesis in offspring many questions remain unanswered including whether increased adipogenic processes are increasingly shown to be controlled by distinct regulatory mechanisms and utilize different subpopulations of adipocyte progenitors.

Methods: In order to answer these pressing questions, we established a mouse model of maternal obesity coupled with offspring high fat diet-induced obesity. Female mice were fed a high fat (45% kcal fat) or chow (7% kcal fat) for 6 weeks prior to pregnancy and during pregnancy and lactation. At weaning (4 wks) offspring were fed a high fat or chow diet until 30 weeks of age. A subset of offspring were sacrificed at weaning. gWAT tissues were obtained for both gene expression and histological analysis. Adipocyte number and volume (using image-J) were determined through image analysis of histological sections (H&E).

Results: We observed that maternal obesity had no effect on offspring developmental adipogenesis in vivo but had a profound effect on offspring obesogenic adipogenesis, in response to a postweaning high fat diet. Furthermore we observed that chow-fed offspring of obese dams had an increased expression of several adipocyte progenitor markers which was attenuated in high fat-fed offspring of obese dams. Moreover, in adipocyte progenitors isolated from the gWAT of offspring from obese dams, we observed increased expression of the cell cycle gene Cyclin D1 in adipocyte progenitors of offspring from obese dams, in response to adipogenic stimulation.

Conclusions: These data demonstrate that while not affecting developmental adipogenesis, maternal obesity had a profound effect on obesogenic adipogenesis in offspring. Our results suggest that this enhanced obesogenic adipogenesis in offspring of obese mothers may be driven, at least in part, by enhanced FTO expression.

PA3.04.08

Glycaemic load and index in pregnancy are associated with postnatal, but not pre-pregnancy, depressive symptoms; Southampton Women’s Survey longitudinal data

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Background: Maternal psychological disorders, before and during pregnancy and postnatally, have long-lasting effects on their children and contribute to the early life stressors that can impact on adult health and well-being. High glycaemic load (GL) and glycaemic index (GI) diets have been linked to poor health across the lifecourse. In cross-sectional studies, associations between GL and GI and psychological disorders have also been identified, though the direction of association has not always been consistent. Few longitudinal data exist and none in relation to associations between GL and GI during pregnancy and postnatal depression. We aimed to assess whether higher GL and GI during pregnancy were associated with increased risk of postnatal depressive symptoms using data from the Southampton Women’s Survey (SWS). The relationship between pre-pregnancy depressive symptoms and GL and GI during pregnancy was also examined in order to check for possible reverse causation.

Methods: The SWS is a population-based cohort study of 12,583 women aged 20-34 years assessed when not pregnant; those enrolled during the latter half of the recruitment period completed the General Health Questionnaire (GHQ-12), a short screening instrument for depressive symptoms. Women who became pregnant (n = 3,158) were followed through pregnancy and their children are being followed-up. Six months post-partum, mothers completed the Edinburgh Postnatal Depression Scale (EPDS) questionnaire to determine postnatal depressive symptoms. Established cut-offs for each depression scale (GHQ-12 and EPDS) were used to determine presence of depressive symptoms before and after pregnancy. At 11 and 34 weeks’ gestation, diet during the preceding 3 months was assessed using an interviewer-administered food-frequency questionnaire, from which GL and GI were determined. Prevalence ratios (PRs) for postnatal depressive symptoms were obtained using Poisson regression with robust variance. Potential confounding factors were listed and a Directed Acyclic Graph was developed to identify those factors that should be included in the models, namely age, educational attainment and smoking during pregnancy. Linear regression was used to assess the relationship between pregnancy GL and GI and pre-pregnancy depressive symptoms.

Results: Postnatal depression data were available for 2856 women, with 2038 and 2429 of them having GL and GI data at 11 and 34 weeks’ gestation respectively. In univariate analyses, postnatal depressive symptoms were positively associated with GL at both pregnancy time points and GI at 34 weeks’ gestation, but were strongest for 34 weeks’ GL: PR 1.12 per 100GL units (95% CI: 1.04-1.20). After adjustment for confounders, 34 weeks’ GL
was the only measure associated with postnatal depressive symptoms: PR 1.09 per 100GL units (95%CI: 1.01-1.17). Notably, there was no association between pre-pregnancy depressive symptoms derived from the GHQ12 and either GL or GI.

**Conclusion:** These findings suggest that improving diet in pregnancy, particularly lowering GL in late pregnancy, might protect against postnatal depressive symptoms. Pre-pregnancy depressive symptoms were not associated with GL and GI in pregnancy indicating that reverse causation is unlikely as an explanation for these findings.

**PA3.04.09**

Maternal fish intake during pregnancy and child growth: a prospective cohort study in Norway


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**Background:** Fish is a rich source of beneficial nutrients but also a well-known route of exposure to pollutants. In the Norwegian population, lean fish intake during pregnancy has been positively associated with birth weight and inversely associated with preterm delivery. Our aim was to examine the associations between maternal seafood consumption during pregnancy and childhood BMI and overweight and obesity up to 8 years.

**Methods:** This study is conducted within the Norwegian Mother and Child Cohort Study (MoBa), a prospective nationwide pregnancy cohort. Maternal seafood intake during the first half of pregnancy was assessed by a validated food frequency questionnaire (FFQ). The exposure variables examined comprised i) total seafood and ii) subcategories lean and fatty fish. For the 51,952 mother-child pairs included in our study, a total of 373,261 weight and 365,578 height/length measurements were reported longitudinally, from 6 weeks to 8 years. We used the Jens-Bayley’s growth model to predict weight and height at 14 age-points (1, 2, 3, 6, 9, 12 and 18 months and 2, 3, 4, 5, 6, 7 and 8 years) and then calculated BMI. We used mixed-effect linear regression models with random intercept and slope for child to assess changes in BMI from 1 month to 8 years. Overweight and obese children were identified using the International Obesity Task Force cut-offs at specific age points (3, 5 and 8 years). Logistic regression models were used to analyse the relationship between seafood intake in categories and being overweight/obese at 3 and 8 years. All analyses were adjusted for maternal age, parity, education, pre-pregnancy BMI, alcohol and smoking during pregnancy and total energy intake.

**Results:** Preliminary results are reported. Thirteen percent of the mothers had low intakes of total seafood (<100g/week) and 14% had high intake (>400g/week). The longitudinal development in child’s BMI is shown in the figure. High total seafood intake was significantly associated with an increased risk for overweight at 8 years (aOR = 1.21, 95%CI: 1.04,1.40). The proportion of subjects in each category of intake of lean fish were: 35%, 41%, 18%, 5% and 1%, for weekly intakes of <100g, 101-200g, 201-300g, 301-400 and >400g, respectively. Lean fish consumption of 101-200g, 201-300g and 301-400g/week was significantly associated with a 7%, 11% and 17% higher risk of overweight at 3 years, respectively. Lean fish consumption >400g/week was associated with higher risk for overweight at 8 years (aOR = 1.36, 95%CI: 1.01,1.83). When considering longitudinal BMI data, lean fish consumption >200g/week but <400g/week was associated with increased BMI (Figure B). No significant associations were found for fatty fish intake.

**Conclusion:** Our results on positive association between total seafood intake and BMI and overweight are in line with a previous pooled analysis of 15 birth cohorts, while the specific association with lean fish consumption is a novel finding. The observed associations with lean fish rather than fatty fish points away from lipophilic environmental contaminants and n−3 fatty acids as a possible biological explanations for the findings.
Background: In pregnancy, increased glucose sensitivity and lipid deposition are necessary metabolic adaptations to sustain fetal growth; however, high pre-pregnancy body mass index (pBMI) and/or excess gestational weight gain can disrupt these processes and may program offspring adiposity and cardiometabolic status. Leptin, an adipokine that normally circulates in proportion to body fat, rises during pregnancy and may play a role in placentalization and maternal-fetal exchange processes regulating growth and development. This research aims to examine the effect of maternal pBMI and current body fat percentage (%BF) on the cardiometabolic and leptin profile of women in early pregnancy.

Methods: The Be Healthy in Pregnancy (BHIP) Study (NCT01689961) recruited healthy pregnant women with pBMI <40 kg/m² from Hamilton, Burlington and London, Ontario, between 12-17 weeks gestation. Fasting plasma glucose and serum lipid profiles (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol) were analyzed by photometric assay. Serum leptin and insulin were analyzed by magnetic Luminex system ELISA (R&D Systems, Minneapolis MN). Maternal adiposity (%BF) was measured by bioelectrical impedance analysis (Tanita BF-350). Cardiometabolic parameters in relation to pBMI classification (normal (18.5-24.9 kg/m²), overweight (25-30 kg/m²) and obese (>30 kg/m²)) and %BF (acceptable (<30%), obese (>30%) were compared using one-way ANOVA followed by Tukey’s post-hoc analysis, and t-test, respectively.

Results: The 158 women were age 31.4±4.1 (mean ± SD) years and mean gestation of 13.87 weeks. Compared to normal pBMI (n=83), obese pBMI (n=26) women had significantly higher blood glucose (5.18±0.42 vs. 4.72±0.45 mmol/L, P<0.01), triglycerides (1.73±0.80 vs. 1.15±0.33 mmol/L, P<0.0001), leptin (58.28±34.73 vs. 21.30±17.00 ng/mL, P<0.0001), insulin (2.70±1.94 vs. 1.00±0.58 mmol/L, P<0.001) and lower HDL (1.54±0.34 vs. 1.86±0.34 mmol/L, P<0.01). Similar trends were observed for women with %BF categorized as obese (n=114) with respect to elevated blood glucose (4.96±0.59 vs. 4.62±0.44, P<0.01), triglycerides (1.37±0.59 vs. 1.11±0.30, P<0.001), leptin (38.60±27.33 vs. 15.46±10.12 mg/mL, P<0.0001) and insulin (1.64±1.32 vs. 0.91±0.50 mmol/L, P<0.0001) compared to women with acceptable %BF (n=44). Although mean values for all pBMI categories were within the normal range, values above the normal laboratory range for non-pregnant women occurred in 17% of participants for triglycerides and 2% for glucose, the majority of whom were overweight/obese.

Conclusions: Excess adiposity both pre-gravid and in early pregnancy as measured by pBMI and %BF significantly elevated blood lipid and glucose profiles and elevated serum leptin and insulin. Thus, excess adiposity is reflected in the maternal cardiometabolic profile. Although the potential for adverse impacts of maternal obesity on pregnancy outcomes and health of the offspring is appreciated by practitioners, the additive effects of pregnancy and obesity-induced metabolic changes have not been delineated. To determine if elevated maternal cardiometabolic profiles in early pregnancy are sustained and have a disruptive effect on fetal metabolism, we will study...
maternal cardiometabolic profiles during and after pregnancy in relation to infant body composition at 6 months of age.

**PA3.06.02**  
*Effect of a lifestyle intervention in obese infertile women on cardiometabolic health and quality of life: A randomized controlled trial*

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**Background:** The prevalence of obesity, an important cardiometabolic risk factor, is rising in women. Lifestyle improvements are the first step in treatment of obesity, but the success depends on factors like timing and motivation. As women are especially receptive to lifestyle advice before and during pregnancy, this intervention could be more successful than lifestyle interventions at any other time in the lifespan. Moreover, if successful, this intervention could not only affect cardiovascular health of women but that of their offspring as well. Therefore, we hypothesize that the pre-pregnancy period provides the perfect window of opportunity to improve cardiometabolic health and quality of life of obese infertile women, by means of a lifestyle intervention.

**Methods:** Between 2009-2012, 577 infertile women between 18 and 39 years of age, with a Body Mass Index of ≥ 29 kg/m², were randomized to a six month lifestyle intervention preceding infertility treatment, or to prompt infertility treatment (LIFESTyle study: Netherlands Trial Register: NTR1530). The goal of the intervention was 5-10% weight loss or a BMI <-3.6 - -1.1 cm; P < .001), hip circumference (-3.0 95% CI: -4.2 - -1.9 cm; P < .001), BMI (-1.2 kg/m² 95% CI: -1.5 - -0.8 kg/m²; P < .001), systolic blood pressure (-2.8 mmHg 95% CI: -5.0 - -0.7 mmHg; P =.01) and HOMA-IR (0.5 95% CI: -0.8 - -0.1; P =.01) were lower in the intervention group compared to controls. Hs-CRP and lipids did not differ between groups. All outcomes were measured by research nurses at randomization, 3 and 6 months. Self-reported quality of life was also measured at 6 months. Results are displayed as estimated mean differences and 95% CI. Insulin, HOMA-IR, hs-CRP, lipids and metabolic syndrome. All outcomes were measured by research nurses at randomization, 3 and 6 months. Efficacy analyses were performed.

**Results:** Results are displayed as estimated mean differences between intervention and control group. Weight (-3.1 kg 95% CI: -4.0 - -2.2 kg; P < .001), waist circumference (-2.4 cm 95% CI: -3.6 - -1.1 cm; P < .001), hip circumference (-3.0 95% CI: -4.2 - -1.9 cm; P < .001), BMI (-1.2 kg/m² 95% CI: -1.5 - -0.8 kg/m²; P < .001), systolic blood pressure (-2.8 mmHg 95% CI: -5.0 - -0.7 mmHg; P = .01) and HOMA-IR (0.5 95% CI: -0.8 - -0.1; P = .01) were lower in the intervention group compared to controls. Hs-CRP and lipids did not differ between groups. The odds ratio for metabolic syndrome in the intervention group was 0.53 (95% CI: 0.33-0.85; P < .01) compared to controls. Physical QoL scores were higher in the lifestyle intervention group (2.2 95% CI: 0.9-3.5; P = .001) while mental QoL scores did not differ.

**Conclusions:** In obese infertile women, a lifestyle intervention prior to infertility treatment improves cardiometabolic health and self-reported physical quality of life. We are currently assessing the long term effects of the intervention on health of the mothers and the children that were conceived during this trial (http://www.WOMB-project.eu).

**PA3.06.03**

*A double hit preeclampsia model results in sex specific growth restriction patterns*

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**Introduction:** Preeclampsia is a multifactorial pregnancy disorder presented with angiogenic imbalance and low-grade systemic inflammation. Next to detrimental consequences for the mother, preeclampsia has severe long-term effects for the offspring. However, animal models which represent these two pathophysiological conditions are missing. Here we introduce a novel double hit animal model which mimics the complex multifactorial conditions present during preeclampsia.

**Methods:** C57Bl/6 mice were injected with adenovirus over-expressing sFlt-1 or empty adenovirus (first hit: angiogenic imbalance) on gestational day GD 8. On GD 10 a second hit (inflammation) was introduced with a low dose of lipopolysaccharide (LPS, 25 ug/kg, i.p.) or PBS (control). Between GD 16 and 17, 24 hrs urine was collected. Blood pressure and blood analysis were performed on GD 18. Fetuses and placentas were collected at GD18.

**Results:** Animals exposed to sFlt-1 and LPS showed increased blood pressure and increased proteins and albumin in 24 hrs urine, the clinical hallmark of preeclampsia. sFlt-1 concentrations were 2x higher in the double hit preeclampsia group. Blood pressure values were positively correlated with the sFlt-1 concentrations. Fetuses were growth restricted: females have symmetrical growth restriction accompanied by smaller placentas. In continuation, male fetuses showed asymmetrical growth restriction, accompanied with brain sparing.

**Conclusion:** Our results show that combined exposure to sFlt-1 and LPS mimics the symptoms of preeclampsia in a mouse model and affects the fetal growth in a sex-specific manner.

**PA3.06.04**

*Early age at menarche as a risk factor for developing gestational diabetes: the mediating role of preconception body mass index*

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Background: Early age at first menarche in girls (menarche ≤11 years) has been identified as a marker of increased risk of type 2 diabetes, partly due to the higher rates of childhood and adulthood obesity among women with early age at menarche. Type 2 diabetes shares many features with gestational diabetes mellitus (GDM), however, it remains unclear if age at menarche also indicates an increased GDM risk. Examining the association between age at menarche and risk of GDM is of significant importance given the global trends of declining age at menarche, and increasing prevalence of obesity and GDM. In this study, we aim to test the hypothesis that declining age at menarche, and increasing prevalence of obesity prior to the index pregnancy was calculated as (odds ratio – 1) / (odds ratio x – 1) × 100%. Analyses were adjusted for early life and preconception covariates (Figure).

Methods: Data were from the 1973-78 cohort of the Australian Longitudinal Study on Women’s Health. At baseline in 2000, women aged 22-27 years reported their age at menarche. At three-yearly survey intervals during 15 years of follow-up, information on GDM diagnosis was obtained for each pregnancy and validated in a subsample. A causal inference framework for mediation analysis was used to estimate the total effect, natural direct effect (NDE), and natural indirect effect (NIE) of early age at menarche on incident GDM. The percentage mediated through preconception BMI at the survey prior to the index pregnancy was calculated as (odds ratio [OR] x OR[NIE] – 1) / (OR[NDE] x OR[NIE] – 1) × 100%

Results: Among 4,017 women with no history of type 2 diabetes, 329 (8.2%) women reported a first diagnosis of GDM. Mean age at menarche was 13 years (SD 1.4) and 12.7% of women had menarche at age 11 or younger. Early age at menarche was associated with a 53% higher GDM risk (OR 1.53, 95% CI 1.11, 2.09) after adjustment for parental education, self-rated childhood weight, parity, and preconception physical activity, energy intake and polycystic ovary syndrome. The percentage of the total effect of early age at menarche on GDM risk that was mediated through preconception BMI was 32%. This substantial mediating effect of BMI resulted in attenuation of the natural direct effect (OR 1.42, 95% CI 1.04, 1.93).

Conclusion: In this population-based study of reproductive-aged women, we demonstrate that early age at menarche is a risk factor for later development of GDM. A substantial proportion of the total effect of early age at menarche on GDM risk was mediated through preconception BMI, suggesting that prevention of overweight and obesity among girls with early age at menarche may lower their risk of GDM. The direct effect of early age at menarche on GDM risk remained significant even after accounting for the mediating effect of preconception BMI. Therefore, further prospective studies that start prenatally or during early childhood are needed to elucidate the effect of early life exposures on the timing of menarche, and subsequent development of GDM.

Hypothesis: early age at menarche is a risk factor for GDM, and this relationship is (partly) mediated through preconception BMI

PA3.06.05

Maternal weight at birth and risk of pregnancy complications

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Background: The intrauterine environment plays a critical role in health after birth. Low birthweight is known to be associated with adult-onset diseases including hypertension, cardiovascular disease (CVD), stroke and type 2 diabetes. Also, emerging evidence demonstrates a strong link between pregnancy complications and subsequent CVD. We examined the influence of maternal birthweight on the risk of development of pregnancy complications including preeclampsia (PE), gestational hypertension (GHTN), small for gestational age (SGA) pregnancy, spontaneous preterm birth (sPTB) and gestational diabetes mellitus (GDM).

Methods: This study includes 5336 women from SCOPE (SCreening fOr Pregnancy Endpoints), a multicentre prospective cohort study. Nulliparous women were recruited at the first antenatal clinic visit during their first pregnancy in Adelaide, Australia; Auckland, New Zealand; Manchester and Leeds, UK and Cork, Ireland. Detailed information was collected at 15 and 20 weeks’ gestation and the women were followed up throughout pregnancy. The woman’s birthweight and gestational age at birth were self-reported and confirmed via medical records when possible. The association between maternal birthweight and pregnancy complications was assessed using logistic regression. A maternal birthweight of 2500-3500g was considered the reference group.
Results: Maternal birthweight <2500g was associated with increased risk of PE (OR = 1.8, 95% CI = 1.2-2.8), having a SGA infant (OR = 1.5, 95% CI = 1.1-2.1), sPTB (OR = 1.9, 95% CI = 1.1-3.1) and GDM (OR = 1.8, 95% CI = 1.0-3.1) compared to the reference group. Maternal birthweight ≥ 4000g was associated with a reduced risk of PE (OR = 0.6, 95% CI = 0.3-0.9) and SGA (OR = 0.4, 95% CI = 0.3-0.6) compared to the reference group. All results remained significant after correcting for maternal age, BMI smoking at 15 weeks’ gestation, infant sex and maternal gestational age at birth.

Conclusion: Our results demonstrate that women who are small at birth are at increased risk of preeclampsia, gestational diabetes, spontaneous preterm birth and SGA infants compared to women who have uncomplicated pregnancies. Considering that women who develop any of these pregnancy complications are at approximately double the risk of subsequent CVD, these findings further add to existing literature that low birthweight appears to be one factor that contributes to the risk for pregnancy complications and subsequent CVD.

PA3.06.06
Second trimester serum metabolomic profiles can predict excessive gestational weight gain
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Background: Pregnancy weight-related issues (including obesity and excessive gestational weight gain – GWG) are the strongest risk factors for future maternal and offspring obesity and metabolic dysregulation. It is believed that maternal obesity is communicated to the fetus in part by the serum metabolome, altering the child’s metabolomic program in early development; however, it remains to be known if these profiles differ by GWG status. Our objective was to characterize the serum metabolomic profile in pregnant women of differing prepregnancy body mass index (BMI) status and to examine the relationship with GWG.

Methods: Women with a BMI of 18-40 kg/m² were recruited from the Ottawa area (Ontario, Canada). Exclusion criteria included smoking, diabetes of any type, fetal growth restriction or hypertensive diseases of pregnancy. A fasting maternal blood sample was obtained via peripheral venipuncture between weeks 25-28 of gestation. Metabolomic profile was measured in 37 serum samples (23 lean, 7 overweight, 7 obese) using 1D 1H nuclear magnetic resonance (NMR). Spectra were binned for metabolic fingerprinting analysis using a bin width of 0.005 ppm. NMR signals of interest were identified using public databases (HMDB, BMRB) and in-house measured spectra of pure compounds. Correlations between different variables and 2nd trimester maternal blood metabolites were analyzed using linear models in R version 3.3.1. Resulting p-values were corrected for multiple testing using a False Discovery Rate correction at the 20% level.

Results: Analysis of metabolite signatures showed distinct metabolomic profiles for lean, overweight and obese women. Four serum metabolites, namely glutamate, lysine, pyruvate and valine, showed significant positive correlations to GWG. These 2nd trimester metabolites, which include three amino acids and an end-product of glycolysis, form a set of predictive biomarkers, as the majority of pregnancy weight gain occurs in the 3rd trimester. To assess the predictive power of this set of metabolites, we performed a cross-validated linear regression of GWG, using the four metabolites and pre-pregnancy BMI levels. We found that GWG can be predicted with high accuracy, especially for women with excessive GWG.

Conclusions: Second trimester metabolite profiles differ between pre-pregnancy BMI categories and for the first time, we have identified a distinct set of markers that are predictive of excessive GWG. If validated in an additional population, this information could aid in guidance of prenatal weight management plans.

PA3.06.07
Developmental origins of perimenopausal disorders: evidence from a Swedish cohort
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Background: Theoretical life course models for women’s reproductive health have been proposed and discussed in the literature. However, to our best knowledge, associations of birth characteristics with incidence of perimenopausal disorders have not been empirically demonstrated to date.

Methods: The life course determinants of perimenopausal disorders were investigated through a linkage of archive birth records and routine register data (Census, Education register, Multigenerational Register, Population Register, Cause of Death Register and National Patient Register). The study subjects were 3212 women from the Uppsala Birth Cohort Multigenerational Study, born from singleton pregnancies, who were aged 40 to 65 years during the follow-up period from 2001 till 2008. Indicators of index women’s health at birth were ponderal index (birth weight [kg]/birth length [meters]13) and length of gestation (completed weeks). The main outcomes were categorized as menopausal symptoms (e.g. flushing, sleeplessness and headache), menopausal bleeding and other menopausal disorders (e.g. atrophic vaginitis and other unspecified disorders) based on ICD codes registered as main or contributing causes of hospitalisation or outpatient visit. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the three outcomes were estimated in Cox regression.
models with study subjects’ age as the underlying timescale. Analyses were adjusted for birth year, mutually adjusted for ponderal index or length of gestation, and robust standard errors were used to account for clustering in sisters. Parental social characteristics and women’s own parity and socio-demographic factors were included in the fully adjusted models. The proportional hazards assumptions were confirmed for all minimally adjusted models. Multiple imputation was used to deal with missing data for length of gestation and life course socio-demographic characteristics.

Results: During the eight years of follow-up, 125 cases of menopausal symptoms, 61 cases of menopausal bleeding and 58 cases of other menopausal disorders were recorded. The hazard ratio for menopausal symptoms corresponding to one standard deviation increase in ponderal index was 1.30 (95% CI: 1.10-1.54; minimally adjusted). Incidence of menopausal bleeding was not statistically significantly associated with either ponderal index or gestational age in minimally adjusted models. The incidence of other menopausal disorders was statistically significantly lower among those born after longer gestation (HR 0.86 per one week increase in gestational age, 95% CI: 0.78-0.94, minimally adjusted). Further adjustments for mother’s parity, life course socio-demographic factors or number of live born children did not alter the results in a significant way.

Conclusions: We found (i) a positive association between ponderal index at birth and incidence of menopausal symptoms; and (ii) a negative association of length of gestation with incidence of other menopausal disorders such as atrophic vaginitis. No associations with birth characteristics were seen for perimenopausal bleeding symptoms. The respective underlying mechanisms still need to be established but do not appear to include socioeconomic position or number of full term pregnancies. A mediating effect of adult body size is plausible.

PA3.06.08

Preconceptional maternal anxiety is associated with childhood emotional problems, independent of the effect of post-natal depression

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Background: Maternal perinatal depression has been associated with behavioural problems in the child. In the ALSPAC cohort, ante- and post-natal depression had independent effects on child behaviour at 4 years. The strongest risk factor for maternal perinatal depression is pre-existing anxiety or depression suggesting that women with perinatal depression are likely to have experienced mental health problems preconception. We examined the association between maternal preconceptional anxiety and child behaviour at age 3 years in the Southampton Women’s Survey (SWS).

Methods: The SWS assessed 12,583 women aged 20-34 years when not pregnant. Women who became pregnant and their children (n = 3,158) were followed up. In the second half of recruitment, women completed the General Health Questionnaire (GHQ-12), a screening instrument with good sensitivity for depression and anxiety disorders; a score ≥ 3 was categorised as positive for significant psychological distress. Post-natal depression was assessed with the Edinburgh Post-natal Depression Scale. At age 3 years, child behaviour was assessed with the Strengths and Difficulties Questionnaire administered to parents and used to characterise hyperactivity, conduct disorders and emotional problems; cases were identified as children who had at least borderline problems under standard definitions. Binary regression was used to derive prevalence rate ratios (PRR) for child behaviour problems. A Directed Acyclic Graph was used to identify confounding factors – maternal educational attainment and number of children.

Results: Of 1,518 children (52% boys) followed to age 3, whose mothers completed the GHQ-12 before pregnancy, 290 (19%) had hyperactivity, 366 (24%) had conduct disorders and 499 (19%) had emotional problems. 27% of mothers had evidence of preconceptional distress and 42% of postnatal depressive symptoms. Univariately, there were strong positive associations between preconceptional distress and all three behaviour problems (risk increases (PRR)): 31% (1.31, 95% CI:1.05-1.63) for hyperactivity, 34% (1.34, 95%CI:1.11-1.61) for conduct disorders, and 48% (1.48, 95%CI:1.19-1.84) for emotional problems. After adjustment for confounding factors, PRRs were largely unchanged and the associations of preconceptional distress with all three behaviour problems remained highly significant. Additional adjustment for postnatal depression attenuated to borderline significance the associations of maternal distress with hyperactivity and emotional problems. The association of maternal distress with emotional problems, however, was little changed (PRR 1.42, 95%CI: 1.14-1.78) and remained highly significant. Further analyses were conducted to examine the effects on child behaviour of pre-and post-natal depression separately and to look at effects on child behaviour for women with both conditions. For hyperactivity and conduct disorders, postnatal depression had a greater effect on risk of behaviour problems than preconceptional distress, the effect being greatest for children of women with both conditions. For emotional problems, however, preconceptional distress alone had a greater effect on child behaviour than post-natal depression alone, (PRRs of 1.43 (95%CI: 1.02- 2.01) and 1.24 (95%CI:0.94-1.63) respectively). Where both conditions were present the PRR for emotional problems was 1.75 (95%CI:1.33-2.31).

Conclusion: Preconceptional distress is associated with emotional problems in children aged 3, independent of postnatal depression. Identifying women with distress might facilitate prevention of childhood emotional problems.
Antenatal synthetic glucocorticoid exposure modifies gene expression in the post-natal blood-testis barrier

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Background: Glucocorticoids are key in the transition from fetal to neonatal life, and may play a role in the maturation of blood-tissue barriers. Antenatal synthetic glucocorticoids (sGC) are administered in the management of preterm birth; however, a proportion of women deliver at term, potentially exposing the fetus to excess glucocorticoids. Recent work in our lab has shown that antenatal sGC exposure programs neural gene expression in juvenile offspring, and that these effects are transmitted over multiple generations. Tight junctions between Sertoli cells make up the blood-testis barrier (BTB), providing immunological protection and are part of the spermatogenic process. Uptake of hormones, drugs, and toxins is also limited by the BTB, through the actions of drug transporters such as P-glycoprotein (PgP; Abcb1) and breast cancer resistance protein (BCRP; Abcg2). Altered BTB function after sGC exposure that persists into post-natal life could have consequences for drug exposure and spermatogenesis. We hypothesize that antenatal sGC treatment will alter the expression of genes related to tight junction function, xenobiotic response, and drug transport at the fetal BTB, and this effect will persist to the juvenile BTB.

Methods: Guinea pigs were chosen for this study as they have a longer gestation, and a similar pattern of neurodevelopment. Testes were collected from offspring at either gestation day (GD) 52 (preterm) or postnatal day (PND) 14 (term). Starting at GD40, pregnant dams were exposed to either 2 (GD 52) or 3 (PND 14) courses of betamethasone (GD52, N = 7; PND14, N = 9) or vehicle (GD52 & PND14, N = 5), 10 days apart. Testes were removed, snap frozen on dry ice, and stored at -80°C until RNA extraction. Levels of drug transporter and tight junction mRNA were measured by qRT-PCR.

Results: At PND14, sGC treatment significantly decreased Cldn5 and Jam-A expression (p < 0.05). Expression levels of Mr, but not Gr, Par, or Car, were significantly (p < 0.05) decreased at PND14 after sGC treatment. sGCs did not affect expression of drug transporters Abcb1, Abcg2, or Abcc4 at PND14, though a trend towards decrease of Abcc1 and Abcc5 was observed. At GD52, exposure to sGCs did not affect expression of any genes of interest.

Conclusion: This is the first study to demonstrate that antenatal sGC programs gene expression in the testes of juvenile offspring. Genes that were significantly decreased at PND14, 25 days after last exposure to sGCs, are related to maintaining tight junction function (Cldn5, Jam-A), and the stress response (Mr). There were no changes in expression of drug transporter genes or xenobiotic response. Interestingly, these changes were not observed in fetal animals, suggesting the timing and number of doses of glucocorticoids plays a role in regulating this pathway. As the BTB plays an essential role in spermatogenesis, these findings may provide insight into the mechanisms underlying transmission of the effects of antenatal sGC. Long-term alterations in baseline barrier function in the testes may also have implications for drug protection and efficacy.
growth are factors that can be influenced and can thus be of pivotal value in improving outcome of this large population.

**PA3.07.03**

**Breast milk exosomal microRNA: A method of listening-on the dialogue between mother and infant**

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Breast milk is a complex source of nutrients and bioactive molecules to nourish and protect newborns by facilitating gastrointestinal development and maturation. Throughout the postnatal period, the gastrointestinal tract (GIT) matures following enteral feeds and colonization with commensal bacteria. The development of the GIT could be delayed or altered in a premature infant, thus predisposing the infant to inflammatory diseases, such as necrotizing enterocolitis (NEC). The pathophysiology of NEC is currently unknown, however, pre-maturity, formula feeding and an abnormal intestinal microbiota are thought to cause an inflammatory response in the intestine leading to sepsis and NEC. Breast milk is the gold standard of infant nutrition and is largely thought to help prevent NEC. Breast milk exosomal microRNA may be one of the components responsible for the development of the GIT. Identifying the microRNAs from human milk exosomes will allow for a deeper understanding of the signals the mother is sending to the gut of her newborn. Exosomal microRNAs are thought to resist degradation and remain biologically active upon ingestion due to the stable structure of the exosome. Because exosomes and their contained microRNA have been shown to play a role in cell-to-cell communication, we propose a method of listening-in on the cross-talk between mother and infant via breastfeeding.

Isolating exosomes from human milk has remained a challenge, as there is no protocol consensus in the literature. After testing six different protocols to isolate exosomes, we determined that ultracentrifugation is the most robust method based on expected size (30-100 nm). We investigated the effects of milk storage on exosome populations. Comparing exosomes from fresh milk, frozen milk (-20°C, 24 hours) and 4 °C stored milk (24 hours), we found differences in the native exosome populations and, in turn, alterations in the abundance of micro-RNA. Fresh milk has an increased concentration of exosomes compared to milk that has been stored at -20°C for 24 hours. Through flow cytometry, we identified the membrane proteome of milk exosomes and variations depending on storage procedures and processing. By testing a range of commercially available kits for RNA extraction, our results support the use of Qiagen exoRNeasy for maximized RNA yield without sacrificing quality. The most abundant exosomal microRNAs from fresh human milk were found to have targets related to inflammatory pathways, demonstrating the further protection the mother provides to her infant. Human milk exosomes must be isolated in a reproducible manner to characterize micro-RNAs and understand their role in gastrointestinal tract maturation and disease states. Depending on the milk fraction analyzed, storage, exosome isolation and RNA extraction methods the miRNA profiles vary. In this critical area of health research, proper preparation of samples and extraction methods is paramount. To gain insight into microRNA communication between mother and her newborn at this nascent stage requires standardized procedures and synchronized approaches.

**PA3.07.04**

**Early life a priori and a posteriori dietary patterns and celiac disease autoimmunity in children from the Generation R Study**

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**Background:** Gut dysbiosis has been suggested as one of the environmental factors associated with the development of celiac disease (CeD). Concurrently, the composition and maturation of the gut microbiome, initiated immediately after birth, appears to be strongly affected by early-life nutrition. In this context, the role of infant feeding practices on the development of pediatric CeD has been previously investigated, but contradicting findings have been reported. Furthermore, such studies have mainly been focused on the effects of breastfeeding and timing of gluten introduction, but not on overall diets. Thus, the aim of this work was to examine the association between early-life dietary patterns and the occurrence of CeD autoimmunity during childhood.

**Methods:** This study was embedded in the Generation R Study, a multiethnic birth cohort in Rotterdam, the Netherlands. Validated food-frequency questionnaires collected at the children’s median age of 14 months were used to assess food consumption (N = 1985). Dietary patterns were defined a priori, based on national and international guidelines, and a posteriori, from principal component analysis of dietary intake. CeD autoimmunity (CDA) was assessed on the basis of serum concentrations of anti-tissue transglutaminase antibodies (TG2A) in the children, at the age of 6 years. TG2A levels were categorized into negative (<7 U/ml) and positive (≥7 U/ml) values.

**Results:** As reported in previous studies, the a priori Diet Quality Score and the a posteriori “health-conscious” dietary pattern are characterized by high intakes of vegetables, grains, vegetable oils, fish and legumes, while the a posteriori “western-like” pattern is characterized by high intakes of snacks and confections, animal fats, and sugary beverages. After adjustment for confounders (children’s age, gender and ethnicity, timing of introduction to gluten, breastfeeding and maternal education level), it was observed that children with higher...
adherence to the “health-conscious” diet pattern had a lower prevalence of TG2A-positivity (OR: 0.52, 95% CI: 0.30 to 0.89), but no significant association was observed between the adherence to a “western-like” diet and TG2A concentrations (OR: 0.96, 95% CI: 0.56 to 1.64). Furthermore, a non-significant association between higher adherence scores to the a priori diet quality index and a lower risk of high TG2A levels was found (OR: 0.85, 95% CI: 0.64 to 1.14).

Conclusions: Our results suggest that early-life dietary patterns characterised by high intakes of vegetables and grains, and low intakes of saturated fats and sugary foods, may be associated with a lower risk of developing CeD autoimmunity during childhood.

PA3.07.05
Duration and exclusiveness of breastfeeding and risk of childhood atopic diseases

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Background: Breastfeeding may have immune modulatory effects that influence the development of childhood allergic sensitization and atopic diseases. We aimed to examine the associations of breastfeeding with childhood allergic sensitization, inhalant or food allergy and eczema. Additionally, we examined whether any association was affected by disease-related modification of the exposure, meaning that early symptoms of allergy or eczema in the child may encourage a mother to alter breastfeeding habits, or modified by maternal history of maternal history of allergy, eczema or asthma.

Methods: This study among 5,828 children was performed in a population-based prospective cohort from fetal life onwards. We collected information on duration (<2 months, 2-4 months, 4-6 months and ≥6 months) and exclusiveness (non-exclusive vs. exclusive for 4 months) of breastfeeding in infancy by postal questionnaires. At age 10 years, inhalant (house dust mite, 5-grass mixture, birch, cat and dog) and food (hazelnut, cashew nut, peanut and peach) allergic sensitization were measured by skin prick tests, and physician-diagnosed inhalant and food allergy by a postal questionnaire. Data on parental-reported eczema were available from birth until age 10 years. We used multivariate logistic regression, multinomial logistic regression or generalized estimating equation models where appropriate. In addition, we performed risk period-specific sensitivity analyses by excluding children who developed eczema during the period of breastfeeding until age 6 months, additional adjustment for ointment use for eczema at age 2 months and cross-lagged modeling to account for potential disease-related modification of the exposure. The modifying effect of maternal history of allergy, eczema or asthma was tested by adding it as product term with the breastfeeding variables in the models.

Results: We observed no association of breastfeeding with any allergic sensitization, physician-diagnosed allergy, or combination of these outcomes. Shorter breastfeeding duration was associated with an overall increased risk of eczema (p-value for trend <0.05). Non-exclusively breastfed children had an overall increased risk of eczema (adjusted odds ratio (95% confidence interval): 1.11 (1.01, 1.23)), compared with children exclusively breastfed for 4 months. Risk period-specific sensitivity analyses, additional adjustment for ointment use for eczema at age 2 months, and cross-lagged modeling showed no consistent results for disease-related modification of the exposure. Results were not modified by maternal history of allergy, eczema or asthma (p-values for interaction <0.05).

Conclusions: Shorter duration or non-exclusiveness of breastfeeding is associated with a weak overall increased risk of eczema but not allergic sensitization or physician-diagnosed allergy at age 10 years. Despite its small protective effect, breastfeeding is encouraged because of its nutritional, immunological and psychosocial benefits.

PA3.07.06
Role of breastfeeding on epigenetic mechanisms underlying early-life growth development and the development origin of obesity

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Obesity is a major global public health problem. The World Health Organization (WHO) estimated in 2010 that there were at least 42 million overweight children under the age of 5-years and one billion overweight adults globally. It is now well established that early life can impact our long-term health, in particular the risk of developing adult diseases such as obesity. Previous research has clearly established a link between early environment (pre-natal and post-natal), genetic, and behavioral factors on the development origin of health and diseases (DOHaD). Among the environmental factors, breastfeeding has been advocated in the prevention of overweight/obesity and is recommended by WHO as the “perfect food for the newborn”. Each month of breastfeeding results in a 4% reduction in risk of being overweight. The beneficial effect of breastfeeding extends beyond healthy children. In a large cohort of 5,590 children from the British Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, we showed that a longer duration of exclusive breastfeeding (EXBF) (i.e at least 5 months) has significant preventive effect on BMI growth trajectories even among genetically susceptible children. The biological mechanisms underlying the role of breastfeeding remain unclear, but a plausible explanation could be through the regulation of epigenetic mechanisms involved in developmental programming. Our goal in to identify new epigenetic marks associated with birth weight and BMI at weight and assess whether EXBF affect these marks during child development. We studied about 1,000 children from the
ALSPAC cohort and modeled their methylation profiles up to 17 years of age. We found several genes that were differentially methylated in relation to birth weight and BMI at birth including TSSC4, RNU5E, PRR5L, IGF2BP1, PLCH1, PLD2 and a few others. Interestingly, the methylation profiles of the genes PRR5L and IGF2BP1 were mediated by EXBF. The gene PRR5L has been shown to be involved in mTORC2 pathway, which is associated with the metabolic and immunologic programming. The gene IGF2BP1 encodes a member of the insulin-like growth factor 2 mRNA-binding protein family. Our study demonstrates therefore that breastfeeding could regulate early life epigenetic modifications involved in developmental programming and potentially reverse DNA methylation.

PA3.07.07

Breast milk concentrations of brominated flame retardants and perfluorooctane sulfonate are associated with decreased gut microbiota diversity in infants

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Background: Early-life environmental toxicant exposure is associated with adverse health later in life. Experimental studies report that toxicant exposure negatively affects gut microbiome composition, possibly contributing to poor health. We investigated whether breastfeeding exposure to a mixture of environmental toxicants negatively impacts the infant gut microbiome at one month.

Methods: We used data from the Norwegian Microbiota Cohort (NoMIC, n = 552, recruitment 2002-2005). Mothers provided breast milk samples and their own and their infants’ fecal samples and completed questionnaires on maternal and infant characteristics. We included 293 mother-child pairs of singleton births with information on both toxicant concentrations in breast milk and gut microbiota composition from fecal samples. Exposures were 28 individual chemicals from five classes of compounds (non-dioxin-like polychlorinated biphenyls (PCBs), dioxin-like mono-ortho PCBs, organochlorine pesticides, polybrominated diphenyl ethers (PBDEs), and per- and polyfluoroalkyl substances (PFAS)). We investigated alpha diversity: Shannon Diversity, Phylogenetic Diversity and number of observed operational taxonomical units (OTUs). We assessed associations between toxicant exposure and infant alpha diversity using: i) principal component analysis to identify mixtures; ii) elastic net regression modelling to select amongst individual correlated toxicants; and, iii) generalized linear models to obtain unbiased estimates, adjusting for potential confounders. Additionally, we compared low (<20th perc.) vs. high (>80th perc.) exposed groups of infants for the elastic net selected exposures, using UniFrac to identify variation in beta diversity and Analysis of Composition of Microbiomes (ANCOM) to detect differentially abundant microbial taxa.

Results: The principle component dominated by PBDEs was significantly associated with a reduction in all diversity measures. The elastic net modelling consistently selected PBDE-100 as associated with reduced infant gut diversity. In the unpenalised generalized linear regression models, a 1 standard deviation (SD) increase in PBDE-100 was associated with -0.15 (95% CI: -0.22, -0.07) change in Shannon diversity, equivalent to a 15% decrease in the interquartile range of Shannon diversity in this cohort. Additionally, analysis of phylogenetic diversity found perfluorooctane sulfonate (PFOS) and (perfluorooctanoic acid) PFOA significantly associated with a -0.18 (95% CI: -0.28, -0.07) a 0.15 (95% CI: 0.05, 0.25) change in phylogenetic diversity per 1SD increase in respective exposures. We did not detect significant differences in beta diversity for any of the selected compounds. In preliminary analyses, we detected significant differential abundance of eight Actinobacteria of the genus Bifidobacterium between the low/high PBDE-100 exposure groups. One of the same Bifidobacterium was also differentially abundant for low/high PFOS exposure, with differences also detected in the genera Staphylococcus and Bacteroides.

Conclusion: In a multipollutant study, we detected a consistent decrease in alpha gut diversity associated with breast milk concentrations of PBDEs, particularly PBDE-100, in infants one month old. PFOS and PFOA showed opposing effects on phylogenetic diversity. Further investigation is required to understand the significance of our findings for child health, particularly in countries with higher toxicant exposures.

PA3.09 - New intervention strategies

PA3.09.01

Designing complex behavior change interventions

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There is a growing recognition that to increase effectiveness, interventions to improve health behaviours need to be carefully planned and appropriate. Though there is substantial support for planning evaluations of interventions, there is currently little that guides new intervention design of the type of complex interventions required to change health behaviour. That which does exist tends either to lack detail enough to guide newcomers through the process of intervention development, or to be so resource-intensive as to be impractical. The current MRC guidelines on developing and evaluating complex interventions are relatively non-specific and largely concern intervention evaluation rather than development.

This talk will discuss approaches to supporting the systematic development of complex interventions. It will present...
intervention development as a sequence of logical steps, aiming to improve intervention feasibility, appropriateness and effectiveness. Some approaches to intervention design are better suited for the development of one type of intervention over another. The Person-Based Approach, for example, has been specifically designed to support the development of digital interventions. The application of these methods to the design of intervention to change maternal diet and nutritional status, child health and development, and other DOHaD related outcomes will be discussed. Examples of such interventions currently planned and underway will be used as illustration.

PA3.09.03

Shortcuts to randomised evidence: Using existing trials in early life for follow-up studies

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There is a paucity of evidence from randomised trials in humans supporting the DOHaD hypothesis, although recent nutrient supplementation trials in pregnancy have shown promise with respect to the primary prevention of childhood asthma. However, setting up de novo trials is expensive and time-consuming. A cheaper, more efficient, and underused approach is to follow up children from existing trial cohorts to collect new outcomes of interest, other than those originally intended. For example, the majority of prenatal interventions have focused on pregnancy/perinatal outcomes, and have not followed up the offspring into childhood, even though the prenatal exposure of interest may have biological relevance to the developmental programming of health and disease later in life. Given that modification of the early life exposure has been randomised, this approach has the potential to provide more robust evidence for causal inference than can be obtained from observational studies which may often be confounded, and can give added value to the original trial. Seif Shaheen will illustrate this ‘short cut’ approach to obtaining randomised evidence with examples of prenatal nutrient supplementation trials which were undertaken with particular outcomes in mind, but which have provided opportunities to measure new childhood outcomes, especially in relation to respiratory health.

PA3.09.05

Vitamin D supplementation in pregnancy to prevent asthma in offspring - Results from the Vitamin D Antenatal Asthma Reduction Trial

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Background: Vitamin D insufficiency and deficiency are prevalent worldwide, and pregnant women and infants are at highest risk for having deficiency. We hypothesized that vitamin D deficiency has contributed to the asthma and allergy epidemic, however, epidemiologic studies investigating the relationship with vitamin D and asthma have shown contradictory results. We conducted a randomized clinical trial to test whether supplementation with vitamin D in pregnancy could lead to prevention of asthma and recurrent wheeze in the offspring by age 3 years.

Methods: The Vitamin D Antenatal Asthma Reduction Trial (VDAART) was a randomized, double-blind, placebo-controlled trial between October 2009 and January 2015 in 3 centers across the United States. 881 pregnant women between the ages of 18 and 39 years at high risk for having children with asthma were randomized at 10-18 weeks gestation. Women were randomized to either daily 4,000 IU vitamin D plus a prenatal vitamin containing 400 IU vitamin D (n = 440) or a placebo plus a prenatal vitamin containing 400 IU vitamin D (n = 436). The main outcome of the trial was parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age in the offspring.

Results: Eight-hundred and ten infants were born in the study, and 806 were included in the analyses for the 3-year outcomes. Two hundred eighteen children developed asthma/recurrent wheeze – 98 (24.3%) in the 4,400 IU/day group vs. 120 (30.4%) in the 400 IU/day group, which resulted in a 20% decreased risk for asthma/recurrent wheeze among children born to mothers in the treatment arm (hazard ratio = 0.8, 95% CI = 0.6-1.0, p = .051). While the main results of the trial have been published, we conducted secondary analyses because of the growing recognition that nutrient trials are different from drug trials, mainly due to the fact that participants have varying levels and intakes of the nutrient, and these analyses were based on the initial and achieved 25OHD levels. Both maternal baseline 25OHD levels (OR for each 5 ng/ml increase in 25OHD = 0.89, 95% CI = 0.82-0.97, p = 0.006) and third trimester 25OHD levels (OR for each 5 ng/ml increase in 25OHD = 0.90 , 95%CI = 0.86-0.96, p = 0.002) were inversely associated with incident asthma/recurrent wheeze by age 3 years (Figure). Children born to mothers who had 25OHD levels both above 30 ng/ml at early pregnancy and at the 3rd trimester had the lowest risks for developing asthma/recurrent wheeze by age 3 years (OR = 0.54, 95%CI = 0.30-0.98). Finally, we show that the effects of supplementation were modified by the initial maternal 25OHD level.
Conclusions: This is the first trial to show that supplementation of vitamin D in pregnancy decreases the incidence of asthma and recurrent wheeze in the mothers’ offspring. Our secondary analyses show that the greatest reduction in asthma and recurrent wheeze in the children occurred when their mothers had high levels throughout pregnancy. Our results suggest that maternal vitamin D status during pregnancy is a modifiable factor that may impact the respiratory health of young children.

Infants of women with GDM have an increased risk for overweight/obesity as young children and increased risk for developing T2DM in later life.

Though the specific pathophysiology of GDM and T2DM are not fully understood, they share common risk factors and complications. Preliminary data suggest healthy diet and physical activity may prevent/delay the onset of diabetes. The transitory nature of GDM and recruitment prior to manifestation of the disease makes clinical studies to investigate prevention or treatment difficult. Thus, generation of animal models capturing the subtleties of GDM is necessary but success has been limited. Our objective was to develop a mouse model of transient and mild hyperglycemia during gestation resulting in clear diet induced obesity in the offspring of GDM mice. Six week old female mice were treated with high fat diet (HFD) and repeated low dose streptozotocin (STZ) injections prior to mating. Pre-treatment resulted in normoglycemic mice (8.8 vs. 7.2 mM random blood glucose [RBG]) prior to mating. Dams developed hyperglycemia in the second half of pregnancy (13.6 vs. 7.0 mM RBG @ E14, p < 0.01 Figure; and 6.2 vs. 5.2 mM fasting blood glucose [FBG] @ E15, p < 0.01), yet recovered from the characteristic hyperglycemia following parturition (8.5 vs. 7.1 mM RBG, p < 0.01, Figure) and post-weaning (8.0 vs. 7.1 mM RBG, Figure; and 7.8 vs. 6.7 mM FBG). A two-month Western diet challenge (low fat diet [LFD] as control) in the offspring started during adolescence (postnatal day 42). Compared to controls, GDM offspring exhibited greater fat mass gain compared to similar lean mass gain, resulting in a shift in overall fat percentage. In addition, GDM offspring had increased fasting insulin level without overt hyperglycemia or glucose intolerance, which resulted in increased homeostatic model assessment-insulin resistance and beta cell function. An experimental diet administered early in life significantly ameliorated the insulin resistance parameters, attenuated the body weight increase and prevented excessive fat mass accumulation in offspring later in life when compared with a group receiving a standard diet. This new mouse model captures the transient gestation-specific hyperglycemia characteristic of GDM in dams as well as susceptibility to obesity and possibly other disorders in offspring. It provides windows of opportunity for various nutritional and pharmacological interventions in GDM mothers and offspring, making it suitable for mechanistic studies of GDM development and associated complications in the offspring, and unique opportunities for exploration of nutritional and pharmacological interventions to improve outcomes.
Body weight (A) and random blood glucose levels (B) of dams: before starting HFD; before STZ administration; before mating; embryonic day 15

PA3.09.07
Does supplementation of the postweaning diet reverse offspring metabolic and immune dysfunction due to poor maternal nutrition in mice?
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Background: The alarming increased incidence of obesity and metabolic diseases in later life raises questions about their origins. Considerable evidence now points to adverse early life exposures, particularly suboptimal nutrition, as lying on the causal pathway to poor development and risk for metabolic dysfunction. We, and others, have shown that offspring born to mothers calorically restricted during pregnancy have low birthweight, altered postnatal growth trajectories, and as adults, are hypertensive, have increased bodyweight, and show signs of glucose intolerance and insulin resistance. As the liver plays a major role in metabolic homeostasis, and metabolically-triggered inflammation is recognised as a key mechanism underlying the pathogenesis of metabolic diseases, we hypothesised that maternal undernutrition would have adverse effects on offspring metabolism and liver phenotype. Furthermore, some evidence suggests that dietary interventions, including omega-3 (n3) fatty acid supplementation, can improve inflammatory phenotypes and reduce metabolic syndrome risk. We therefore also hypothesised that a postnatal diet enriched with n3 would prevent or lessen the adverse effects of poor maternal nutrition on offspring metabolic and inflammatory phenotype in adulthood.

Methods: Female mice were fed a control diet during pregnancy (CON), or a 30% calorie reduced diet from day 5.5-18.5 of pregnancy (term = 19.5 days; CR), after which all dams received ad libitum diet until weaning. Postweaning offspring were randomised to receive either control diet (-con; 1% omega-3 [n3] fatty acids) or n3-supplemented diet (-n3; 35% n3 fatty acids) for the remainder of the study. Male offspring underwent a glucose tolerance test (GTT) and DEXA scan at 12 months of age, followed by necropsy when blood and tissues were collected. Liver protein lysates were assayed for a panel of 27 cytokines and chemokines and liver sections were stained with Oil Red O, haematoxylin and Masson's Trichrome to assess steatosis, inflammation, ballooning and fibrosis. Groups were compared by two-way ANOVA, p < 0.05; Tukey’s post hoc.

Results: At 12 months of age, CR-con offspring had greater percentage body fat and fat:lean ratio than all CON offspring (p < 0.01). A postweaning n3-rich diet prevented these increases (p < 0.01) and was associated with lower HOMA-IR (p < 0.05). Maternal CR was associated with greater glucose and insulin area under the curve (AUC) in offspring following GTT (vs. CON, p < 0.05). In contrast, postweaning n3-rich diet was associated with lower glucose and insulin AUC (vs. con, p < 0.05). Further, maternal CR was associated with increased hepatic inflammation in offspring, and postweaning n3-rich diet attenuated this increase. Hepatic IL-3, IL-9 and IL-17 levels were significantly elevated by maternal CR (vs. CON, p < 0.05), and hepatic IL-6, IL-13, MIP-1b and TNF-a levels were lower in offspring fed a postweaning n3-rich diet (vs. con, p < 0.01). Hepatic histopathological scores are pending.

Conclusions: Caloric restriction in pregnancy is permissive of offspring obesity and hepatic inflammation, and may contribute to insulin resistance, phenotypes that are partially reversed by omega-3 diet supplementation. Our data suggest that postnatal diet interventions may prevent adverse outcomes associated with exposure to suboptimal nutrition in early life in offspring that would otherwise suffer from metabolic compromise.

PA3.09.08
Antenatal non-medical risk assessment and care pathways to improve pregnancy outcomes: a cluster randomized controlled trial
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Background: Social deprivation negatively affects health outcomes. In addition to the negative impact of medical and obstetric risk factors, multiple studies have shown a strong association between non-medical risk factors and adverse pregnancy outcomes. Risk assessment and subsequent implementation of preventive measures in antenatal health care with the aim to reduce adverse pregnancy outcomes should, therefore, take both medical and non-medical risk factors into account. The aim of this study was to determine whether a combination of risk assessment for non-medical factors during pregnancy, with subsequent use of care pathways, and the institution of personalised preventive care decreases the incidence of adverse neonatal outcomes at birth.

Methods: Cluster randomized controlled trial in 14 urban municipalities across the Netherlands. The combined intervention consisted of antenatal risk assessment, focused on non-medical risk factors, lifestyle factors, and medical risk factors, using the Rotterdam Reproductive Risk Reduction (R4U) scorecard, and the subsequent institution of risk-specific care pathways and multidisciplinary consultation between care providers from the curative and the public health sector. The primary outcome was delivery of a preterm and/or a small for gestational age baby, analyzed with multilevel mixed-effects logistic regression analysis adjusting for cluster and individual baseline characteristics.
Results: Data from 4302 participants across ten clusters was included in the intention to treat analysis. The intervention had no demonstrable impact on the primary outcome: adjusted odds ratio (aOR) 1.17 (95% CI 0.84 to 1.63). There was a statistically significant improvement in early detection of threatening preterm delivery and/or fetal growth restriction during pregnancy in the intervention clusters: aOR 1.27 (95% CI 1.01 to 1.61).

Conclusions: Implementation of additional non-medical risk assessment and preventive strategies into general practices is feasible but did not decrease the incidence of our primary outcome in the index pregnancy in deprived urban areas.

PA3.09.09
LifeLab Southampton: Improving science literacy as a tool for increasing health literacy in teenagers - a pilot cluster-randomised controlled trial

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Background: Behavioural risk factors are the largest contributor to the non-communicable disease burden, and those of parents can affect prenatal and infant development with lasting impact on the long-term health of the offspring. Adolescence offers a window of opportunity during which improvements in health behaviours would not only benefit long-term health of individuals, but also enable them to be better prepared for parenthood and pass better health prospects to their children. We have developed an educational intervention, LifeLab, based around a purpose-built laboratory in University Hospital Southampton with support from teachers, to engage adolescents in understanding effects of their health behaviours for themselves and their future children.

Aims: To assess whether engaging adolescents with the science behind health messages increases their science literacy, improving health literacy and hence health behaviours, as a pilot study prior to a large cluster-randomised trial of LifeLab.

Methods: In a pilot study in six schools preparing for a large cluster randomised trial of LifeLab, we assessed the effects of LifeLab in changing in knowledge, attitudes and intended and actual behaviour in relation to diet and lifestyle; three schools were randomised to intervention, with three controls. 392 students completed online questionnaires at baseline and 12 month follow up. Summary statistics were used to examine differences between groups. The categorical outcome variables were dichotomised and Poisson regression with robust variance used to obtain prevalence rate ratios (PRRs) for the outcome in relation to the intervention, adjusted for baseline values, sex and Index of Deprivation Affecting Children (IDACI) score.

Results: The study demonstrated that schools could successfully be recruited to a cluster randomised trial, showing a high level of engagement from the schools. Compared to control students, at follow-up intervention students had greater understanding of the influences of health behaviours on their long term health and that of their children, but no sustained changes in behaviours were identified. The effects observed on knowledge were, however, consistent with those observed in our previous feasibility work.

Compared with control students those in the intervention were more likely to agree that nutrition starts to affect the health of his children (PRR 4.05 (95%CI: 2.34-7.01)), but no more likely to agree that it was important to eat healthy food now (PRR 1.19 95%CI: 0.79-1.79)). The students in the intervention groups took similar amounts of exercise and their diets were comparable to those in the control group.

Discussion: Students’ scientific awareness and health literacy can be improved and maintained as measured 12 months after the intervention, but this does not necessarily translate into behaviour change. Knowledge is easier to acquire than to act upon; embedding behaviour change is challenging and interventions require more than knowledge acquisition in order to motivate and sustain behaviour change. Nonetheless, acquiring the knowledge is a first step in behaviour change and LifeLab shows promise as part of a more extensive intervention to improve behaviours.

PA3.10 – Early origins of asthma

PA3.10.01
Early risk factors for respiratory morbidity

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Previous studies have suggested that chronic respiratory diseases have at least part of its origins in early life. Low birth weight has been shown to be associated with increased risks of asthma, chronic obstructive airway disease, and impaired lung function in children and adults. The developmental plasticity
hypothesis suggests that the associations between low birth weight and diseases in later life are explained by adaptation mechanisms in fetal life and infancy in response to various adverse exposures. Various pathways leading from adverse fetal and infant exposures to growth adaptations and respiratory health outcomes have been studied, including fetal and early infant growth patterns, maternal smoking and diet, children’s diet, respiratory tract infections and acetylcholine use, and genetic susceptibility. Both environmental and genetic factors in various periods of life, and their suggested epigenetic mechanisms may underlie the complex associations of low birth weight with chronic respiratory diseases in later life, but are not yet fully understood. This topic is focused on specific adverse fetal and infant growth patterns and exposures, genetic susceptibility, and epigenetic mechanisms in relation to chronic respiratory diseases throughout the life course.

**PA3.10.03**

**Fatty acids in pregnancy and childhood asthma**

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Asthma is one of the main causes for health care utilization in childhood with an increasing prevalence in westernized countries in recent decades. Concomitantly, changing dietary patterns have resulted in an increase in the intake of n-6 polyunsaturated fatty acids (PUFA) and a decrease in n-3 PUFA, especially the long chain PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish, and this has been hypothesized to be a potential cause of asthma and related disorders. Long chain PUFA has immune regulatory effects, and observational studies have reported an association between n-3 LCPUFA deprived diet during pregnancy and increased risk of asthma and related disorders in the offspring. However, randomized controlled trials (RCTs) of n-3 long chain PUFA supplementation to pregnant women have generally been underpowered and shown ambiguous results. Based on these observations, we conducted an RCT of n-3 long chain PUFA supplementation during third trimester of pregnancy in an unsel ected group of 743 pregnant Danish women in the COPSAC-2010 study. The offspring were prospectively monitored from birth with the primary aim to assess the risk of persistent wheeze or asthma. We found that n-3 long chain PUFA supplementation during pregnancy was associated with approximately 30% reduced risk of wheeze or asthma in the offspring. This effect was most pronounced in children of mothers with low blood levels of EPA and DHA prior to the intervention and children of mothers with a fatty acid desaturase (FADS) genotype associated with low EPA and DHA levels. These findings raise the possibility of a simple and safe prevention strategy that may relieve the burden of wheezing and related lung disorders in children. Furthermore, they provide evidence of intrauterine programming of asthma.

**PA3.10.05**

**Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 37 European cohorts.**

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**Background:** Early-life respiratory tract infections can affect airway obstruction and increase the risk of asthma in later life. We examined the associations of early-life respiratory tract infections with lung function and asthma in children.

**Methods:** We used individual participant data of 154,492 children from 37 birth cohorts to examine the associations of upper (ear infection, throat infection, (pseudo)croup, pertussis, rhinitis and cold) and lower respiratory tract infections (bronchitis, bronchiolitis, pneumonia, chest infection) by the age of 6 months, 1, 2, 3, 4 and 5 years with forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow at 75% of FVC (FEF75) and asthma at a mean age of 7 (SD 2) years. The associations of both upper and lower respiratory tract infections with lung function and asthma were examined at all ages separately. We used multilevel mixed effect models, to take clustering of participants within cohorts into account, and adjusted for socio-economic, lifestyle and growth factors.

**Results:** Upper respiratory tract infections were not associated with lung function. Upper respiratory tract infections at all ages were associated with an increased risk of asthma (OR 95% CI): ranging from 1.25 (1.15, 1.34) to 1.56 (1.47, 1.66). Lower respiratory tract infections at all ages were associated with a lower FEV1, FEV1/FVC and FEF75 (Z-score 95% CI): ranging from -0.07 (-0.14, -0.00) to -0.24 (-0.38, -0.10), except for lower respiratory tract infections at age 6 months with FEF75. Lower respiratory tract infections at all ages were associated with an increased risk of asthma (OR 95% CI): ranging from 2.00 (1.85, 2.10) to 3.72 (3.19, 3.85).

**Conclusion:** Early-life lower respiratory tract infections are associated with lower lung function and increased risk of asthma in later life, while upper respiratory tract infections are associated with asthma only. These findings might support the hypothesis that early-life respiratory tract infections might affect long-term respiratory morbidity. However, further
studies with both respiratory tract infections and lung function measurements from birth onwards are needed to disentangle the direction of these associations.

**PA3.10.06**

**Prenatal omega-3 LCPUFA supplementation and longitudinal allergic disease symptoms and sensitisation in offspring to 6 years of age**


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**Background:** Randomised controlled trials of prenatal omega (ω-3) long chain polyunsaturated fatty acid (LCPUFA) supplementation are suggestive of protective effects on atopic sensitisation and some symptoms of allergic disease in childhood; although most trials report heterogenous results. Due to the nature of the atopic march, assessment of offspring at multiple time-points throughout childhood may be most informative. We performed a longitudinal analysis to investigate the effects of prenatal ω-3 LCPUFA supplementation on symptoms of allergic disease and allergen sensitisation in the child from 1 to 6 years of age.

**Methods:** Follow-up of children (n = 706) with familial risk of allergy from the Docosahexaenoic Acid to Optimize Mother Infant Outcome (DOMInO) trial. The intervention group was randomly allocated to receive fish oil capsules containing 900mg of ω-3 LCPUFA daily from 21 weeks gestation until delivery; the control group received matched vegetable oil capsules without ω-3 LCPUFA. Allergic disease symptoms were assessed at 1, 3 and 6 years of age using the ‘International Study of Asthma and Allergies in Childhood’ questionnaire and allergen sensitisation was measured by skin prick test.

**Results:** Parent reported symptoms of eczema, wheeze, rhinitis and rhino-conjunctivitis (with or without sensitisation) and sensitisation results from skin prick testing did not differ between the ω-3 LCPUFA and control groups over time (group by time interaction p-values > 0.05) or across all time points. Treatment with ω-3 LCPUFA reduced the risk of hen’s egg sensitisation (aRR 0.62, 0.41 to 0.93; P = 0.02) and wheeze with sensitisation (aRR 0.52, 0.29 to 0.94, P = 0.03) at 1 year of age; and house dust mite sensitisation (D. farinae) at 6 years of age (aRR 0.62, 0.41 to 0.93, P = 0.02). Hen’s egg sensitisation at 1 year was strongly associated with house dust mite sensitisation at 6 years (p < 0.0001).

**Conclusions:** Prenatal ω-3 LCPUFA supplementation from <21 weeks gestation until delivery, did not change the risk of allergic disease symptoms or sensitisation over time, however significant early effects on sensitisation were evident.

**PA3.10.07**

**Epigenome wide meta-analysis reveals association of reduced DNA methylation at 14 CpG sites with childhood asthma**


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**Rationale:** Asthma results from many genetic and environmental factors. We hypothesized that DNA methylation profiles are associated with childhood asthma and tested this in an epigenome-wide discovery and replication study.

**Methods:** The discovery study investigated epigenome-wide DNA methylation by Infinium HumanMethylation450 BeadChips in whole blood DNA of 207 asthma cases and 610 controls at age 4/5 years, and 185 cases and 546 control samples at age 8 years from four European birth cohorts. The replication study investigated the top 27 CpG sites by iPLEX assays in 3,847 independent blood DNA samples from 4 to 16-year-old children of 7 cohorts. We tested if replicated CpG sites predicted asthma development later in life in 1,909 cord-blood DNA samples and addressed cell type specificity in respiratory epithelial cell DNA of 455 16-year-old children.

**Results:** Fourteen of top 27 CpG sites from the discovery analyses were significantly replicated and reached genome-wide significance (p < 1.14 × 10^-7) after meta-analysis, with the most significant sites annotated to DICER1, AMD1 and STX3. Consistent lower methylation in asthma was observed across childhood, but not at birth. These 14 sites were localized in...
enhancer regions. Annotated genes were linked to plausible biological pathways and strongly co-expressed with known asthma genes in respiratory epithelium. Five of these 14 CpG sites were associated with asthma in respiratory epithelial cell DNA.

**Conclusion:** Reduced DNA methylation at 14 CpG sites was associated with childhood asthma. This may reveal novel biological pathways relevant to the development of childhood asthma.

**Study design**

**PA3.10.08**

**Individuals born preterm more likely to be admitted for pneumonia - follow-up until adulthood of the Finnish 1987-1990 birth cohort**

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**Background:** In developed countries worldwide 5-10% of infants are born preterm. Preterm infants are more prone to infections and more likely to die of sepsis in the neonatal period. In addition, those with small diameters or restrictions in airways may be at higher risk for pneumonia. Our aim was to study the long-term susceptibility to pneumonia of individuals in six gestational age categories.

**Methods:** The participants born in 1987-1990 were identified through the Finnish Medical Birth Registry. There were 237,375 participants, 99.3% with valid personal ID numbers. The study looked at individuals with a diagnosis of pneumonia while on hospital admission, and/or, visits to hospital outpatient clinics from 1998 onwards. Data for the study were obtained from the Finnish Care Register for Health Care. The diagnosis criteria for pneumonia were based on ICD 9 (from 1987 to 1995) codes- 480-486, 4870A and 0032B; and ICD 10 (from 1996 onwards) codes- J10.0, J11.0, J12-J18 and B20.6.

Admission or visit rates for pneumonia were calculated for those before, and for those above 1 year of age. In our sex-adjusted Cox regression, gestational age categories <32, 32-33, 34-36, 37-38, 39-41 and ≥42 full weeks served as exposure variables. We assumed potential mediating mechanisms would vary according to gestational age at birth.

**Results:** The rates for any hospital admissions or specialized outpatients visits due to pneumonia per gestational age categories were 4.5%, 1.5%, 1.2%, 0.6%, 0.5% and 0.5% respectively in children below 1 year of age. The rates for the respective gestational age groups for any pneumonia admission or visit after 1 year of age were respectively 9.6%, 6.6%, 4.3%, 3.5%, 3.1% and 3.1%. The corresponding hazard ratios, adjusted for sex, rose exponentially reaching a ten-fold hazard among the extreme preterm group (see figure).

The admission rate due to pneumonia was higher among male participants in both analyses; for admissions before and after 1 year of age (male: female 0.7%: 0.4%, and 3.6%: 3.0%). The hazard ratio for male sex was 1.6 (95% CI, 1.4-1.7).

**Conclusions:** In summary, we describe an association between gestational age at birth and the rate of pneumonia-related hospital admissions and visits to hospital outpatient clinics. Individuals born preterm, and especially those born before 34 weeks, had higher rates of hospital admissions or outpatient visits due to pneumonia after 1 year of age.

Forest plot for pneumonia admissions or visits after age 1 per gestational age against a reference range of 39-41 weeks
PA3.10.09
Assessment of lung function among adult members of the New Delhi Birth Cohort, India


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Background: In India chronic respiratory disorders, including asthma and Chronic Obstructive Pulmonary Disease (COPD) are among the four major contributors in Non-Communicable Disease (NCD) deaths. In terms of Years of Life Lost (YLL), it is among the top five causes of mortality in 2014. Respiratory morbidity can be associated with early life exposure to adverse factors that affect lung development and function later in life. Longitudinal studies, like the New Delhi Birth Cohort (NDBC) with multiphase growth data throughout life can be of immense importance in investigating respiratory morbidity in relation with early life influences.

Methods: The NDBC is a longitudinal follow-up of 8181 children born between 1969-1972 to mothers in a defined area of South Delhi, India. The cohort (F1, N = 2221) has been followed from birth, through infancy and childhood, with studies so far on their parents (F0), spouses and children (F2) largely covering cardiometabolic diseases. Lung Function assessments using spirometry was conducted on 271 consenting adult members (F1) of the New Delhi Birth Cohort (NDBC). Trained staff used a validated instrument NDD EasyOne Spirometer linked with software for the assessments. A minimum of three and maximum of eight blows were attempted and spiromgrams (flow-volume and time-volume curves) and categories of pulmonary function (normal, restrictive, obstructive) for each test were generated. Additional questionnaire – based information on household demography, lifestyle factors, environmental exposures to ambient and indoor air-pollution and medical history were collected. Early life serial growth data, collected in earlier phases will be used to find its association with adult lung function. Spirometry of 232 subjects were satisfactory and preliminary results are presented here.

Results: A total of 232 (male-151, female-81, av. age = 48 years) satisfactory spirometry data were used for analysis. Among the total sample population, 9.9% (N = 23) lung function test results showed presence of some degree of obstruction and 39.2% (N = 91) indicate probable restriction while breathing. Among females, occurrence of restriction is slightly higher compared to males while among males, occurrence of obstruction is approximately 5 times higher compared to females. Amongst male smokers alone, restrictive, rather than obstructive lung function was more common. The relation of lung function to early growth and exposures will be analysed.

Conclusion: The preliminary results show that nearly half (49.1%) of the sample population have altered lung function, with either restrictive (39.2%) or obstructive (9.9%) lung function patterns. Males of the sample population have higher percentage of obstructive lung function compared to females whereas restrictive lung functions are slightly higher among females. Lung function data will be further analyzed in relation to early life exposures of the subjects to investigate the pattern of association and influence on altered lung function/ respiratory morbidity in adulthood.

PA3.11 – Brain and neurodevelopment

PA3.11.01
Early adversity, brain development and childhood behavioural problems. Research findings from the Generation R Study

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Background: Epidemiological studies showed that early adversities underlie the vulnerability for behavioural disorders like autism and ADHD. These studies relied on psychiatric assessments and thus our knowledge about how early life adversity shape brain development and whether this mediates behavioral problems is limited. Imaging studies designed to optimally evaluate the role of multiple environmental factors on brain development require both large sample sizes and the prospective collection of environmental exposures.

Methods: The Generation R Study is a large, prospective, prenatal-cohort study of nearly 10,000 children that began in 2002 in Rotterdam, the Netherlands. From September of 2009, 6–11 year old children from the Generation R Study were invited to participate in a magnetic resonance imaging component of the study. I will provide an overview of the study design and results for the first 5000 children recruited for the neuroimaging component of the study.

Results: The focus of my presentation will be on how prenatal exposure to maternal thyroid deficiency and postnatal depression shapes global brain development; the specific effects of insensitive parenting on grey matter development, and the even more specific effects of childhood bullying and emotional problems on changes in brain connectivity are shown. Also, I will discuss methodological challenges such as reversed causality and future plans.

PA3.11.03
Traffic air pollution, APOE e4 status and neurodevelopment in school children

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Background: Traffic air pollution is emerging as a risk factor for Alzheimer’s disease (AD) as well as for brain development impairment. We aimed to test whether the association between traffic air pollution and neurodevelopment is modulated by APOE ε4 status, the strongest genetic risk factor for AD.

Methods: Within the BREATHE project, behavioural problems and attention-deficit hyperactivity disorder symptoms (assessed using questionnaires), cognitive performance trajectories (inattentiveness and working memory) after four repeated measurements (assessed using computer tests), and APOE genotypes were evaluated in 1667 children aged 7–11 years. Basal ganglia volumes (putamen, caudate and globus pallidum) were assessed in a subsample of 163 children who underwent MRI scanning. Outdoor levels of polycyclic aromatic hydrocarbons (PAHs), elemental carbon (EC) and nitrogen dioxide (NO₂) were assessed at each school. Sensitivity analyses adjusting by inverse probability weighting (IPW) were performed to control for selection bias.

Results: APOE modified the PAHs, EC and NO₂ associations with behavioural problems, inattentiveness trajectories and caudate volume (P values for interactions with NO₂ were 0.037, 0.076 and 0.029, respectively). The adverse effects of these pollutants were stronger among APOE ε4 allele carriers than noncarriers.

Conclusions: Brain development was more vulnerable among the adverse effects of traffic air pollution among APOE ε4 allele carriers. These findings suggest that mechanisms linked to APOE and involved in AD could also intervene in the neuro-developmental effects of air pollution in childhood.

PA3.11.05

Maternal plasma mineral concentrations and children’s neurocognitive development in the first two years of life: the GUSTO study

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Background: There is compelling evidence that deficiency of some minerals in mothers during pregnancy, or during early infancy and childhood is associated with poorer neurocognitive development in infants or children. However, evidence linking maternal plasma mineral concentrations to childhood neurocognitive development in well-nourished populations is sparse. We related maternal plasma iron, ferritin, selenium and magnesium concentrations to neurocognitive development in children at 2 years of age using data from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study.

Methods: Maternal plasma iron, ferritin, selenium and magnesium concentrations were measured at 26 weeks’ gestation. The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) was used to assess five domains of neurocognitive development in children at 2 years: cognition, receptive language, expressive language, fine motor, and gross motor. Analysis was conducted on 440 mother-child pairs with data on maternal nutrient biomarkers and BSID-III in children. Associations were examined using linear regressions adjusted for confounders: maternal age, ethnicity, education, pre-pregnancy BMI, gestational weight gain, and physical activity level, depression and anxiety scores during pregnancy; and infant birth weight and length. Due to the multiple statistical tests performed, P < 0.013 was considered significant, and P < 0.05 was considered as suggestive evidence.

Results: Mean ± SD concentrations of maternal plasma iron, ferritin, selenium and magnesium were 1183 ± 566μg/L, 26.7 ± 10.9μg/L, 99.1 ± 14.6μg/L, and 19.8 ± 1.7μg/L respectively. A large percentage of pregnant women had marginal magnesium status (71% <20.68mg/L), while the prevalences of iron (6% <558.66μg/L), ferritin (6% <15μg/L) and selenium (9% <80μg/L) deficiencies were low. Higher maternal plasma iron was associated with a higher gross motor score in children (0.31 per SD increment in iron, P = 0.013). Likewise, higher maternal magnesium was associated with a higher cognitive score (0.34 per SD increment in magnesium, P = 0.009), and children whose mothers had sufficient magnesium concentrations (≥20.68mg/L) scored 0.59 higher in the cognitive domain (suggestive evidence) compared to children of mothers with marginal magnesium status (P = 0.034). Additionally, there was suggestive evidence that higher maternal magnesium was associated with a higher fine motor score (0.27 per SD increment in magnesium, P = 0.023), and children whose mothers had sufficient magnesium concentrations during pregnancy scored 0.62 higher in receptive language (P = 0.040) and 0.60 higher in fine motor (P = 0.021) domains, respectively compared to children of mothers with marginal magnesium status. There was suggestive evidence that higher maternal selenium was associated with higher expressive language score (0.24 per SD increment in selenium, P = 0.049) and higher fine motor score (0.23 per SD increment in selenium, P = 0.045) in children. In contrast, children of mothers with a higher concentration of serum ferritin (>25th percentile) scored 0.94-1.07 lower in expressive language (P < 0.003), compared to children of mothers with a low plasma ferritin concentration (<25th percentile).

Conclusions: Having adequate concentrations of plasma magnesium and higher concentrations of plasma iron and selenium during pregnancy were associated with better neurocognitive development in children at 2 years of age. These
observations raise the possibility that improving mineral status during pregnancy may enhance neurocognitive outcomes in children.

### PA3.11.06

IGF2 DNA methylation is associated with externalizing behaviours in adolescence independent of BMI

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**Background:** Studies have shown that imprinted regions of DNA at birth, including that for Insulin-like growth factor 2 (IGF2) are associated with growth and body size. Recent studies have also shown associations with infant temperament, suggesting that DNA methylation at birth may affect later infant temperament. It is uncertain if these associations persist in older life, such as young adulthood, and if it is mediated by obesity. Our aim was to investigate if H19/IGF2 DNA methylation at 17 years old is associated with behavioural scores at 17 years old.

**Methods:** Two hundred and twelve adolescents from the Western Australian Pregnancy Cohort (Raine study) had H19/IGF2 methylation measured from whole blood at 17 years and the Youth Self Report (YSR) Questionnaire which measures total, internalising (withdrawn/depressed) and externalising (aggressive/delinquent) behaviour scores. Maternal stress score was ascertained using a 10-item questionnaire based on the Tennant and Andrews (1977) Life Stress Inventory collected at 18 and 34 weeks gestation. H19/IGF2 methylation was measured at twelve cytosine-phosphate-guanine sites (CpGs), analysed as sequenom MassARRAY EpiTYPER units within the H19/IGF2 imprinting control region (ICR). Principle components analysis was undertaken on the 12 CpGs. Methylation principle components were investigated for their association with total, internalising and externalising scores, using adjusted linear regression models. Cell count (neutrophil, lymphocyte, monocyte) (x109 / L) was ascertained by full blood count and differential, taken concurrently with blood from which DNA was extracted.

**Results:** There were 118 males and 94 females participants. The second principal component of H19/IGF2 methylation positively correlated with total (β = 1.4, 95% CI 0.05 to 2.7, p = 0.043) and externalizing (β = 2.02, 95% CI 0.6 to 3.4, p = 0.005) T scores, adjusted for age, sex and measured cell count. CpG23 (most representative of the CpGs of PC2) was associated with total (β = 21.6, 95% CI 1.7 to 41.6, p = 0.033) and externalizing (β = 26.3, 95% CI 5.4 to 47.1, p = 0.013) T scores. The associations remained after adjusting for BMI at 17 years old and adolescent smoking and maternal smoking and stress score during pregnancy (β = 21.8, 95% CI 2.4 to 17.1, p = 0.028).

**Conclusions:** H19/IGF2 DNA methylation at specific sites is associated with externalizing behaviours in adolescents/young adults, independent of contemporaneous BMI and smoking. The association was robust after adjusting for maternal smoking and maternal stress score. Discussion: This suggests that H19/IGF2 DNA methylation may contribute independently to externalizing behaviours, probably not solely mediated by adolescent obesity, maternal smoking or stress during pregnancy. Further tissue specific studies investigating the role of changes in H19/IGF2 DNA methylation changes in the brain is likely to progress understanding of the mechanisms underlying this association.

### PA3.11.07

Effect of inadequate iodine status in pregnant women on infant developmental skills: results from the Little in Norway cohort


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**Background:** Iodine deficiency is considered one of the most common nutritional disorders in the world and the world’s largest single cause of preventable brain damage. Iodine is an essential nutrient for the synthesis of thyroid hormones triiodothyronine (T3) and thyroxine (T4). In the fetal brain, inadequate thyroid hormone impairs myelination, cell migration, differentiation and maturation. Suboptimal iodine status is common, and nine in ten pregnant women in Europe are iodine deficient.

**Methods:** Little in Norway (LiN) study is a population-based prospective cohort established to investigate pre- and postnatal risk factors influencing developmental plasticity from pregnancy to age 18 months. In total, 1041 families from nine different sites were enrolled. We excluded 33 participants due to stillbirth, multiple births or missing urine sampled in pregnancy. Further, 92 dyads were excluded due to premature birth, low gestational weight, urinary iodine concentration (UIC) >500 g/L, or reported use of thyroid hormone drug therapy. Spot urine samples were collected in pregnancy to determine the UIC using inductively coupled plasma-mass spectrometry (n = 911). Infant development was assessed at the age of six months (n = 767), 12 months (n = 727) and 18 months (n = 692) by testing the child’s cognitive, language, and fine- and gross motor development using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Data collection also included questionnaires completed repeatedly by the parents and well-baby nurses.
Results: The median UIC was 79 μg/L (IQR 82), classifying this group as having mild-to-moderate iodine deficiency (UIC 50-150 μg/L). Of 911 mothers, 27% (n = 248) were classified as having severe iodine deficiency (UIC <50 μg/L). In the unadjusted model, children of mothers categorised as having severe iodine deficiency in pregnancy were more than twice as likely to have suboptimal development of their receptive language at the age of six months than children of mothers categorised as not having iodine deficiency in pregnancy (OR 2.10, 95% confidence interval [CI] 1.30-3.35, p = 0.002). The OR changed minimally after adjusting for maternal age, iodine containing supplement use in pregnancy, marine omega-3 intake in pregnancy, breastfeeding, height at six months of age, gender, and a maternal screening index: a maternal cumulative risk index consisting of a combination of socio-demographic information in addition to information about mental health, alcohol, nicotine and drug use (OR 2.04, [CI] 1.22-3.45, p = 0.006). In multiple regression analysis, maternal UIC significantly predicted infant language skills at the age of six and 12 months, while controlling for confounding factors (figure). No significant association was found at 18 months.

Conclusions: This study provides further evidence that iodine deficiency during pregnancy may adversely impact on infant development. However, in this population associations were found between maternal UIC in pregnancy and developmental domains tested at 6 and 12 months and not at 18 months. The value of screening pregnant women for ID requires further assessment and health-care professionals should stress the importance of securing sufficient iodine intake prior to or in the beginning of pregnancy.

Background: Exposure to air pollution has been related to impaired brain development but the relationship with white matter microstructure has not been tested. Here, we aimed to assess whether pre- and postnatal exposure to a wide range of different air pollutants is related to white matter integrity in school-age children.

Methods: We used data from 2977 children aged between 8-10 years from a population-based birth cohort set up in Rotterdam, The Netherlands (2002-2006). Exposure to nitrogen dioxide (NO₂), nitrogen oxides (NOₓ), particulate matter in various diameter sizes: less than 10μm (PM10); between 10 and 2.5μm (PMcoarse); less than 2.5μm (PM2.5); and less than 0.1 μm (UFPs - ultrafine particles), PM2.5 absorbance, oxidative potential of PM2.5, different components of PM2.5, and black carbon at home addresses were estimated using land-use regression models for the entire prenatal period and from birth until the day of the visit at the research center when the children were 8-10 years old. Diffusion tensor images were obtained during the magnetic resonance imaging session; whole brain fractional anisotropy and mean diffusivity parameters were computed from the obtained scans. Models were adjusted for various parental socioeconomic and lifestyle characteristics. Multiple imputation and inverse probability weighting were applied to account for selection and attrition biases.

Results: Exposure to multiple individual air pollutants was associated with a global decrease in fractional anisotropy and a global increase in mean diffusivity. These results were consistent from fetal life to childhood, yet more profound with postnatal air pollution exposures (e.g. a decrease in fractional anisotropy of 0.13 [95% Confidence Interval (CI) -0.23 to -0.02] and an increase in mean diffusivity of 0.02 [95% CI 0.01 to 0.03] for each 10 μg/m³ increase in NO₂ during childhood).

Discussion: Exposures to various air pollutants during fetal life and particularly during childhood were associated with alterations in white matter microstructure in school-age children. In general, lower fractional anisotropy values and higher mean diffusivity values indicate atypical brain development or acquired brain damage and thus considering the ubiquity of the exposure, these results raise concern and point out the need for further research in this area.

PA3.11.09

Prenatal and postnatal acetaminophen use and autism spectrum symptoms in childhood


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Means (95% CIs) for infant developmental domains according to maternal urinary iodine concentration in pregnancy. Values are adjusted for mate
Background: Converging evidence has linked prenatal acetaminophen exposure and detrimental effects on cognition and behaviour including an increased risk for autism spectrum disorder (ASD). Furthermore, postnatal exposure to acetaminophen may have cumulative effects on neurodevelopment, but as yet, no study has investigated this possibility. To fill this gap in literature and increase generalizability of the results, the present study aimed to assess whether prenatal and postnatal acetaminophen exposure is associated with ASD and ADHD in six European birth-cohorts including ALSPAC (United Kingdom), DNBC (Denmark), GASPII (Italy), Generation R (The Netherlands), INMA (Spain) and RHEA (Greece). Preliminary results on ASD symptoms from INMA cohort are presented.

Methods: A total of 1467 mother-child pairs spanning births from 2004 through 2008 from INMA cohort were included. From these mother-child pairs, postnatal exposure (from birth to 14 months) was also available for 1005 children. Prenatal and postnatal acetaminophen exposure was prospectively assessed through questionnaires administered by a trained interviewer to the mothers. Childhood ASD symptoms were assessed using the Childhood Asperger Syndrome Test (CAST) at age 4. Multivariable linear regression models were adjusted by maternal socioeconomic status, child’s sex, age at assessment, gestational age, maternal chronic illness, maternal fever and maternal infection during pregnancy, and INMA region.

Results: Over 40% and 78% children were exposed to acetaminophen during the prenatal and postnatal periods, respectively. Ever-exposed males to prenatal ($\beta = 0.63$, 95% CI: 0.09; 1.18) but not postnatal acetaminophen ($\beta = 0.40$, 95% CI: -0.31; 1.10) use presented higher CAST scores. In females, prenatal exposure was negatively associated with CAST scores ($\beta = -0.51$, 95% CI:-0.98; -0.05) while no association was observed with postnatal exposure ($\beta = -0.30$, 95% CI:0.65; 0.59).

Conclusions: Our preliminary findings suggest that prenatal but not postnatal acetaminophen use is associated with child ASD symptoms only among males. In Liew et al. (2016) this association was limited to ASD cases accompanied by hyperkinetic features in both females and males. Further analyses within this collaborative study will help to establish the role of sex differences and whether these associations are independent from the presence of ADHD symptoms and limited to prenatal acetaminophen exposure. Given the extended use of acetaminophen during pregnancy, the results are likely to have relevant implications for public health.
should achieve a weight and body composition similar to their term-equivalent, remains unclear. The aim of the study is to compare different approaches to create individualized postnatal growth trajectories for the period between birth and 42 + 0/7 weeks PMA, that consider the physiologic weight loss.

Methods: Three approaches to achieve growth similar to healthy term infants at 42 + 0/7 weeks PMA on WHO growth standards (target weight) were tested for infants born at 24-34 weeks PMA and for birth weights at 7 major percentiles. The three approaches include: 1) following the birth percentile (Birth-Weight-Percentile Approach), 2) following the new percentile achieved at DOL 21 after postnatal weight loss (Postnatal-Percentile Approach); 3) using day-specific fetal median growth velocities starting at DOL 21 (Growth-Velocity Approach). Primary outcome was the difference between achieved and target weight at 42 + 0/7 weeks. Secondary outcome was the deviation from target weights vs. % fat in a cohort of 20 disease-free VLBW infants.

Results: The weights following the Birth-Weight-Percentile and Postnatal-Percentile approaches deviated significantly from target weights. Weights using the Growth-Velocity approach merged with the target weights after introducing a single correction factor. %fat and deviation from target weight correlated best with term equivalent %fat using the Growth-Velocity approach. The figure demonstrates an individualized growth trajectory using the Growth-Velocity approach for a male preterm, born at 31 + 0/7 weeks, with a birth weight of 1980g.

Conclusions: The Growth-Velocity approach provides an evidence-based approach for individualized growth trajectories. The Growth-Velocity approach is based on physiological data incorporating that phenomenon that healthy preterm infants adjust their postnatal trajectory below their birth percentile. After postnatal adjustment, the Growth-Velocity Approach applies the median fetal growth velocity. The Growth-Velocity approach matches consistently with term-equivalent weights at 42 + 0/7 weeks. The Growth-Velocity approach has been integrated into a bedside tool that can be used to aid clinicians in monitoring growth, guiding nutrition and minimizing chronic adult disease risks (DOHaD) as a consequence of unguided, inappropriate growth.

Individual Trajectory - Growth Velocity Approach

PA3.12.04
Assessing the merits and limitations of using fathers as a negative control exposure to test DOHaD using a Swedish case-study

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Background: Developmental Origins of Health and Disease Hypothesis (DOHaD) studies are often observational in nature and are therefore prone to biases from loss to follow-up and residual confounding. Register-based studies can reduce these issues since they allow almost complete follow-up and provide information on fathers that can be used in a negative control analysis to assess the impact of unmeasured confounding. The aim was to propose a causal model for testing DOHaD using paternal exposure as a negative control, and to assess its merits and limitations using an application from Swedish register data: fetal exposure to distress and the risk of asthma.

Methods: A causal diagram including shared (L1 and U1) and parent-specific (L2, U2, L3, U3) measured (L) and unmeasured (U) confounders for maternal (fetal) and paternal exposures is proposed (see Figure). The case-study consisted of all children born in Sweden from July 2006 to December 2008 (n = 254 150). Information about childhood asthma, parental distress and covariates was obtained from the Swedish National health registers. Associations between maternal and paternal distress during pregnancy and offspring asthma at age 5 years were assessed separately and with mutual adjustment for the other parent’s distress measure, as well as for shared confounders.

Results: Negative control exposure studies are useful for eliminating shared residual confounding but may continue to be biased by unshared confounding. The beauty of using fathers as a negative control exposure is that in most cases the parent-specific unmeasured confounders are likely to be of a similar type and risk for both parents eg common genetic pathways, disease status. Therefore U2 and U3 could be considered to act like shared confounders. In addition, if there is a robust association between maternal and paternal exposures it is likely that both maternal and paternal causal pathways share all unmeasured confounders U1-U3, therefore the paternal model can act as a sufficient negative control. However, if parent-specific unmeasured confounders are not of similar risk or direction then interpretation is more difficult. Our case-study found that maternal distress during pregnancy was associated with offspring asthma risk; adjusted Odds Ratio (OR) 1.32 (95% CI 1.23, 1.43). The mutually adjusted paternal distress-offspring asthma analysis (OR 1.05 95% CI 0.97, 1.13) indicated no evidence for unmeasured confounding. One important limitation highlighted by the case-study was maternal exposure misclassification bias, as we found that the rate of maternal distress during pregnancy was lower than expected, possibly due to mother’s not wishing to take anxiolytic or antidepressant drugs when pregnant. This not only means the effect size will...
be pushed towards the null but the association between paternal distress on maternal distress will also be subject to misclassification.

Conclusions: Using paternal exposure in a negative control model to test the robustness of fetal programming hypotheses can be a relatively simple extension of conventional observational studies. However, although a null finding for the paternal exposure association likely suggests a lack of residual confounding in the maternal exposure association, a positive finding is harder to interpret.

Causal diagram for an ideal negative control exposure study testing in utero programming effects.

PA3.12.05
Postnatal growth velocity calculation: accuracy of different methods
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Background: Postnatal growth in premature infants is an indirect measure of health status, nutritional adequacy, and long-term health outcome. Growth is usually assessed as an increase in weight over time. However, an absolute weight gain has different clinical implications depending on the weight of the infant. Hence, growth velocity (GV) that is normalized for body weight expressed as g/kg/day is an important parameter of growth assessment, for clinical management and research. Currently, there is no agreement for the calculation of GV. This study aims to assess the accuracy of different GV calculations.

Objective: to compare different methods of growth velocity calculation in real infant dataset

Methods: Real weight data of 220 infants (<35 weeks gestational age at birth) was used with six different methods of GV calculation: 1) 2-point linear 2) 2-point exponential 3) daily average method 4) linear regression 5) exponential regression 6) generalized reduced algorithm. The first two are 2-point methods whereas the first and last weights are used for GV calculation. The third is a modification of a 2-point method where daily GV is calculated using two points, and averaged over a period. The next three are regression methods where all available weight data are incorporated into the calculation. We calculated GV using six methods, and then predicted weight values and calculated mean absolute error from the observed values.

Results: GV calculated with the generalized reduced algorithm method and exponential regression had the lowest mean absolute error (17.54 ± 7.33g, 17.58 ± 7.33g respectively). The mean absolute error for the remaining methods was as follows: linear regression (19.92 ± 7.85g), daily average method (25.43 ± 25.17g), 2-point exponential (25.42 ± 25.17g) and 2-point linear (32.71 ± 29.76g).

Conclusion: The GV estimates vary depending on the method of calculation. The regression methods have the lowest mean absolute error among the methods tested. 2-point methods have a high risk to overestimate low growth rates and underestimate high growth rates. This has significant implications for clinical trials as it could mask a potential effect. The deviation from true growth rate by using 2-point methods is 2-3 g/kg/day, which is at a size clinical trials are often powered to detect a difference. Incorporating all available weight data using regression methods for GV calculation appears to be better than using only 2 points. GV calculation needs to be standardized to allow for comparison across nutritional studies.

PA3.12.06
Effect of gestational age correction on association between length-for-age z-scores during infancy and cognitive development at 6 years of age
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Background: Linear growth in early childhood has been associated with several outcomes in later life, including cognitive development. The timing of birth, measured by gestational age (GA), influences postnatal growth trajectories and should be accounted for in the evaluation of postnatal growth. The WHO Child Growth Standards (WHO-GS), which are the most commonly used normative growth standards, do not account for GA of preterm born children (i.e. births <37 weeks GA). Clinical guidelines recommend using gestational age-corrected age (CA) [postnatal age – (40 weeks – GA at birth)] for preterm-born children in the application of the WHO-GS. Yet, CA is rarely used in population-based epidemiologic studies of child growth in which both term- and preterm-born children are included. We hypothesized that ignoring GA in the calculation of z-scores may lead to biased population-
average estimates of associations between early childhood growth and later outcomes.

**Methods:** We aimed to estimate and compare cross-sectional associations between mean length-for-age z-score (LAZ), and stunting (LAZ < -2 SD), at birth, 3- and 12-months of age, and cognitive ability at 6 years of age in the 2004 Pelotas (Brazil) Birth Cohort. LAZ during infancy was derived using two methods: (i) Intergrowth-21st GA-specific newborn size references/standards at birth, in conjunction with the WHO-GS using CA for preterm-born children (‘GA-corrected strategy’), or (ii) WHO-GS using postnatal age for all infants (‘postnatal age strategy’). Cognitive outcomes at 6 years were measured using Wechsler’s full-scale intelligence quotient (IQ) and transformed into standard deviation (SD) scores. Mean change/difference (95% CI) in LAZ-IQ and stunting-IQ associations were estimated using unadjusted and covariate-adjusted linear regression.

**Results:** Overall, 11% (n = 274) infants were born preterm and mean ± SD IQ standardized score at 6 years of age was 0.05 ± 1.0. Mean LAZ at birth (n = 2491) using GA-corrected vs postnatal age strategy was -0.37 ± 1.18 vs -0.66 ± 1.29, respectively. Using GA-correction (vs postnatal age strategy) attenuated the association between LAZ at birth and IQ at 6 years of age [adjusted mean change in IQ per 1-unit change in LAZ (95%CI): 0.077 (0.047, 0.107) vs 0.085 (0.058, 0.112)], but strengthened the association between stunting at birth and IQ at 6 years of age [adjusted mean difference (95% CI): -0.306 (-0.433, -0.179) vs -0.213 (-0.322, -0.104)]. At 3- and 12-months, absolute differences in magnitudes of LAZ-IQ and stunting-IQ associations were even smaller. The direction of between-method differences (under- or over-estimation) varied unpredictably by association and follow-up time. Similarly small differences between the two approaches were found in an analysis restricted to preterm-born children.

**Conclusions:** There are conceptual advantages of using a GA-corrected strategy to calculate LAZ in cohorts that include preterm-born infants. However, inferences were unchanged and there were small absolute differences in the magnitude of associations between infant LAZ and mid-childhood IQ when a GA-corrected strategy was used. GA-correction may not necessarily lead to meaningful differences in associations between early-life growth and later health outcomes.

**PA3.12.07**

**A Comparison of Early Infancy Weight Velocities in Relation To Childhood Cardio-metabolic Risk Markers: Significance of Infant Peak Weight Velocity**


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**Background:** Rapid weight gain in early infancy (0–6 months) is an important risk factor for later cardio-metabolic disease, but it is still unclear as to which interval during early infancy is the most sensitive for such outcomes. We analyzed associations between weight velocities at various intervals in early infancy with adiposity and blood pressure measures in later childhood.

**Methods:** A prospective Asian mother-offspring cohort study (Growing Up in Singapore Towards healthy Outcomes) provided data on early infancy growth (at birth, 1 and 3 weeks, 3 and 6 months; n = 1075), body composition (sum of skinfolds, n = 820; fat- and lean-mass index, n = 242) and blood pressure (systolic and diastolic, n = 757) at age 5 years. Child obesity was defined as age- and sex-specific body mass index two standard deviations higher than the median of the WHO reference. Child prehypertension was defined as systolic or diastolic blood pressure above 90th percentile for the child’s sex, age and height. Early infancy growth was modelled using mixed-effects parametric Reed1 models, to estimate infant peak weight velocity and weight velocities at four intervals during early infancy (0–1 week, 1–3 weeks, 3 weeks–3 months and 3–6 months). Weight velocities were standardized to z-scores within the study cohort to allow direct comparison of effect estimates across different time intervals. Associations between infant weight velocities and cardio-metabolic outcomes at 5 years were estimated via multivariable regression models.

**Results:** The estimated mean (SD) age of infant peak weight velocity for boys and girls respectively was 13.3 (3.8) and 13.2 (0.9) days post-delivery, with a magnitude of 0.059 (0.005) and 0.048 (0.004) kg/day. Independent of size-at-birth and other confounders, each SD-unit increase in infant peak weight velocity was associated with higher sum of skinfolds [3.01 mm (95% CI 2.18, 3.84)], fat-mass index [0.27 kg/m2 (0.10, 0.43)], lean-mass index [0.20 kg/m2 (0.07, 0.34)], systolic [1.78 mmHg (1.06, 2.50)] and diastolic blood pressure [0.85 mmHg (0.36, 1.35)], as well as increased risk of obesity [1.82 (1.39–2.41)] and prehypertension [1.43 (1.12–1.86)] at age 5 years. Similarly, infant weight velocities at other intervals (0–1 week, 1–3 weeks and 3 weeks–3 months) were positively associated with increased adiposity and blood pressure at 5 years. For the same 1-SD increase, infant peak weight velocity was found to exhibit stronger associations with increased adiposity, blood pressure and risk of obesity at 5 years, when compared to weight velocities at other intervals in early infancy.

**Conclusions:** A higher infant peak weight velocity, which occurs within the first 2 weeks after birth, may be an important and more sensitive marker in early infancy for increased cardio-metabolic risk in later childhood.
PA3.12.08

Understanding the direct and BMI-mediated association between birth weight and childhood cardio-metabolic health - findings from a prospective birth cohort

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Background: Birth weight has been associated with future cardio-metabolic risk, but different directions of this association have been found, especially in children. The mediating effect of attained adiposity is not always taken into account, which may be the key to explain the diversity of results found in the literature.

Objective: To disentangle the direct and body mass index (BMI)-mediated association of birth weight with childhood cardio-metabolic traits.

Methods: This study included 4881 children from the Portuguese birth cohort Generation XXI. Birth weight was abstracted from clinical records. At age 4 and 7, children were measured and had a fasting blood sample collected. The cardio-metabolic traits analyzed were glucose, triglycerides, LDL-cholesterol, systolic (SBP) and diastolic blood pressure (DBP) age- and sex-specific z-scores (and height-specific for SBP and DBP). Path analysis was used to compute adjusted regression coefficients and respective 95% confidence intervals [β (95% CI)]. The fit of the model was tested with several confounders and the final model included maternal pre-pregnancy BMI and tobacco smoke during the 3rd pregnancy trimester as confounders.

Results: After adjustment for confounding factors, birth weight had an inverse total effect on SBP at 4 [-0.007 (-0.012; -0.002)] and 7 [-0.011 (-0.016; -0.006)] and DBP at 7 [-0.011 (-0.015; -0.007)] and a positive total effect on DBP at 4 [0.005 (0.001; 0.010)]. The association paths are depicted in figure. The inverse total effects observed were explained by inverse direct effects found for SBP at 4 and 7, and DBP at 7. Despite no total effect being found for LDL-cholesterol, a negative direct effect was found at 7 years of age [-0.060 (-0.105; -0.014)]. No total or direct effects of birth weight on glucose or triglycerides were found. Regarding BMI-mediated associations, higher birth weight was associated with higher childhood BMI, which in turn was associated with higher glucose, triglycerides, LDL-cholesterol, SBP and DBP levels. This positive indirect effect explained the positive total effect on DBP at 4.

Focusing on the paths between 4 and 7 years of age, it is reflected the high tracking effect of BMI and of cardio-metabolic traits between those ages. The specific path from BMI at 4 to cardio-metabolic traits at 7 is adjusted for BMI at 7, so it is actually representing the decrease in BMI from 4 to 7 years of age (for a given fixed BMI at 7, a higher BMI at 4 implies a higher decrease in BMI between 4 and 7). So, the higher the decrease in BMI between 4 and 7 years of age, the lower the cardio-metabolic traits at 7 years of age.

Conclusions: A BMI-mediated effect of birth weight on cardio-metabolic health was present in childhood, such as higher birth weight led to higher BMI, which led to adverse levels of cardio-metabolic traits. In addition, a decrease in BMI during childhood instigated an improvement of cardio-metabolic traits. However, opposite direction direct associations of birth weight with LDL-cholesterol, SBP and DBP were found, which may explain the diversity of results observed in the literature.
Path analysis of the associations of birth weight with cardio-metabolic traits z-scores at ages 4 and 7.

PA3.14 - Epigenetic programming

PA3.14.01

Programmed Hyperphagia in Small for Gestational Age Offspring via Epigenetic DNA Methylation-mediated Neuronal Differentiation

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Objective: Small-for-gestational age (SGA) human newborns have an increased risk of adult obesity. In rodents, SGA newborns demonstrate marked hyperphagia, rapid catch-up growth and adult obesity. In hypothalamic tissue (appetite regulatory site), SGA newborns exhibit an increase in appetite (AgRP; agouti-related protein) vs satiety (POMC; pro-opiomelanocortin) neurons. In culture, SGA hypothalamic neural stem cells (NSCs) demonstrate reduced proliferation and neuronal differentiation, and consistent with tissue expression, the neuronal differentiation is preferentially biased towards AgRP versus POMC neurons. DNA methylation (DNA methyltransferase; DNMT1) regulates neurogenesis by maintaining NSC proliferation and suppressing premature differentiation. Once differentiation ensues, DNMT1 preferentially inhibits neuronal and promotes astroglial fate. We hypothesized that the programmed dysregulation of NSC proliferation and differentiation in SGA offspring is epigenetically mediated via DNMT1.

Methods: Control dams received ad libitum food, whereas study dams were 50% food-restricted from pregnancy day 10 to term to create SGA newborns. Primary hypothalamic NSCs from 1 day old SGA and Controls newborns were cultured in complete or differentiation media and transfected with nonspecific or DNMT1-specific siRNA (20 nM). At day 5 of siRNA transfection, NSC proliferation and protein expression of specific markers of NSC (nestin), neuroproliferative factor (Hes1), neurons (Tuj1) and astrocytes (GFAP) were determined.

Results: Under basal conditions, SGA NSCs exhibited decreased DNMT1 and reduced proliferation and neurogenesis, but increased GFAP, as compared to controls. DNMT1 siRNA markedly decreased protein expression of DNMT1, confirming silencing. In both SGA and controls in complete media, DNMT1 siRNA inhibited NPC proliferation (0.5-fold), consistent with reduced expression of nestin (0.5-fold) and Hes1 (0.4-fold). In differentiation media, DNMT1 siRNA decreased expression of Tuj1 (0.6-fold) but increased GFAP (1.4-fold).

Conclusion: In SGA newborns, impaired neurogenesis is epigenetically mediated via reduction in DNMT1 expression and suppression of the neuroproliferative factor Hes1. Premature NSC differentiation to astrocytes limits neuronal differentiation, though with a preferential expression to appetite vs satiety neurons.

PA3.14.02

Maternal alcohol consumption during pregnancy and offspring epigenome-wide DNA methylation: findings from the Pregnancy and Childhood Epigenetics (PACE) Consortium


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Background: There is evidence to suggest that moderate alcohol consumption during pregnancy is associated with adverse outcomes in the offspring, but the precise biological mechanisms underlying such associations are currently unknown. Epigenetic modifications have been suggested to play a mediating role.

Methods: To investigate genome-wide DNA methylation in the cord blood of newborns differentially exposed to alcohol in utero, we meta-analysed epigenome wide association study (EWAS) summary statistics from six population-based cohort studies (n mother-child pairs = 3,075) within the Pregnancy and Childhood Epigenetics (PACE) Consortium. We were primarily interested in the effects of sustained consumption throughout pregnancy, which represents a prolonged prenatal exposure to alcohol, but we also explored binge-drinking and timing-specific exposures.

Results: No single CpG-sites were associated with any of our alcohol exposure measures after correction for multiple testing. In a region-based analysis, we identified 19 regions differentially methylated in the offspring of mothers who drank throughout pregnancy compared to the offspring of mothers who gave up drinking at the start of pregnancy. However, we did not validate this result using another regional analysis method.

Conclusion: In this multi-cohort study we found no evidence that (mostly light-to-moderate) maternal alcohol consumption during pregnancy is associated with offspring cord blood DNA methylation. However, it is possible that a combination of a larger sample size, higher doses, different timings of exposure and a more global assessment of genomic DNA methylation might show evidence of effect.

PA3.14.03

DNA methylation of Musashi RNA binding protein 2 (MSI2) associates with subcutaneous fatness, early life environment and childhood growth trajectories

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Background: There is evidence to suggest that moderate alcohol consumption during pregnancy is associated with adverse outcomes in the offspring, but the precise biological mechanisms underlying such associations are currently unknown. Epigenetic modifications have been suggested to play a mediating role.

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Results: No single CpG-sites were associated with any of our alcohol exposure measures after correction for multiple testing. In a region-based analysis, we identified 19 regions differentially methylated in the offspring of mothers who drank throughout pregnancy compared to the offspring of mothers who gave up drinking at the start of pregnancy. However, we did not validate this result using another regional analysis method.

Conclusion: In this multi-cohort study we found no evidence that (mostly light-to-moderate) maternal alcohol consumption during pregnancy is associated with offspring cord blood DNA methylation. However, it is possible that a combination of a larger sample size, higher doses, different timings of exposure and a more global assessment of genomic DNA methylation might show evidence of effect.
Background: Epigenetic changes are associated with the development of non-communicable diseases. In the Raine Study, Infinium 450K array EWAS identified Musashi RNA binding protein 2 (MSI2) methylation as associated with concurrent BMI at age 17 years. MSI2 encodes a transcriptional regulator that targets genes involved in development and cell cycle regulation. The identified locus is intronic and within a Hidden Markov Model predicted CpG island. As fat distribution (central and visceral) is linked with cardio-metabolic risk, this study aimed to evaluate if MSI2 methylation at age 17 years: 1) is associated with fat distribution and related anthropometry, 2) predicts future body composition in adult life age 20 years, 3) is associated with early life environmental influences (pre-pregnancy maternal BMI, gestational weight gain, smoking, alcohol, caffeine consumption and stress, and breastfeeding duration), and 4) is predicted by postnatal adiposity trajectories.

Methods: 842 individuals from the Western Australian Pregnancy Cohort (Raine study) had MSI2 methylation at 3 CpGs measured by pyrosequencing in whole blood age 17 years and body composition measured by Dual Energy X-Ray Absorptiometry (DEXA) at age 20 years. Using adjusted linear regression models, we analysed MSI2 DNA methylation at the 3 CpGs in relation to anthropometry at age 17 years, DEXA measures at age 20 years and early life environmental influences and trajectories.

Results: DNA methylation (%) at all three MSI2 CpGs was positively associated with BMI at age 17 years ($\beta = 0.007, p < 0.001$), as well as waist circumference (cm) ($\beta = 0.005, p = 0.001$), subcutaneous fat thickness ($\beta = 0.018, p = 0.005$) and skinfold thickness at multiple sites (all $p < 0.05$), but not visceral fat thickness ($p = 0.002, p = 0.559$). It was associated with total lean mass (g) ($\beta = 0.003, p = 0.014$) and soft tissue (combined fat and lean mass) (g) ($\beta = 0.004, p = 0.020$), as measured by DEXA three years subsequent to DNA methylation measurement at age 17 years. It was not associated with total fat mass (g) at age 20 years ($p = 0.006, p = 0.181$). Two early life factors were associated with higher MSI2 methylation, namely higher maternal pre-pregnancy BMI (kg/m2) ($\beta = 0.107, p = 0.020$) and shorter duration of exclusive breastfeeding (months) ($\beta = -0.038, p = 0.046$). Of seven childhood adiposity trajectories examined, two trajectories (2 and 4 in Figure) were associated with MSI2 methylation: accelerated velocity of adiposity gain (“catch up growth”) ($\beta = 1.41, p = 0.006; \beta = 0.99, p = 0.013$) and constantly high adiposity from birth (Trajectory 1 in Figure) ($\beta = 1.03, p = 0.012$).

Conclusions and Discussion: MSI2 methylation, identified through 450K arrays, was confirmed with pyrosequencing to associate with BMI, particularly with a body fat distributed in subcutaneous regions. Maternal pre-pregnancy BMI, duration of breastfeeding and childhood adiposity trajectories were associated with MSI2 methylation in adolescence. This study provides evidence that methylation of specific loci is associated with body fat distribution patterns known to associate with differential cardiovascular risk. The associations with childhood adiposity trajectories raises the possibility that targeting interventions in infants exposed to adverse early life environments may reverse DNA methylation related to obesity.


Postnatal adiposity trajectories formed using semi-parametric mixture modelling from longitudinal BMI z scores at 7 time-points. (1)
long-term morbidities including obesity and diabetes. Whilst the beneficial effects of breastfeeding are well documented, the biological mechanism(s) by which some of these effects are transferred are still unclear. Early life nutrition has been shown to induce epigenetic variations such as changes in DNA methylation and may represent a mechanism whereby breast milk induces physiological effects that persist beyond cessation of breastfeeding. We sought to investigate the long-term effect of breastfeeding on offspring’s genome-wide DNA methylation.

**Methods:** DNA was extracted from peripheral blood samples taken at 10 and 18 years of age, from 74 and 367 participants respectively in the Isle of Wight 1989 birth cohort. DNA methylation levels at >480,000 cytosine-phosphate-guanine (CpG) sites were measured using Illumina Infinium Human450 Beadchips, and data were pre-processed for quality control, batch effect correction and cell type correction. An Epigenome-wide Association Study was conducted using robust linear regression models to assess the association between breastfeeding exposure and methylation levels at 18 years of age. This was adjusted for associated cohort characteristics, including maternal socioeconomic status, maternal age, maternal smoking during pregnancy, child sex and child’s birth weight. False discovery rate (10% FDR) correction was used to correct for multiple-hypothesis testing, inferring an adjusted p-value for each of the ~480,000 CpG sites. Separate models were run, each comparing non-breastfed controls against an exposure group, categorized by the total duration that the participants were breastfed either non-exclusively or exclusively. Pathway analyses using Ingenuity Pathway Analysis (IPA) were performed on significantly associated genes to identify enrichment for biological pathways. The level and direction of methylation on these genes from the primary results for age 18 samples, were compared with samples taken from the same participants at 10 years.

**Results:** At 18 years, non-exclusive breastfeeding >6 months was significantly associated with DNA methylation at four CpG sites. Exclusive breastfeeding >3 months was significantly associated with DNA methylation at five CpG sites, four being hyper-methylated and one hypo-methylated. Three of these sites showed the same direction of methylation change in a subset of the participants at age 10 years. Pathway analyses highlighted that certain implicated genes, including *Npy2r* and *Scap*, are associated with obesity and type 2 diabetes.

**Conclusions:** The total duration of breastfeeding and duration of exclusive breastfeeding is associated with changes in blood DNA methylation at 18 years of age. Associated CpGs included those in genes known to be involved in obesity, metabolism and insulin control. This supports the hypothesis that DNA methylation could mechanistically underlie the long-term effects of breastfeeding, including well-known protection against obesity, although other mechanisms are also likely to be involved.

**PA3.14.05**

**Horvath DNA methylation biological age at the transition from adolescence to adulthood: A measure of dynamic response to environmental stress**


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**Background:** Blood DNA methylation age (DNAmAge) (Horvath) predicts death in the elderly. Change of clock CpG methylation occurs logarithmically in childhood, before slowing to linear dependence in adulthood. Rate of change is also highly heritable. Therefore, we hypothesize that DNAmAge in late adolescence may predict disease risk, and be influenced by parental factors. We investigated if DNAmAge at age 17 years was associated with cardio-metabolic risk factors at 17, 20 and 22 years, and with childhood growth trajectories. Also, we aimed to understand parental factors influencing DNAmAge.

**Methods:** DNA methylation was measured in 1,260 peripheral blood (58 replicates) samples from participants in the Western Australian Pregnancy Cohort (Raine study) at age 17 years-old using the HumanMethylation450K BeadChip. 710 participants (52% males, chronological age 17.0 ±0.2 years) completed a full clinical examination at the 17-year follow-up. The Horvath calculator was applied to beta-mixture quantile-normalised 450K data to calculate BioAge4HO, defined as weighted averages based on four epigenetic inputs. Robust linear models were fitted, assessing associations between DNAmAge with cardio-metabolic risk factors, including covariates of chronological age, gender and cell correction. Similarly, linear models were fitted to assess whether parental factors associated with DNAmAge.

**Results:** Classic cardio-metabolic risk factors (BMI, waist circumference, fasting triglycerides, LDL, HDL, systolic and diastolic blood pressure) were not associated with BioAge4HO (a generalized measure of DNAmAge). However, fasting serum insulin mU/L (β = 0.15, p = 0.003), HOMA (β = 0.15, p = 0.004) and the metabolic cluster (β = 0.55, p = 0.025) were associated with DNAmAge. No association was detected with visceral fat, but there was an association with subcutaneous fat (cm) (β = 0.12, p = 0.018) and skin-fold thickness (mm) (suprailiac β = 0.08, p = 0.004; abdominal β = 0.76, p = 0.003; subscapular β = 0.06, p = 0.005). A positive association was noted with serum leptin (μg/L) (β = 0.23, p = 0.001), but not with adiponectin (β = 0.07, p = 0.088), or other circulating inflammatory markers. These associations did...
not persist 3 or 5 years subsequently. Predictors of advanced DNAmAge, included lighter placenta weight (kg) ($\beta$ = -28.4, $p$ = 0.015), accelerated childhood growth trajectories (OR = 1.15, $p$ = 0.013) and greater number of maternal IDF metabolic factors ($\beta$ = 0.34, $p$ = 0.031). Non-significant trends for DNAmAge with birthweight (g) (higher in father ($\beta$ = 130, $p$ = 0.077) and lower in mothers ($\beta$ = -91, $p$ = 0.072)) were observed.

Conclusions and Discussion: DNAmAge is associated with subcutaneous fat deposition and increased insulin, only at the measured time-point. This suggests that DNAmAge indicates activity of an epigenetic maintenance system, which is increased in response to environmental stress. Unlike the elderly, where environmental stress predicts death, in the young, work done by an epigenetic maintenance system may reflect beneficial coping (preferential deposition in subcutaneous rather than metabolically harmful visceral fat, and increased insulin production to maintain glucose homeostasis), that is potentially reversible prior to end-disease, such as type 2 diabetes mellitus. Accelerated DNAmAge was associated with smaller placental size and accelerated growth from below average birth-size and maternal risk factors, supporting its inter-generational transmission. Further work is required to understand how influences on the level of activity of an epigenetic maintenance system are partitioned between shared environment and fixed genetics.

PA3.14.06
Telomere length: Population epidemiology and concordance in 11-12 year old Australians and their parents.

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Background: Telomeres function to protect DNA integrity and prevent fusion of adjoining chromosomal ends. Telomere shortening has been associated with morbidity and mortality from both communicable and non-communicable diseases, including cardiovascular disease, hypertension and diabetes. Telomere length is partly heritable, although the extent to which it is influenced by genetics and environmental factors is unclear. Relatively little is known about normative telomere lengths in healthy individuals, especially in children. In the Child Health CheckPoint study, a population-derived cross-sectional sample within the Longitudinal Study of Australian Children, we aimed to (1) describe child and adult telomere length epidemiology, and (2) investigate parent-child telomere length concordance.

Methods: The study’s data collection phase ran from February 2015 to March 2016. Data were collected across Australia in main (major cities) and mini (regional cities) assessment centres, with home visits offered to those who couldn’t attend an assessment centre. Children and their attending parent rotated through a series of physical and biomarker stations, from “Young Blood” (venous blood collection) to “Measure up” (height and weight measurement). Relative telomere length (T/S ratio) was calculated by comparing telomeric DNA (T) level to the single copy (S) beta-globin gene in venous blood-derived genomic DNA by quantitative real-time PCR. Child and adult telomere length distributions were examined using means and standard deviations and density plots. Parent-child telomere length concordance was assessed using linear regression models. All models were minimally adjusted for parent age, parent sex and child sex. As a secondary analysis, we investigated parent-child telomere length concordance by tertiles of parent age and using interaction analysis.

Results: Telomere length data was obtained for 2529 individuals (1199 children and 1330 parents), including 1143 parent-child pairs used for concordance analyses. Mean T/S ratio for all children, boys and girls was 1.09 (SD 0.55), 1.08 (SD 0.53) and 1.11 (SD 0.57), respectively. Mean T/S ratio for all parents, fathers and mothers was 0.81 (SD 0.38), 0.86 (SD 0.47) and 0.80 (SD 0.36), respectively. For every unit increase in parent T/S ratio, the child’s increased by 0.36 ($p$ < 0.001). Father-child concordance was stronger than mother-child concordance ($\beta$ = 0.46 vs. $\beta$ = 0.34). Parent-child concordance was higher in the youngest parent group than the middle and oldest group ($\beta$ = 0.49, $\beta$ = 0.35 and 0.26, respectively). Father-child concordance was higher in the youngest father group than the middle and oldest group ($\beta$ = 0.83, $\beta$ = 0.48 and 0.18, respectively). Mother-child concordance was higher in the youngest mother group than the middle and oldest group ($\beta$ = 0.43, $\beta$ = 0.32 and 0.28, respectively). Father-child concordance was higher than mother-child concordance for all parental age tertiles.

Conclusions: As expected, T/S in adults was shorter than in children. There was modest evidence of parent-child T/S concordance, which was stronger in father-child than mother-child pairs. Interestingly, there was evidence for stronger parent-child concordance in younger parents with the concordance decreasing with increasing parent age.

PA3.14.07
A case/control study of epigenome-wide DNA methylation in infants with cleft lip and palate in California

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Background: Cleft lip with or without cleft palate (CLP) is among the most frequent of human birth defects, occurring in 1 in 940 births in the U.S. Etiologies of CLP remain elusive. The etiologic role of 1-carbon metabolic factors such as folate is debated, and recent genetic analyses of CLP by our group support a role for rare variants in folate metabolism pathways. Here, we provide the first large-scale epigenome-wide DNA methylation analysis of CLP. Our analytic goal was to identify constitutive epigenetic differences between CLP cases and nonmalformed control infants at birth using a hypothesis-free approach.

Methods: CLP cases and nonmalformed controls were identified by the active surveillance program—California Birth Defects Monitoring Program. Included for study were 94 CLP cases and 88 controls from California infants born 1988-1996, prior to folate fortification. DNA methylation levels of cases and controls were assessed from infant’s newborn blood spots and analyzed with the Illumina® Human Beadchip 450K array. Differentially methylated positions (DMPs) and differentially methylated regions (DMRs) were discovered by epigenome-wide associations studies (EWAS) and bump hunting (BH) methods while stratifying by Hispanic ethnicity. BH results were further validated by DMRcate—another DMR finding method. Models were adjusted for cell-mixture using Refactor and ancestry using Epistructure. Bootstrapping was used to identify significant and replicating DMPs and DMRs in both Hispanic and non-Hispanic ethnic groups.

Results: Seventy-four Hispanic cases, 69 Hispanic controls, 20 NonHispanic cases, and 19 NonHispanic controls were analyzed. Among total CpG sites assessed, cases were significantly less methylated than controls (61% of associations were negative in Hispanics and 62% in nonHispanics, Chi-square’s p for both <0.001). The most significant DMPs concordant in both ethnic groups were cg23874078 (in CEPTT), cg24317002 (in LRRCC1), cg16852767 (in PCF11), cg07779777 and cg14017045 (both in ZBTB7A), all less methylated in cases than in controls (all with bootstrap p <0.01 in both ethnic groups). A region encompassing VTRNA2-1 (5q31) was concordantly less methylated in cases than in controls in both ethnic groups (FWER p = 0.014 in BH and <0.0001 in DMRcate, see Figure).

Discussion: CLP cases showed decreased DNA methylation globally, suggesting exposure to a restricted amount of methyl-donors such as folate or other 1-carbon metabolism cofactors, from maternal intake or genetic variants in relevant pathways. Additionally, the observed decreased DNA methylation in VTRNA2-1—a metastable epiallele whose DNA methylation was previously shown to be sensitive to maternal dietary intake of 1-carbon metabolism cofactors at the time of conception in a Gambian study—further supports the evidence base for women’s intake of 1-methyl carbon donors before conception and during the pertinent embryonic development period for clefting.

Differentially methylated region of VTRNA2-1 (aka MIR-886) according to cleft status.

PA3.14.08

Hypertensive disorder of pregnancy and DNA methylation of newborns: Findings from the Pregnancy and Childhood Epigenetics (PACE) Consortium

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Background: Hypertensive disorders of pregnancy (HDP), including gestational hypertension (hypertension detected between 20 weeks of gestation and delivery) and pre-eclampsia (PE; gestational hypertension in addition with at least one episode of proteinuria), are associated with both maternal and neonatal morbidity. The mechanisms by which such disorders associate with adverse offspring outcomes at birth and later in life remain poorly understood, but epigenetics may offer one potential explanation.

Methods: We performed a meta-analysis across ten independent cohorts (n = 5229) from the Pregnancy And Childhhood Epigenetics (PACE) Consortium to test the association between maternal HDP and epigenome-wide DNA methylation in cord blood measured using the Illumina Human Methylation450 Beadchip. We also investigated changes in birth-related methylation during childhood (age 7-9 years) and adolescence (age 15-17 years) in participants from the Avon Longitudinal Study of Parents and Children (n = 658).
Results: In models adjusted for estimated cell counts and covariates (maternal age, parity, maternal smoking status, gestational diabetes, maternal pre-pregnancy BMI and offspring sex), maternal HDP and PE were associated with neonatal DNA methylation at 1075 and 542 sites respectively at a false discovery rate 5% including 43/1075 and 26/542 sites using a more stringent Bonferroni corrected threshold (p < 1.05 × 10^-7, 473,864 tests). There were five Bonferroni significant sites common between fully adjusted models of HDP and PE. We found 93 and 43 regions where there were multiple differentially methylated CpGs in association to HDP and PE respectively (for example DLEU7, RPTOR, PPT2, STRA6, PLCH1, AVP and ARID3A). 10/43 and 7/26 Bonferroni significant sites identified in relation to HDP and PE were in (or near) genes that were previously been associated with early onset preeclampsia with similar direction of association. A majority of the associations identified here have been previously reported in studies of birth weight, preterm birth and gestational age and with consistent direction of association. Methylation differences over time in offspring exposed or unexposed to maternal HDP were also explored but neither HDP nor PE was strongly associated with methylation at adolescence. These results might suggest resolution of differential methylation by early childhood or a small sample size (n = 658) was underpowered to detect differential methylation at adolescence.

Conclusion: In this large-scale meta-analysis, we identified associations of maternal HDP with DNA methylation at several loci in the blood of newborns. Our findings suggest that differential methylation may mediate associations between HDP/PE and offspring health.

PA3.14.09

Epigenetic marks in neonates are associated with BMI and insulin sensitivity in early childhood

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Background: Epigenetic marks present at birth have been implicated in early life origins of disease, and may have the potential to predict an individual’s future risk of obesity and type 2 diabetes. While animal studies have linked stable epigenetic alterations induced by environmental perturbations in utero with an increased risk of obesity and metabolic diseases, whether there are specific epigenetic markers that are linked to future risk of these diseases in humans is less clear. Here we report a number of DNA methylation regions at birth that are associated with obesity or insulin sensitivity measurements in childhood.

Methods: DNA methylation was measured in blood spot samples of 439 children within 3 days of birth. At 5 years of age, these same children were assessed for associations between their DNA methylation status at birth and BMI z-scores, body fat mass, fasting plasma glucose, insulin and HOMA-IR.

Results: DNA methylation in 69 genomic regions at birth was associated with BMI z-scores at age 5 years, and in 63 regions with HOMA-IR. The methylation changes were generally small (<5%), except for a region near the non-coding RNA VTRNA2-I, where a clear link between methylation status at birth and BMI in childhood was observed (P = 0.001). No individual methylation sites at birth were associated with obesity or insulin sensitivity measures at 5 years. Associations between DNA methylation, maternal smoking, and birth weight were also found.

Conclusions: These findings provide further support that epigenetics have a role in programming of obesity and metabolic health. Whether many of these small changes in DNA methylation are causally related to the health outcomes, and of clinical relevance remains to be determined, but the VTRNA2-I region seems a promising obesity risk marker that warrants further investigation.

PA3.15 - Cardiovascular and diabetes risk

PA3.15.01

Cardiac remodeling in preadolescents who suffered fetal growth restriction

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Background: Fetal growth restriction (FGR) affects 5% to 10% of newborns and is associated with increased cardiovascular mortality in adulthood. We have previously demonstrated the presence of cardiovascular remodeling in fetuses and children with FGR.

Aim: To evaluate the persistence of cardiovascular remodeling in preadolescents with fetal growth restriction that were previously evaluated in childhood and further evaluate the presence of electrical changes at preadolescent age.

Methods: A cohort study of 58 FGR (defined as birth weight below 10th centile) and 94 normally grown fetuses (controls) identified in utero and followed up to preadolescent age (10-14 years of age). Cardiac remodeling and function was evaluated by conventional echocardiography, computational left ventricular shape analysis, 2D strain and electrocardiography (EKG). Vascular remodeling was assessed by carotid intima media thickness measured by ultrasound.
Results: Compared with controls, preadolescents born after FGR had a different cardiac shape, with more spherical and smaller hearts. Left ventricular ejection fraction was similar among groups, while FGR had decreased longitudinal ventricular motion (decreased mitral annular excursion and annular peak velocities: controls m/s 0.11 (0.01) vs FGR m/s 0.09 (0.01), p < 0.0001) and impaired relaxation (isovolumic relaxation time: controls 0.21 ms (0.03) vs FGR 0.35 ms (0.02), p < 0.001). In addition, ventricular deformation was also altered with a decreased global longitudinal strain (controls -22.4% (1.37) vs FGR -21.5% (1.16), p < 0.001) compensated by an increased circumferential strain and with a higher prevalence of post-systolic shortening in FGR as compared to preadolescent controls. In addition, the timings in the EKG were shorter in FGR when compared to controls (P wave: 86.17 ms (11.83) vs 79.82 ms (13), PR interval 140 ms (30) vs 120 (27)) and QRS wave: 100 ms (25) vs 90 ms (15)). The initial increment in the EKG was higher prevalence of post-systolic shortening in FGR as compared to preadolescent controls. In addition, the timings in the EKG were shorter in FGR when compared to controls (P wave: 86.17 ms (11.83) vs 79.82 ms (13), PR interval 140 ms (30) vs 120 (27)) and QRS wave: 100 ms (25) vs 90 ms (15)). The initial increment in the EKG was shorter in FGR when compared to controls (P wave: 86.17 ms (11.83) vs 79.82 ms (13), PR interval 140 ms (30) vs 120 (27)) and QRS wave: 100 ms (25) vs 90 ms (15)). The initial increment in the EKG was shorter in FGR when compared to controls (P wave: 86.17 ms (11.83) vs 79.82 ms (13), PR interval 140 ms (30) vs 120 (27)) and QRS wave: 100 ms (25) vs 90 ms (15)). The initial increment in the EKG was shorter in FGR when compared to controls (P wave: 86.17 ms (11.83) vs 79.82 ms (13), PR interval 140 ms (30) vs 120 (27)) and QRS wave: 100 ms (25) vs 90 ms (15)). The initial increment in the EKG was shorter in FGR when compared to controls (P wave: 86.17 ms (11.83) vs 79.82 ms (13), PR interval 140 ms (30) vs 120 (27)) and QRS wave: 100 ms (25) vs 90 ms (15)).

Conclusions: In our cohort, cardiac but not vascular remodeling induced by FGR persists until preadolescence. Electrical changes were also observed at preadolescent age. The findings support the hypothesis of primary cardiac programming in FGR underlying the association between low birthweight and increased cardiovascular risk in adulthood.

Cardiac function (strain, upper panel) and structure (shape, lower panel) in fetal growth restricted and adequate for gestational age preadolescents

PA3.15.02

GLP-1 profile during glucose tolerance test in gestational diabetes: a prospective case-control study

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Background: Glucagon like peptide-1 (GLP-1) is an incretin hormone which is responsible for around two-thirds of the insulin response after an oral glucose load. GLP-1 concentrations are reduced by 20 to 50% in type 2 diabetes but studies in women with gestational diabetes mellitus (GDM) are inconclusive. Our aim was to study the GLP-1 profile during a 2-hour 75g glucose tolerance test (GTT) at GDM diagnosis.

Methods: A prospective case-control study of high-risk pregnant women selectively screened to undergo a GTT was conducted. Plasma samples for GLP-1 were collected, after addition of a dipeptidyl peptidase-4 inhibitor inhibitor, at 30 minute intervals during the GTT and analysed by radioimmunoassay. GDM was diagnosed according to the UK NICE guidelines (glucose0min ≥5.6mmol/l or glucose120min ≥7.8mmol/l). Pregnancy history and maternal anthropometric data were recorded in early pregnancy and at time of GTT. Statistical analysis was done by analysis of variance (ANOVA) for comparison of means and multivariate linear regression to determine predictors of glucose120min.

Results: 145 women were recruited into the study at a mean of 26+6 weeks gestation. Of these, 19 went on to develop GDM (glucose120min range 7.8 to 12.1 mmol/l). 19 controls, with the lowest glucose120min values in our cohort (range 4.0 to 4.5mmol/l), were identified. GDM women had higher baseline body mass index (BMI), waist circumference, glucose0min and glucose120min but similar triceps and subscapular skinfold thickness and gestational weight gain. GLP30min concentrations were significantly lower in GDM women than controls after adjusting for age, ethnicity, smoking and BMI (unadjusted p = 0.01, adjusted p = 0.04) (Image). GLP-1 total area under the curve (AUC) was reduced by 13% in GDM (adjusted p < 0.05) but mean GLP-1 and incremental AUC were similar. Aside from glucose0min, GLP30min was a predictor of glucose120min in regression models that adjusted for the above confounders and gestational weight gain (β-coefficient -0.31, p = 0.02). There were no associations between GLP-1 levels at other time-points and any glucose parameters.

Conclusion: Our findings suggest that early GLP-1 response, measured by GLP30min, is reduced by 20% in GDM and it independently predicts higher glucose levels at 120 minutes after a GTT. This suggests a novel mechanism to explain the pathogenesis of GDM and could be a target of future interventions.
PA3.15.03

The role of maternal and offspring lifestyle behaviours in the relationship between depression and adiposity in young adults

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Background: The increasing incidence of overweight and obesity in children and adolescents has been paralleled by an increase in mental health disorders. Obesity often co-occurs with depression in children and adolescents, and more than one-third of adults with depression symptoms are obese. The nature of the depression-obesity association is likely complex, with possible common underlying familial and environmental influences. For example, maternal smoking in pregnancy has been independently associated with both offspring obesity and childhood behavioural problems. This study aimed to investigate the influence of antenatal and postnatal factors that may underlie any association between adiposity and depressive tendencies in young adults, with a focus on maternal smoking in pregnancy, socioeconomic status and gender.

Methods: Data from the Western Australian Pregnancy Cohort (Raine) Study including 1056 adults aged 20 years were analyzed using multivariable models for associations between offspring depression scores (DASS-21 Depression scale) and body mass index (BMI), adjusting for pregnancy and early life factors and offspring behaviours.

Results: Males had lower average depression, anxiety and stress scores compared with females. Depression diagnosed by a medical practitioner was reported in 16% of the participants. In these participants depression scores were 8.25 units (P < 0.001) higher compared with those not clinically diagnosed with depression. Multivariable regression analysis showed a significant interaction between maternal prenatal smoking and depression-score (interaction coefficient = 0.096; P = 0.037), indicating the relationship between depression scores and BMI differed according to the maternal prenatal smoking status. A positive association between BMI and Depression score in offspring of maternal prenatal smokers (coefficient = 0.133; P = 0.001) was independent of gender and hormonal contraceptive use in females, maternal age, and pre-pregnancy BMI. It equated to 1.1kg/m² increase in BMI for every 1 SD (8 units) increase in depression score. There was no significant association between BMI and Depression score in offspring of mothers that did not smoke in pregnancy. Substituting low family income during pregnancy for maternal prenatal smoking in the interaction (interaction coefficient = 0.091; P = 0.027) showed a positive association between BMI and depression score only among offspring of mothers with a low family income during pregnancy (coefficient = 0.118; P < 0.001). There were no significant differences between genders in these associations.

Conclusion: These findings indicate important maternal behavioural and socioeconomic factors that identify individuals vulnerable to the coexistence of obesity and depression in early adulthood. Identifying those most at risk of the co-association of adiposity and depressive symptoms is a public health priority which will need to be tackled at a societal level.

PA3.15.04

Life course evolution of body fat and its association with insulin resistance among rural Indian boys and girls

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Introduction: Indians have a “thin-Fat” body composition which predisposes them to increased risk of diabetes. Cross-sectional studies show association of adiposity with insulin resistance and diabetes at different ages. However, there are few studies of serial measurements of body composition by reference techniques. PMNS is a pre-conceptional birth cohort with serial information on children from birth to 18y of age and body composition (DXA) measurements at 6, 12 and 18y. This provides an unique opportunity to establish evolution of whole and regional body fat patterns in an undernourished contemporary rural Indian cohort and its association with insulin resistance.

Methods: PMNS children were serially followed up from birth to 18y for body size measurements (anthropometry). Insulin resistance (HOMA-R) and body composition (Lunar- DXA machines) were measured at 6, 12 and 18y. We studied patterns of serial body fat deposition and explored its association with insulin resistance.

Results: We studied 356 boys and 306 girls. Their average birth weight was 2.6 kg, 74% were SGA by INTERGROWTH criteria, none were LGA. Eleven percent children were born preterm. At 18y, boys weighed 57 kg and girls 46 kg; 50% were underweight (BMI <18.5 kg/m²), 5% were overweight (WHO 1995). At all ages boys were taller, heavier and had higher lean and bone mass, while girls had higher skinfolds and fat mass. From 6y to 18y, body fat % remained constant in boys (~17% of weight) while in girls there was a substantial increase between 12y and 18y (20 to 29%). In both genders distribution of body fat in trunk, arms and legs remained relatively constant between 6y and 12y. Between 12y and 18y there was an increase in the trunk fat % in both genders, leg fat % increased in girls. On MLRA, body fat % at 18y was more related to fat gain from 12y to 18y (19% variance) than 6 to 12y (10% variance). SGA girls had significantly higher fat % at 12y and 18y (21.4 Vs 18.3% and 30.1 Vs 27.7%, respectively p <0.05 all). Preterm girls had higher fat % at 6y and 12y (22.2 Vs 20.3%, 21.9 Vs 18.6%), There were no differences in boys. Insulin resistance progressively increased from 6y to 18y (0.6 to 1.4 HOMA units). Higher insulin resistance at 18y was predicted by lower skinfolds at birth and lower fat% at 6y, but higher fat % at 18y. Higher insulin resistance was associated with higher trunk but lower leg fat. These associations were independent of gestational age, birth weight, breast feeding practices and pubertal development.

Conclusion: Our results provide first description of life-course evolution of body fat patterns in a relatively undernourished
population. SGA and preterm children were more adipose as adults. Smaller fat at birth and in childhood coupled with pubertal fat gain predicted higher insulin resistance. Trunk and leg fat have independent, opposite association with insulin resistance.

PA3.15.05
Maternal circulating PlGF levels in relation to insulin sensitivity and β-cell function in infants born small-for-gestational-age
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Background: Small-for-gestational-age (SGA) infants are at increased risk of type 2 diabetes in adulthood. There is a lack of biomarkers for phenotyping SGA infants regarding future metabolic health. We assessed whether third-trimester maternal circulating placenta growth factor (PlGF), an indicator of placental function, is associated with insulin sensitivity and β-cell function in SGA infants.

Methods: This was a nested study in a large prospective pregnancy cohort (the 3D cohort), including 162 SGA (birth weight <10th percentile) and 161 randomly selected AGA (appropriate-for-gestational-age) control singleton infants matched by gestational age, maternal ethnicity and smoking status. The primary outcomes were homeostasis assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) in infants at 2-y.

Results: Maternal plasma PlGF concentrations at 32-35 weeks’ gestation were substantially lower in SGA versus AGA infants (median, 444.1 vs. 825.6 pg/ml, P < 0.0001). Maternal PlGF was positively correlated with cord plasma insulin-like growth factor-1 (IGF-1) (r = 0.29, p < 0.0001), and tended to be positively correlated to HOMA-β at 2-y (r = 0.16, p = 0.08). Adjusting for pregnancy, delivery and infant characteristics, each log unit increase in maternal plasma PlGF concentration was associated with a 13% increase in HOMA-β (P = 0.038). SGA newborns with low maternal PlGF levels (<25th percentile) tended to have lower HOMA-β (adjusted P=0.058) than AGA infants at birth, but there were no differences in HOMA-IR and HOMA-β at 2-y.

Conclusions: Higher maternal circulating PlGF levels were associated with better β-cell function in infants at 2-y. However, maternal PlGF alone could not phenotype SGA infants in terms of metabolic health status at 2-y of age.

PA3.15.06
Prenatal environmental exposure and child blood pressure: an exposome-wide approach in HELIX project
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Background: Cardiovascular disease is one of the leading causes of death and high blood pressure (BP) is a major contributing factor. Until recently, control and prevention of hypertension mainly concerned adults, but studies now report that children with elevated BP are more likely to become hypertensive adults, showing the relevance of BP control earlier in life. The rapid rises in the prevalence of children with high BP that have been documented, are of particular concern and there is growing evidence about the fetal origins of hypertension.

A number of individual risk factors for high BP have been identified and there is emerging evidence that environmental exposures may be important risk factors. However, results to date have been heterogeneous and have been limited primarily by the lack of a global view of how a broad suite of correlated exposures (commonly referred to the exposome) jointly impact on the development of high BP during critical developmental periods. This study aims to evaluate the effect of the prenatal exposome on child BP.

Methods: This study is part of the HELIX project which followed 1,300 children at 7-10 years old, from 6 European cohorts. Diastolic and systolic BPs were measured during the clinical examination of the child using a standardized protocol. A wide range of prenatal exposures (>90) were evaluated including the outdoor exposome (air pollution, built environment, meteorology, natural spaces, traffic, and noise) assessed by geographic information system, the individual exposome (metals, persistent organic pollutants, pre- and polyfluoroalkyl substances, phthalates, phenols, organophosphates, and cotinine) assessed by biomarkers, as well as lifestyle factors (maternal diet, physical activity) assessed by questionnaire. As a first statistical analysis, linear regression models were used to assess the associations between each prenatal exposure and child BP, adjusted for potential confounders. The threshold for statistical significance was set to 0.05 and estimates and their 95% confidence interval (CI) were calculated for a change in the interquartile range of exposure.

Results: We observed significant increases in systolic BP with outdoor temperature during pregnancy (β[95% CI] = 2.4 [0.9;3.9]), concentrations of caesium (1.3[0.2;2.4]), concentrations of bisphenol-A (1.1[0.3;1.9]), and fish intake (1.1[0.2;1.9]), and significant decreases with some markers of the built environment (eg, walkability index: -1.4[-2.4;-0.4]), concentrations of polychlorinated biphenyl 138 (-1.2[-2.2;-0.3]) and concentrations of mono-4-methyl-7-hydroxyoctyl phthalate (-0.5[-1.0;-0.04]). Significant increases in diastolic BP were also observed with outdoor temperature (2.1[0.6;3.5]), concentrations of caesium (1.6 [0.6;2.6]) and bisphenol-A (0.8[0.1;1.6]) as well as a significant decrease with increasing outdoor humidity (-3.2[-6.1;-0.3]). Few findings remained significant after correction for false discovery rate.

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Conclusions: Exposure to several environmental exposures during pregnancy, including meteorological conditions, built environment markers, and some chemicals contaminants, was associated with child BP. These results should be confirmed by further statistical analyses to account for multiple co-exposures using variables selection models, and to include postnatal environmental exposures. Quantifying the potential contribution of early-life environmental exposures to child BP is of critical importance since some exposures are modifiable (through individual behaviors or government regulation) and early intervention has the potential for significant benefits in reducing cardiovascular disease risk.

PA3.15.07

Ideal cardiovascular health and intermediate risk phenotypes in child-parent dyads: the Longitudinal Study of Australian Children

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Background: The concept of ideal cardiovascular (CV) health, first introduced by the American Heart Association (AHA) in 2010, summarises seven health behaviors (body mass index, physical activity, non-smoking, and diet) and factors (blood pressure, glucose, and cholesterol levels) that are first established in childhood. We investigated the association between ideal CV health and intermediate CV risk phenotypes in a population-based sample of 11-12 year old Australian children and their mid-life parents.

Methods: Data from 1874 families participating in the cross-sectional Child Health CheckPoint, nested within the Longitudinal Study of Australian Children, were obtained during a single assessment center visit and used to generate ideal CV health scores. We used pre-defined cut-offs to dichotomise participants into ideal, or non-ideal health for each CV metric; the sum of ideal health over seven metrics determined their ideal CV health score, ranging from 0 (poor health) to 7 (ideal health). This score was used as a quasi-continuous exposure in linear regression models to predict three intermediate cardiovascular risk outcomes – carotid intima-media thickness, carotid-femoral pulse wave velocity, and carotid artery elasticity – separately in children and parents. Complete case analysis was used to generate these data, and will be supplemented with multiple imputation to account for potential bias from missing data in final analysis.

Results: Ideal CV health (score of 7) was found in 6.6% of children and 1.0% of their parents; 76.9% and 30.5% respectively had a score of 5 or higher. Parent non-ideal health was associated with child non-ideal health in each of the seven metrics except physical activity (odds ratios from logistic regression ranged from 1.56-10.83 in analyses adjusted for child and parental age, sex and socioeconomic position). Ideal CV health score strongly predicted CV outcomes in parents ($P < 0.001$) and children ($P < 0.002$, except for child carotid intima-media thickness ($P = 0.74$)) (Figure). In multivariable analyses, blood pressure and body mass index status predicted intermediate cardiovascular risk outcomes independently of other ideal CV health factors and behaviors, and potential confounders such as age, sex, and socioeconomic position. Associations in parents explained more variance in outcomes than in children ($R^2$ in parents 0.21-0.32, compared to $R^2$ in children 0.01-0.11).

Conclusion: Ideal cardiovascular health is infrequent even in mid-childhood, and is rare with increasing age. Even by 11-12 years of age, lower ideal CV health scores predict worse intermediate CV risk phenotypes, suggesting that early life interventions, especially addressing childhood hypertension and obesity, are required to reduce the growing burden of CV disease. Moreover, our observation that both structural and functional phenotypes are associated in adulthood, but only functional phenotypes are associated in childhood imply that there is an opportunity to prevent structural vascular changes in mid-childhood.
Ideal Cardiovascular health score predicting intermediate cardiovascular risk phenotypes in parents (light grey) and children (black)

PA3.15.08

Maternal treatment with the mitochondria-targeted antioxidant MitoQ prevents the programming of cardiac dysfunction in adult offspring by developmental hypoxia

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Background: Pregnancy complicated by chronic fetal hypoxia programmes cardiac dysfunction in the adult offspring via mechanisms including oxidative stress (Giussani et al. PLoS One. 2012; 7(2):e31017; Xue et al. J Pharm Exp Ther. 2009; 330(2): 624; Rueda-Clausen et al. Card Res. 2009; 81(4): 713). We showed that maternal treatment with high doses of the antioxidant vitamin C in hypoxic pregnancy prevents this developmental programming of cardiovascular dysfunction, providing proof of principle on possible intervention (Giussani et al. PLoS One 2012; 7(2):e31017). However, high doses of vitamin C can cause oxaluria and kidney stones in humans (Massey et al. J Nutr. 2005; 135(7):1673), thereby offering little clinical translational value. Since mitochondria are the major site of reactive oxygen species generation, targeting them specifically in complicated pregnancy may offer better translational value for human clinical intervention. Here, we investigated whether maternal treatment with MitoQ, a mitochondria-targeted antioxidant, can prevent the cardiac dysfunction programmed by developmental hypoxia using our established rodent model.

Methods: Female Wistar rats (n = 40) were randomly divided into normoxic (N: 21% O₂) or hypoxic (H: 13% O₂) pregnancy, with or without maternal treatment with MitoQ (1 mg/Kg/day in drinking water) from days 6-20 of gestation. This experimental model of hypoxia does not affect maternal food intake. At birth, litters were culled to 8 pups (4 males and 4 females) and weighed weekly. At 4 months, following euthanasia, hearts were isolated from 1 male per litter to control for sex and within-litter differences and cardiac function was examined in a Langendorff preparation.

Results: Adult offspring from hypoxic pregnancy showed elevated left ventricular end diastolic pressure (LVEDP, Figure 1A), enhanced left ventricular contractility index (Figure 1B) and cardiac sympathetic dominance (Figure 1C). Maternal treatment with MitoQ in hypoxic pregnancy restored all indices of cardiac dysfunction towards control levels. At 4 months, there was no difference in body weight or heart weight between offspring from untreated or treated hypoxic or normoxic pregnancy.

Conclusions: Maternal treatment with the mitochondria-targeted antioxidant MitoQ protects against cardiac dysfunction at adulthood programmed by developmental hypoxia.

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PA3.15.09

Fish-oil supplementation in pregnancy causes a proportional increase in body bone-fat-, and lean- mass at 6 years: Randomized, Controlled, Double-Blind, Clinical Trial

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Background: Some observational studies suggest that maternal fish intake during pregnancy affect offspring growth during childhood, but the findings are ambiguous. Therefore, we examined the effect of fish oil supplementation in pregnancy on anthropometrics and body composition during childhood in a large randomized trial.

Method: This was a single-center, double-blind, randomized controlled trial conducted among 736 pregnant women and their offspring, participating in the Copenhagen Prospective Studies on Asthma in Childhood2010 (COPSAC2010) mother-child cohort. The women were recruited in pregnancy week 24 and randomized to capsules containing either 2.4g of n-3 long-chained polyunsaturated fatty acids (fish oil) or control (olive oil) daily until one week after birth. We investigated the effect of fish oil on development of length/height, weight, head and waist circumference from 0-6yrs and body composition determined by dual-energy X-ray absorptiometry (DXA) scans at 3.5yrs and 6yrs (secondary end-points in the study design).

Results: The fish oil supplementation resulted in significantly higher mean z-score BMI from 0-6 years compared to control: β-coefficient 0.14; 95% confidence interval (CI) [0.03; 0.15]; p = 0.006. This led to higher z-score BMI at age 6yrs (mean difference fish oil vs. control: 0.19; 95% CI [0.06; 0.32], p = 0.004) and a larger waist circumference (0.64cm; 95% CI [0.02; 1.21], p = 0.04), but not a higher proportion of children in risk of obesity (5% (N = 16) vs 3% (N = 14), p = 0.89). The DXA scan at age 6 years showed a higher fat free mass in the fish oil vs. control group (height-adjusted mean difference: 304g (95% CI [102; 507]), p = 0.003), a higher bone mineral content (13g (95% CI [5; 21]), p = 0.002), and a higher bone
mineral density (0.01g/cm² (95% CI [0.00; 0.01]), p = 0.02). However, no difference in total body fat percentage (0.13%, (95% CI [-0.76; 1.02]), p = 0.78.

**Conclusion:** Fish oil supplementation from 24th week of pregnancy led to an increased BMI from 0-6 years of age characterized by a body composition at age 6 years with a proportional increase in lean mass, bone mass and fat mass and no increase in obese children or children at risk of obesity

**Trial Registration:** ClinicalTrials.gov: NCT0079822

**LM3.01.01**

**How to write a paper for a high impact journal**

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Writing a paper that presents and describes your research findings in a way that is appealing to a broad scientific audience can be a challenge. Only a small percentage of scientific papers ultimately get published in high-impact journals. How can researchers increase their chances? What are the do’s and don’ts? In this workshop, Dr. Julie Ingelfinger, Deputy Editor at the New England Journal of Medicine, will discuss how to approach writing a manuscript that aims for publication in a high-impact journal. Dr. Ingelfinger is Professor of Pediatrics and Senior Consultant in Pediatric Nephrology at Harvard Medical School and MassGeneral Hospital for Children at MGH in Boston. Besides her current position as Deputy Editor of the New England Journal of Medicine, Dr. Ingelfinger has been a member of the Editorial Board of multiple international scientific journals including Pediatrics, Hypertension, American Journal of Physiology and Pediatric Nephrology.

**LM3.02.01**

**Klotho’s effects on cognition and brain in early life**

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**Background:** Variation in the klotho (KL) gene is linked to differences in health outcomes: KL allele KL-VS heterozygosity is associated with longevity, improved health, cognition and greater right frontal grey matter volume in late life. However, some reports contradict these benefits, and suggest that KL-VS’s effect on health might be age-dependent. Here we examine the relationship between KL-VS genotype, cognition and brain in early life, and whether any links with KL-VS were moderated by age, sex or socioeconomic circumstance.

**Methods:** We investigated the associations of KL-VS carrier status in 1379 children and adolescents between the ages of 3 to 21 years in the Pediatric Imaging, Neurocognition and Genetics (PING) cohort. General linear modelling examined differences in cognition, total brain volume, grey matter volume and white matter volume (corrected for total intracranial volume). Differences in regional brain volumes, cortical thickness and surface area were examined using the PING data portal.

**Results:** KL-VS × age was significantly associated (p <.05) with cognition, total grey matter volume, and total brain volume. KL-VS heterozygotes had higher cognition than non-carriers before age 11, but lower cognition after age 11. Heterozygotes have smaller brains than non-carriers do in early childhood, but catch up when older. KL-VS × sex was significantly associated with total white matter volume. Among girls, KL-VS heterozygotes had smaller total white matter volumes than non-carriers. Among boys, heterozygotes had greater white matter volumes than non-carriers. No other brain differences were found.

**Conclusions:** In early life, KL-VS’s effect on cognition and brain development is influenced by a person’s age and sex, but not by socioeconomic circumstance. Our results suggest that previous contradictory reports may be explained by differences in sex and/or the age range of the samples. Furthermore, KL-VS’s effects in late life might be partially attributable to differential development in childhood.

**LM3.02.02**

**Maternal prenatal aggression and sex differences in offspring externalizing behavior and substance use**

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**Background:** Maternal psychological stress during the prenatal period predicts lasting change in offspring emotion and behavior, including increased externalizing behavior. Recent work has suggested sex-specific vulnerability periods for the effect of maternal stress on fetal development, with boys generally at greater risk than girls. Inasmuch as the presence of externalizing symptoms, including aggression, increases risk for substance use more strongly for boys than girls, we hypothesized that maternal prenatal aggression would increase offspring risk of developing externalizing symptoms which in turn would predict substance use, and that this relationship would be stronger for boys than girls.
Methods: As part of the Teen Cohort Study, 413 pregnant teens (67.8% African American and 32.2% Caucasian) were recruited from the local regional community obstetric clinic. Mother-child dyads were tracked from around 17 weeks gestation to offspring age 16. Maternal aggression was measured using the Youth Self-Report and Profile during the second trimester for the prenatal period and again at offspring age 6. Offspring externalizing symptoms were rated by the caregiver at age 6 using the Child-Behavior Checklist. Offspring Substance Use was measured at age 16 and included yes/no of past month marijuana, alcohol, and cigarette use. A multi-group Structural Equation Modeling (SEM) was performed on the model for each gender using mean and variance adjusted weighted least squares estimation method, with key covariates included (MPlus v7).

Results: For each SD increase in age 6 externalizing symptoms, female offspring were more likely to use substances at age 16 as follows: marijuana 30%, alcohol 24%, and cigarette 35%. Males were 27% more likely to use cigarettes at age 16 for one SD increase in age 6 externalizing symptoms, but there was no relation to marijuana or alcohol use. For both male and female offspring, prenatal maternal aggression predicted maternal aggression six years later, and offspring externalizing behavior at age 6 predicted their substance use at age 16, with about 11 to 24% of the variability of substance use at age 16 explained by the predictors. There was good model-data fit for both male and female offspring models. However, the relationship from maternal prenatal aggression to offspring behavior (age 6) and substance use (age 16) was only significant for females. Possible prenatal sex-specific vulnerabilities will also be considered.

Conclusions: The influence of maternal prenatal stress on offspring outcomes may vary by sex/gender of offspring. Contrary to our hypothesis, the effect of maternal aggression during pregnancy and externalizing symptoms on adolescent substance use was stronger for females. Additional research is needed to replicate these findings in other datasets and determine if offspring sex differences during the prenatal period contribute to the observed variations.


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LM3.02.03

Timing of natural menopause remains associated with verbal memory across adult life after controlling for childhood cognitive ability.

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Background: Whether later menopause is associated with better cognition, slower cognitive decline and a reduced risk of dementia has long been of interest. Lifelong studies are required as there is evidence from several cohorts that higher childhood cognitive ability is associated with later age at menopause; and animal studies show that estrogen has pleiotropic effects on the central and peripheral nervous systems and reproductive system right across life. Data from the MRC National Survey of Health and Development, the oldest of the British birth cohort studies, were used to investigate whether adult cognition and its change across adult life was associated with timing of natural or surgical menopause, taking account of hormone replacement therapy (HT) use. We hypothesised that later menopause would be associated with higher adult cognition and slower change; but that any associations would be explained by childhood cognitive ability, or by socio-behavioural factors.

Methods: Verbal memory (word learning recall) and processing speed (timed visual search) were assessed at ages 43,53,60-64 and 69. Age at period cessation was derived from 11 questionnaires between 43 and 64 years. There were 1303 women with a known age and type of menopause and up to four scores on verbal memory or processing speed. For each test, multilevel models were fitted with linear and quadratic age terms, stratified by type of menopause (natural or surgical). Sequential adjustments were made for HT use, body mass index and smoking at each cognitive assessment; and for adult occupational class, educational qualifications, and childhood cognitive ability at age 8.

Results: Later age at natural menopause was consistently associated with better verbal memory from 43 to 69 years (0.18 words per year, 95% CI 0.08,0.27, p-value < .001) but not with change in memory. An association remained after adjustment for all adult covariates (0.14 words per year, 95% CI 0.06,0.22, p-value < .001). Additional adjustment for childhood cognitive ability (which was strongly related to adult verbal memory) further reduced this estimate but a modest association remained (0.10 words per year, 95%CI: 0.03,0.18, p-value = .007). Later age at surgical menopause was also associated with better memory (0.16, 95% CI 0.08,0.27, p value < .001) but not with change in memory; however, this estimate was halved after adjustment for adult covariates and further attenuated by adjusting for childhood cognitive ability. Search speed was not associated with age at natural or surgical menopause.

Conclusion: Our longitudinal findings show a modest association between timing of natural menopause and verbal memory that is present throughout adult life, persisting into the seventh decade. This is not fully explained by prior cognitive ability or sociobehavioural factors. Our findings suggest that lifelong processes (such as lifelong oestrogen metabolism) may be the underlying mechanism, rather than short-term hormonal fluctuations during the menopause transition. Modifiable factors that promote cognitive development or delay reproductive ageing could have beneficial effects on adult memory.
Too small to sleep: The longitudinal associations between maternal depressive symptoms and child sleep in SGA children

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Background: Sleep is a dynamic construct. On the one hand, it is influenced by several factors ranging from environmental to individual characteristics. On the other hand, it plays an essential role in healthy development. The consolidation of the sleep-wake schedule serves as an early indicator for the development of arousal, emotion and attention regulation and the infant’s neurobehavioral maturation. It is, thus, crucial to understand what factors may promote or impair sleep. Although developmental research often assumes that most children are equally affected by the same environmental factors, a growing number of studies provide evidence that individual characteristics appear to modulate the influence of early life experiences. One such potential moderating factor is growth restriction. Albeit scarce, literature shows that children born small for gestational age (SGA) present with immature sleep organization (Watt & Strongman, 1984). SGA children are at increased risk for behavioral inhibition and shyness in childhood, all of which appear to be predictors of mood disorders in later life (Sykes et al. 1997). They are also at significantly greater risk for type II diabetes, visceral obesity, and hypertension (Matthews, 2001). One may thus hypothesize that the increased vulnerability SGA children are prone to will also lead to an increased susceptibility to their rearing environment. Hence, we aimed to study the impact of maternal symptoms of depression on child sleep as a function of their SGA status. We hypothesized that SGA children would be more affected by their mothers’ mood than their non-SGA counterparts as reflected in shorter sleep duration.

Methods: Our representative community sample consisted of 211 mother-child dyads recruited in the prenatal period and that were part of a longitudinal study: the MAVAN (Maternal Adversity, Vulnerability, and Neurodevelopment). Maternal symptoms of depression were repeatedly assessed postnatally (from 6 to 72 months) with the Center for Epidemiological Study for Depression scale (CES-D; Radloff, 1977). Total scores were averaged over time. Children were classified into SGA or not based on the birth weight ratio (observed birth weight/mean populational age, sex and gestational age specific), in which children with BWR below 0.85 were considered SGA. Child sleep duration was assessed with mother-reports from 6 to 72 months. A cumulative sleep measure was derived using mixed models.

Results: Moderation analyses revealed a significant interaction between longitudinal symptoms of maternal depression and child SGA status in association with child cumulative sleep duration. Results showed increasing symptoms of maternal depression were associated with decreased sleep duration but only for children born SGA ($b=-.04$, SE = .02, $p =.03$). Non-SGA children were, contrastingly, not affected ($b=-.0003$, SE = .0075, ns).

Conclusions: The results suggest that higher symptoms of maternal depression from 6 to 72 months postpartum were associated with shorter cumulative sleep duration in SGA children from 6 to 72 months. Contrastingly, non-SGA children’s sleep was not influenced by maternal symptoms of depression. This suggests increased susceptibility to the environment for SGA children.

The genetic architecture of differential susceptibility to childhood adversity; a genome-wide approach

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Background: Mental health outcomes following exposure to adversity vary considerably reflecting individual differences in susceptibility/resilience to stress. Such a ‘differential susceptibility’ to adverse environmental conditions is apparent in studies of exposures occurring in both childhood and later life. While the candidate gene studies reveal the importance of genotype in moderating the impact of environmental adversity, this approach bears weaknesses. Here we describe the use of a genome wide profiling approach to the study of differential susceptibility to childhood adversity.

Methods: We studied susceptibility in the context of substance dependency upon exposure to adversity in the Study of Addiction, Genes and Environments (SAGE) data set. Susceptible individuals were defined as those subjects with a substance dependence and a history of adversity (composite measure of childhood adversity and life time adversity). Resilient individuals...
were defined as subjects with no evidence for substance dependence, but likewise positive for a history of adversity. We performed a genome-wide association study (GWAS) of susceptibility. We then used the GWAS data to devise a polygenic risk score (PRSsus) to reflect the genetic risk for susceptibility to adversity.

**Results:** A GWAS of susceptibility revealed 59 SNPs that passed a suggestive threshold ($p < 1 \times 10^{-5}$). In an independent subset of data, our PRSsus differentiated between susceptible and resilient individuals. Receiver operator curve analysis shows that our PRSsus is highly specific and sensitive in predicting substance dependency only among individuals with a history of adversity (AUC = 0.85, accuracy = 0.89) and not in subjects with no history of adversity (AUC = 0.54 and accuracy = 0.55). The above results were also observed when the adversity variable was restricted to a history of childhood abuse. We, further, examined the predictive validity of our PRSsus in second independent replication cohort- a study of adults with objective measures of childhood adversity (physical or sexual abuse) and data on current mental health. We found a positive and significant association between PRSsus and externalizing diagnoses only among participants with a history of child maltreatment.

**Conclusion:** Thus we validated our PRSsus by examining two mental health outcomes, substance dependency and externalizing diagnosis. We propose that our PRSsus reflects the underlying genetic architecture of differential susceptibility to adversity, including childhood adversity, and not directly to the specific mental health outcome. Our proposed polygenic measure of susceptibility has implications for the definition of high-risk individuals exposed to childhood adversity.

**Figure:** Predictive validity of the PRS in the replication sample

Predictive validity of the PRS for childhood adversity in the replication dataset

**LM3.02.06**

**Psychological distress and suicidal ideation in Indigenous Australians from adolescence to young adulthood**

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**Background:** Almost half (45.5%) of Australian adults experience mental illness (psychological distress, affective or substance use disorder) at some point in their lifetime. Indigenous adults have higher rates of psychological distress and suicide compared to non-Indigenous Australians. The Northern Territory (NT) has the highest rates of suicide of all Australian jurisdictions over recent decades, particularly in Indigenous young adults. Mental health disorders are associated with suicidal ideation and risk of self-harm.

**Methods:** Indigenous participants of the Darwin, NT, Australia based Aboriginal Birth Cohort study, recruited at birth (1987-1990) and assessed in adolescence at age 16-20 years ($n = 469$) and in young adulthood at age 22-27 years ($n = 459$). Emotional status was assessed at both time points; suicidal ideation and self-harm questions was assessed by the strong souls (SS) questionnaire and psychological distress by the SSA in adolescence and Kessler-5 in young adulthood. In adolescence, 5 questions from the SS equivalent to the Kessler-5 (K5) were used and converted from 4 point Likert score to 5 point ($K5 = \text{SS x } 5$). K5 score $\geq 12$ ($75^{th}$ centile internal reference at both time points) was used to define psychological distress which is the same cut-off as that used clinically. Analysis was restricted to those with complete data at both time points ($n = 266$).

**Results:** Significantly higher rates of psychological distress, suicidal ideation and risk of self-harm were seen in women both at adolescence and young adulthood. Participants with psychological distress reported significantly higher suicidal ideation and risk of self-harm both in adolescence and young adulthood, irrespective of gender. After adjusting for gender, a trend was seen in risk of self-harm (OR 2.02; CI 1.02, 4.01) between adolescence and young adulthood, no association was seen for psychological distress (OR 1.14; CI 0.62, 2.11) and suicidal ideation (OR 2.16; CI 0.78, 6.00).

**Conclusions:** One in four participants in this cohort reported psychological distress both in adolescence and young adulthood. With the increasing awareness of the intergenerational effects of maternal stress of particular concern are the higher rates seen in women of childbearing age (one in three). These high rates of distress both in adolescence and young adulthood, emphasize the need for tailored, culturally appropriate, gender specific programs targeting early screening and treatment not only in adolescence but continuing into adulthood.
Rates of psychological distress, suicidal ideation & self-harm in adolescence and young adulthood by gender

**LM3.02.07**

**Associations of maternal lifetime exposure to violence and gestational cortisol, with offspring mitochondrial-DNA copy number**

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**Background:** Mitochondrial dysfunction has been associated with a higher risk of numerous diseases. Such condition might be programmed in utero, both by concurrent gestational exposures or by maternal life-time determined characteristics. Exposure to violence can permanently alter a woman’s physiology through acute or chronic stress, leading to excess cortisol concentrations and eventually disrupting allostasis. We examined mitochondrial-DNA copy number (mtDNA-C) a compensatory response for cellular-redoximbalance in cord blood and its association with maternal lifetime exposure to violence (EV) (during childhood, adolescence, pre-pregnancy and pregnancy stages) and pregnancy cortisol.

**Methods:** Cord blood mtDNA-C, maternal salivary cortisol, and pregnancy violence was studied in 439 mother-offspring pairs in the Mexican PROGRESS birth cohort. mtDNA-C was measured using quantitative PCR; cortisol was measured 5 times/day at timed intervals over 2 days to capture diurnal variation, and summary indicators calculated: area under de the curve (AUC) and cortisol awakening response (CAR); EV was assessed at ages: <11 years old (childhood), between 11 and 18 years old (adolescence), and > age 18 years old before the current pregnancy (pre-pregnancy), and during pregnancy, using the Childhood Trauma Questionnaire. We fit finite mixture models to evaluate the association pattern between EV and cortisol with mtDNA-C. Models included interaction terms between EV stages (e.g., childhood*adolescence).

**Results:** Exploratory analysis on mtDNA-C identified three different groups in the study population, therefore, it was analyzed as a mixture of three normal populations. Cortisol indicators revealed a mixture of 2 normal groups. As for EV, we derived 4 scores, one for each life stage using a Poisson mixture model. We observed that the mean scores for violence decreased throughout life and found patterns between consecutive stages as the most significant ones. Preliminary results show association patterns between EV and the CAR. Pre-pregnancy violence was associated with an increased CAR. However this was not parallel with the AUC. Models including EV and cortisol CAR and AUC indicated different association patterns within each groups of mtDNA-C. For group 1 (which reflected the subpopulation with average mtDNA-C) EV during pregnancy and pre-pregnancy, as well as a higher CAR was associated with increased mtDNA-C, no associations were found for AUC. For group 2, (with higher mtDNA-C) no associations were found with EV or AUC however, a decrease in mtDNA-C was associated with higher CAR. Group 3 (with the lowest mtDNA-C) showed decreased mtDNA-C associated with EV, CAR and AUC.

**Conclusions:** Cord blood mtDNA-C showed a normal mixture distribution. This behavior is especially relevant since different associations with EV and cortisol can be found for each of these derived groups (subpopulations). We will continue our analyses of cord blood mtDNA-C which could be a marker of fetal programming of adult disease, associated with maternal gestational cortisol and lifetime EV.

**LM3.02.08**

**A two-step Mendelian randomization study of DNA methylation as intermediate between maternal vitamin B12 during pregnancy and offspring’s cognition**

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**Background:** An adequate intake of vitamin B₁₂ during pregnancy plays an important role in offspring neurodevelopment, potentially via epigenetic processes. Here we present a two-step Mendelian randomization approach to assess whether DNA methylation plays a mediating and causal role in the association between maternal vitamin B₁₂ status and offspring’s cognition.
Methods: Firstly, we estimated the causal effect of maternal vitamin B12 levels on cord blood DNA methylation using the maternal FUT2 genotypes rs492602:A > G and rs1047781: A > T as proxies for circulating vitamin B12 levels in the Avon Longitudinal Study of Parents and Children (ALSPAC) and we tested the observed associations in the Genetics of Overweight Young Adults (GOYA) replication cohort. Secondly, we estimated the causal effect of DNA methylation on IQ using the offspring genotype at sites close to the methylated CpG site as a proxy for DNA methylation in ALSPAC and in the Social Science Genetic Association Consortium (SSGAC) replication sample. We used two-sample instrumental variable analysis in both steps.

Results: The first step estimated that maternal vitamin B12 had a small causal effect on DNA methylation in offspring at three CpG sites, upstream of the USP29 gene and in the APOL2 and RCSD1 genes. The effect was replicated for the USP29 site. The second step found weak evidence of a causal effect of DNA methylation at APOL2 and RCSD1 on Performance IQ. The effect was replicated for APOL2. We could not perform the second step analysis for the USP29 site due to lack of valid instruments.

Conclusions: Our findings support a causal effect of maternal vitamin B12 levels on cord blood DNA methylation and a causal effect of vitamin B12-responsive DNA methylation changes on children’s cognition. We will discuss the strengths of this study and the limitations of this approach.

LM3.02.09
The association between obesogenic eating behavior and body composition across childhood: evidence for reversed causality
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Background: Unhealthy eating behavior is considered as a modifiable risk factor for childhood obesity. However, longitudinal data with repeated measures of both eating behavior and child body composition is missing. Therefore, reversed causality cannot be ruled-out. We aimed to examine the bi-directional association between obesogenic eating behavior and body composition in children from age 4 to 10 years.

Methods: Longitudinal data were available for 3331 children participating in the Generation R Study. BMI was measured when children were 4 and 10 years old. Fat Mass Index (FMI) and Fat Free Mass Index (FFMI) was measured at 6 and 10 years of age with DXA. When children were 4 and 10 years old, mothers reported on the Child Eating behavior Questionnaire (CEBQ); the subscales Food Responsiveness, Satiety Responsiveness, Enjoyment of Food and Emotional Overeating were examined.

Results: More emotional overeating at 4 years was only modestly associated with a higher BMI and FMI at 10 years (for BMI SD score, β = 0.03, 95% CI = 0.00, 0.06), whereas more satiety responsiveness was associated with a lower BMI and FFMI. In contrast, we found very consistent evidence for the reversed association. A higher BMI, FMI and FFMI in preschool age predicted more emotional overeating, food responsiveness, enjoyment of food, and less satiety responsiveness at age 10 years, with strongest associations for FMI (i.e. food responsiveness, per FMI SD score: β = 0.36, 95%CI: 0.31, 0.40). Cross-lagged models of associations between child BMI and eating behavior confirmed our findings: a higher child BMI at the age of 4 years predicted higher food responsiveness and enjoyment of food and lower satiety responsiveness at the age of 10 years, but no association was found in the opposite direction in this bi-directional model.

Conclusions: Results from this prospective study with repeated measures showed that a higher BMI, FMI and FFMI at preschool age predicted higher levels of obesogenic eating behavior at the age of 10 years, whereas little evidence for the often hypothesized effect of eating behavior on body composition was found. Thus, in young children a higher BMI precedes the change in eating behavior. This suggests that increased adiposity in early childhood might upregulate appetite and related unhealthy eating behavior.

LM3.02.10
Robust Early Life Determinants of Neurocognitive Development in Children: Evidence from the Pune Maternal Nutrition Study (PMNS)
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Background: We investigate the impact of intrauterine and postnatal environment influences on neurocognitive development at age 12. Majority of studies report associations within a short time of exposure.

Methods: The PMNS is a pre-conception birth cohort established in 1993 and has data on a range of maternal characteristics (size, socio-economic factors, anthropometry, physical activity, nutrition, and circulating levels of nutrients and metabolic endocrine markers) during pregnancy. Children and parents have been followed-up regularly after delivery for similar measurements. Neurocognitive assessment was done in children at 12 years of age. The battery of tests include Raven’s Color Progressive Matrices, Block Design, Picture Completion, Digit Span, Trail Making, and Auditory verbal learning test. The PMNS data therefore allows us to control for remedial interventions during the lifecycle of the child after birth when investigating the impact of in utero environment. We introduce the idea of theory open-endedness and its implications on
model uncertainty into this area of research. We argue that existing findings on the impact of in utero nutrient deficiencies on child outcomes are based on approaches that ignore model uncertainty. Currently, the standard approach is for the researcher to specify an ad hoc “baseline” regression model, and then to check for robustness by examining the consequence of small deviations from this baseline model. We argue that this approach places an undue burden on the reader to accept the preponderance of prior knowledge on the part of the researcher that is not always explicitly articulated nor justified.

We advocate an approach that moves the focus of analysis away from findings based on any single a priori chosen model to estimates that do not depend on a particular model specification but that are instead conditional on the space of models generated from the set of plausible explanatory variables for the outcome of interest. Specifically, we employ Bayesian model averaging (BMA) methods to produce robust estimates for the treatment effect by assigning evidentiary weights based on the data (i.e., posterior model probabilities) to each model in the model space, and then taking an average of model-specific estimates using these weights.

Results: Our findings suggest that a range of early factors such as mother’s B12 levels, fasting glucose levels, triglycerides, and HDL during pregnancy; child’s head circumference and height at birth remain important determinants of child’s neurocognitive development at age 12 even after controlling for subsequent changes in child health and nutritional status after birth. However, our results also highlight the critical role of father’s education, mother’s education and socioeconomic status in determining a child’s neurocognitive development. Father’s education seems to be especially important with a positive and significant impact on most cognitive measures. Other socioeconomic factors also appear to be significant in explaining these cognitive measures.

Conclusion: Overall, our findings, which emphasize the importance of both initial conditions as well as post-birth family environment on child neurocognitive outcomes, affirm the substantive importance of DOHaD as an organizing framework for thinking about the later life implications of early disadvantages.

LM3.02.11

How body composition influence hearing status at two important life stages: early adolescence and mid-life

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Background: Because of its impacts on health and quality of life, reported recent upswings in the prevalence of child and adult hearing loss are concerning. They are also plausible in the context of the changing epidemiology of not only mechanical (eg noise exposure) but also novel non-communicable disease (eg obesity, inflammation) risk factors. This study aims to determine which, if any, body composition measure best predicts hearing parameters in 11-12 year old children and their mid-life parents, and whether longitudinal body mass index (BMI) trajectories are more predictive than concurrent BMI.

Methods: Design & Participants: 11 to 12 year olds and their mothers participating in the Child Health CheckPoint, a one-off biophysical wave nested between Waves 6 and 7 of the population-based Longitudinal Study of Australian Children (LSAC). Body composition: BMI, fat/lean mass indices, waist-to-height ratio at the CheckPoint; biennial repeated BMI from LSAC waves 2 to 6. Audiometry (CheckPoint): Mean hearing threshold calculated in four ways - high Fletcher Index (1, 2, 4 kHz), four frequency average (1, 2, 4, 8 kHz), low-frequency average (1, 2 kHz), high-frequency average (4, 8 kHz). Hearing loss was defined as mean thresholds > 15 dB HL in the better ear. Analysis: Fat/lean mass indices and children’s BMI were transformed to z-scores. BMI trajectories were created using mixed growth curve models. Regression models determined associations of body composition /trajectories with hearing threshold (linear) and loss (logistic).

Results: 1468 children (49.7% boys) and 1287 mothers had both body composition and audiometric data. Five BMI z-score trajectories emerged for children (5.7% low, 30.4% average, 4.9% low to high, 44.6% high, and 12.2% very high), and four for mothers (45.2% normal, 30.3% overweight, 11.7% obese, and 2.3% severely obese). In cross-sectional analyses, associations between waist-to-height ratio and hearing thresholds were stronger for mothers than children, and for thresholds incorporating lower than higher frequencies (high Fletcher Index: children, β = 7.4, 95% CI 1.1 to 13.7, p = 0.02 and mothers, β = 10.0, 95% CI 5.6 to 14.4, p < 0.001; low-frequency average: children, β = 7.5, 95% CI 1.0 to 14.1, p = 0.02 and mothers, β = 9.3, 95% CI 4.8 to 13.8, p < 0.001). Similar associations were noted for fat mass index, but not concurrent BMI or lean mass index. Higher maternal BMI trajectories were associated with higher maternal hearing thresholds (all indices p < 0.05) and hearing loss on high Fletcher Index, four frequency and low-frequency average (p for trend 0.006, 0.008 and 0.001, respectively). Children’s hearing was not predicted by their own lifetime BMI trajectories, but showed some associations with those of their mothers.

Conclusions: In this population-based study, markers of visceral adiposity (fat mass index, waist-to-height ratio) and 10-year BMI trajectories predicted poorer hearing, particularly in the lower audiometric frequencies, with relationships strengthening with age. This suggests that obesity may play a role in the rising global burden of presbycusis (the slow deterioration of hearing across the lifecourse), possibly via systemic (eg inflammation) rather than local (eg vascular flow restriction) mechanisms. Replication, mechanistic and segmental body compositional studies could elucidate the nature of any causal relationships.
DOHaD Associated Groups
D. Sloboda

The International DOHaD Society encourages and supports its Associated Groups, where groups of individuals that share a language, a geographical region, or a coordinated strategic mission, can come together for common DOHaD-focussed objectives. Our Associated Groups foster research interests in DOHaD internationally, support Society membership, and promote international research collegiality. This is a closed meeting for the executives of our Associated Groups.

Altered catecholamines in the right atrium of fetuses of obese baboons at term
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Introduction: Maternal obesity predisposes offspring to cardiovascular disease as a result at least in part by developmental programming of cardiovascular function and increased sympathetic activity (PMID: 19901159). To evaluate potential mechanisms we have developed a baboon, nonhuman primate model of maternal obesity prior to pregnancy. Evidence exists for norepinephrine (NE)-induced epigenetic changes in fetal rat hearts (PMID 20733009). There is also evidence that increased NE produces epigenetic changes that are due to oxidative stress and may impair cardio-protection and increase vulnerability of the developing heart to environmental challenges (PMID 22441984). We have shown structural and miRNA changes in the hearts of fetuses of obese baboon mothers (PMID 23922128). Our aim in this study was to determine catecholamine levels in the hearts of fetuses of obese mothers.

Methods: Healthy female baboons (Papio hamadryas) of similar body weight (1015 kg) were fed normal chow (CTR n = 24; 12% energy from fat with 0.29% glucose and 0.32% fructose) or a high-energy diet (FAT n = 19; 45% energy from fat with 4.62% glucose and 5.64% fructose) plus ad libitum fructose sodas for at least nine months prior to pregnancy. Fetuses were removed by C-Section at 0.9 gestation while the mother was under general anesthesia; the fetal heart was removed and the right atrium dissected and frozen for catecholamine analysis. Norepinephrine, epinephrine, dopamine, DOPAC, 5HT, and 5HIAA were quantified after extraction using HPLC with coulometric detection. Data are presented as mean ± SEM; analysis by Student’s t-test.

Results: The figure shows observed changes in key catecholamine pathway products in hearts of control and FAT mothers.

Conclusions: There are few data on maternal obesity effects directly on the nonhuman primate fetal heart. Our data are in agreement with the hypothesis that programming by maternal obesity involves altered catecholamine production within the heart, thereby potentially leading to arrhythmias and modifying contractility through impaired sympathetic function.

Human clinically relevant antenatal glucocorticoid therapy programmes cardiac dysfunction and fibrosis in adult offspring

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Introduction: Antenatal glucocorticoid therapy (AGT) in threatened preterm labour is globally implemented, as it reduces the incidence of respiratory distress and death in preterm infants (Roberts & Dalziel. Cochrane Dat Syst Rev. 3: CD004454, 2006). Both synthetic glucocorticoids as well as preterm birth may have adverse long-term effects on cardiovascular function (Kelly et al. Pediatrics 129(5):e1282, 2012; Parkinson et al. Pediatrics 131(4):e1240, 2013). However, this is difficult to prove in humans as ex-preterm adults have likely been exposed to synthetic glucocorticoids during the perinatal period. Here, we isolated the long-term effects of AGT used in humans on cardiovascular function at adulthood in sheep not born preterm.

Methods: At 0.8 of gestation, pregnant ewes carrying singletons were treated with steroids (2 × 12mg dexamethasone i.m. 24h apart; D; n = 10) while the other received saline vehicle.
i.m. (C; n = 12). After natural delivery, offspring were maintained until 9 months, and then chronically instrumented with vascular catheters and a femoral flow probe to determine in vivo cardiovascular physiology. Following this, ex vivo cardiac function (Langendorff) and cardiac and aortic fibrosis (picrosirius red) were determined.

**Results:** Both C and D ewes delivered at term (148±3 vs. 148±2 d). At adulthood, C and D offspring had similar basal arterial blood pressure (89.8±1.8 vs. 92.8±2.6 mmHg) and heart rate (97.5±3.2 vs. 97.3±8.5 bpm). However, D offspring showed an increase in cardiac baroreflex gain (Fig. 1 a). Isolated hearts from D relative to C offspring showed markedly elevated left ventricular end diastolic pressure (LVEDP), an index of diastolic dysfunction, and impaired dP/dtmax, a measure of myocardial contractility (Fig. 1 b & c). In addition, D relative to C offspring showed increased cardiac and aortic wall fibrosis (Fig. 1 d & e).

**Conclusions:** Human AGT adversely affects cardiovascular function in adult offspring independent of preterm birth.

**Funding:** British Heart Foundation

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**LM3.04.04**

**Preterm birth and cardiovascular risk factors in young adulthood: prospective and sibling studies in the Norwegian HUNT Study**

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**Background:** Accumulating evidence suggests that individuals born prematurely (<37 weeks of gestation) have more adverse cardiovascular health in later life. Whether this association reflects a pregnancy specific effect or is driven by shared genetic or other familial characteristics remains unclear.

**Methods:** Data from the HUNT studies in Norway were linked to information from the Medical Birth Registry of Norway and are used here. HUNT consists of three population-based surveys in Nord-Trøndelag county in Norway: HUNT1 (1984–1986), HUNT2 (1995–1997), and HUNT3 (2006–2008). At each survey, all residents ≥20 years of age were invited to participate. Blood pressure, anthropometry, serum lipids, and C-reactive protein were assessed.

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**LM3.04.03**

**Maternal verbal aggressive behavior in infancy is associated with higher systolic blood pressure in the child at age 5-6**

L.J.C.A. Smarius¹, T.G.A. Strieder², T.A.H. Doreleijers³, T.G.M. Vrijkotte¹, R.J.B.J. Gemke¹, S. de Rooij¹

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**Background:** Early life stress has been shown to contribute to alterations in biobehavioral regulation. The present study examined whether maternal verbal aggressive behavior in early infancy is associated with child’s resting heart rate and blood pressure at age 5-6 and whether presence of postnatal maternal depressive symptoms or pleasure in infant care moderates this association.

**Methods:** In the Amsterdam Born Children and their Development (ABCD) study, a large prospective, observational, population-based multiethnic birth cohort, maternal verbal aggressive behavior (angry speaking to the infant), depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D)) and pleasure in infant care were assessed in the 13th week after birth (range 11 – 25 weeks, SD 2 weeks) using a questionnaire. Blood pressure and heart rate were measured in supine and sitting position during rest. Exclusion criteria: preterm born babies or congenital disorders (N = 2516 included).

**Results:** Maternal verbal aggressive behavior in infancy (9.4%) was associated with a higher systolic blood pressure at age 5-6, both in supine and sitting position (B 1.00 mmHg CI (0.06-1.94); B 1.14 mmHg (-0.01-2.30)), but not with diastolic blood pressure or resting heart rate. The association between maternal verbal aggressive behavior in infancy and systolic blood pressure in childhood was only present in children whose mothers did not show symptoms of depression or reported pleasure in infant care.

**Conclusions:** Presence of maternal verbal aggressive behavior in early infancy was associated with a higher systolic blood pressure at age 5-6, only in children whose mothers did not show symptoms of depression or reported pleasure in infant care. Further investigation of maternal verbal aggressive behavior may be valuable for cardiovascular health later in life.

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**LM3.04.03**

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L.J.C.A. Smarius¹, T.G.A. Strieder², T.A.H. Doreleijers³, T.G.M. Vrijkotte¹, R.J.B.J. Gemke¹, S. de Rooij¹

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**Conclusions:** Presence of maternal verbal aggressive behavior in early infancy was associated with a higher systolic blood pressure at age 5-6, only in children whose mothers did not show symptoms of depression or reported pleasure in infant care. Further investigation of maternal verbal aggressive behavior may be valuable for cardiovascular health later in life.
12,698 participants (mean age: 29.5 years), from 9,504 sibling groups, of whom 3,194 had at least one participating sibling were included here. We used random-, fixed-, and between-effects linear regression to estimate associations in the overall population, between and within sibships.

**Results:** 492 (4%) participants were born prematurely. Amongst unrelated participants, those born prematurely had higher body mass index (0.43 kg/m²; 95%CI: -0.02, 0.88), waist circumference (1.93 cm; 0.74, 3.12), systolic blood pressure (1.62 mmHg; 0.39, 2.85), and C-reactive protein (25.7%; 11.4, 40.1) after adjustment for age, sex, HUNT survey, maternal age, parity, smoking, education, BMI and pregnancy induced hypertension. There was weaker evidence of associations with diastolic blood pressure (0.86 mmHg; -0.08, 1.80), and HDL cholesterol (-0.03 mmol/L; -0.06, 0.004) and no evidence of associations with non-HDL cholesterol and triglycerides. 200 sibships were discordant for prematurity. Within sibships, the magnitude of associations of prematurity with greater body mass index, and systolic blood pressure remained similar, although confidence intervals were wider. Premature siblings were 0.37 kg/m² (-0.33, 1.06) heavier on average than their term siblings, and higher systolic blood pressure (1.48 mmHg; -0.53, 3.48), whilst effect estimates with waist circumference, diastolic blood pressure, C-reactive protein and HDL cholesterol were smaller than those observed amongst non-related participants. When we repeated analyses excluding offspring born to mothers with pregnancy induced hypertension, results were essentially unchanged.

**Conclusions:** The modestly greater adulthood body mass index and higher systolic blood pressure in adults born prematurely compared to those born at term observed in the general population may reflect a pregnancy specific direct effect and are not completely explained by shared genetics or unmeasured maternal characteristics.

**LM3.04.05**

**Maternal early-pregnancy BMI and determinants of childhood heart rate variability and blood pressure at 6 years: Children of SCOPE**

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**Background:** Recent epidemiological and animal studies suggest that maternal obesity may permanently change the central regulatory pathways involved in offspring blood pressure (BP) regulation. Rodent studies have shown maternal obesity results in deleterious consequences for offspring cardiovascular function. Offspring of obese rats are hypertensive and demonstrate enhanced cardiovascular stress reactivity and an increase in low/ high frequency ratio of power spectral analysis of heart rate variability (HRV), indicative of increased sympathetic tone. We hypothesized that maternal obesity is associated with altered autonomic control of BP in childhood.

**Methods:** From a sample of the New Zealand Children of SCOPE Study weighted to over-represent higher maternal body mass index (BMI) categories, offspring were randomly selected for HRV analysis. The exposure of interest was maternal BMI at 14-16 week’s gestation. Outcomes included offspring BP and HRV at 6 years-of-age under resting conditions. Following routine blood pressure measurements, HRV was obtained by recording 20-minute heart rate series by electrocardiograph monitoring. Analysis was performed according to the methodological standards recommended by the Task Force on HRV. Time domain parameters of HRV were quantified by means of different indices of the standard deviation of normal-to normal RR intervals (SDNN) and frequency domain parameters were derived from power spectral analysis of the HRV. Linear regression was used to examine associations, adjusting for child’s current BMI z-score, sex, maternal age at delivery, mode of delivery and parity. All results obtained from offspring of overweight (BMI 25-29.9 kg/m²) and obese (BMI ≥30 kg/m²) mothers were compared to results from the reference group (offspring of mothers with BMI 18.5-24.9 kg/m²).

**Results:** Results from 398 children born to 91 obese, 197 overweight, and 110 mothers in the reference group were obtained. In the time domain, mean SDNN was 1.17 times greater (95% CI 1.00-1.38) in the obese category compared to the reference group. In the frequency domain, very low frequency (VLF) and low frequency (LF) values were 1.29 (95% CI 1.00-1.70) and 1.46 (95% CI 1.07-2.00) times greater in the obese group compared to the reference group, respectively. In the overweight and obese groups, absolute HF values were 1.38 (95% CI 1.00-1.91) and 1.49 (95% CI 1.03-2.26) times greater than the normal maternal BMI category. These associations were observed after adjustment for confounders. There were no apparent differences in LF/HF ratio, SBP, DBP or MAP between the BMI categories.

**Conclusion:** Maternal obesity was associated with substantial increases in both offspring sympathetic and parasympathetic (vagal) activity, with no apparent effect on the overall sympatho-vagal balance or blood pressure at 6 years. Increased sympathetic activity is positively associated with cardiovascular risk, however, the clinical significance of a parallel increase in parasympathetic vagal activity, with apparently normal sympatho-vagal balance, is less clear.

**Funding:** Children of SCOPE Study was funded by Health Research Council of New Zealand, Cure Kids and Gravida
Coronary artery disease (CAD) is the leading cause of death worldwide. Many of the risk factors have long been established to be modifiable exposures such as low-density lipoprotein cholesterol levels (LDL), smoking and hypertension. In the developed world, the average age of developing Angina Pectoris, often the first clinical sign of CAD, is typically over 60. However, it is known that fatty streaks, the precursors to atherosclerosis and thus CAD, develop in almost all adolescents’ arteries. Through genome-wide association studies (GWAS), human genetics has begun to explore the heritable contributions to this complex disease. There are currently 58 single nucleotide polymorphisms (SNPs) with reliable evidence for association with an increased risk of CAD in adulthood. These SNPs, which are likely to be exerting their effect through a diverse collection of mechanisms, are common variants and exert relatively small effects on disease outcome singularly. In aggregate, these variants explain roughly 12% of CAD heritability. It is unclear, however what effect these variants are having on CAD pertinent phenotypes at an earlier age (i.e. latent disease).

Using data from 4,482 adolescent participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) we analysed the effect genetic risk of CAD was having on the metabolome at a young age. SNPs were weighted by multiplying the log_{10} of their odds ratio, in relation to CAD, by their dosage. The weighted scores of the SNPs were summed to produce a genetic risk score (GRS). A linear regression model was fitted to investigate how this score associated with the concentrations of 151 metabolites. The score associated with 59 metabolites (FDR < 0.05), which consisted predominantly of lipoproteins and fatty acids. To assess what component of the GRS was driving this association we produced a lipoprotein specific GRS, consisting of 7 SNPs known explicitly to be lipoprotein related. This score associated with 114 metabolites (FDR < 0.05). The average absolute effect estimate for FDR significant GRS-metabolite associations was 2.1 when using the lipoprotein specific GRS and only 0.4 using the total GRS. Furthermore, when the lipoprotein SNPs were removed from the total GRS, the association between the residual GRS and metabolites attenuated to the null. Additionally, we analysed individual SNP-metabolite associations as well as biologically grouped lipoproteins (grouped based on whether they were of a particle size which sufficiently small to cross the intima). This revealed that SNPs in the regions of SORT1, APOA, APOCE, and LPL, associated with multiple metabolites at a conservative Bonferroni threshold of P < 6.5 x 10^{-6} and that the genetic risk conveyed by these SNPs was most highly associated with an increase in harmful subclasses of lipoproteins such as LDL and IDL cholesterol.

Our results suggest that certain SNPs are associated with a metabolic profile at a young age and this is likely to deliver increased risk to CAD in later life. Furthermore, if this changed metabolome in early life is contributing to increased risk of CAD then interventions can be put in place for high-risk individuals, helping prevent onset of CAD.

**LM3.04.07**

**Childhood stature and linear growth in relation to first ever ischemic or intracerebral hemorrhagic stroke**

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**Background:** Adult height, an indicator of genetic potential and the growth-environment during childhood, appears to be inversely associated with ischemic and hemorrhagic stroke, but the evidence is still sparse. Investigating childhood height and height growth may provide important insights into the origins of stroke.

**Methods:** We used information from the Copenhagen School Health Records Register on Danish schoolchildren born from 1930-1989, with measured heights from ages 7-13 years, to investigate associations of both childhood height and of growth in height with risk of ischemic and intracerebral hemorrhagic stroke in adult life. Cox proportional hazards regressions were performed to estimate hazard ratios (HRs) and confidence intervals (CIs) separately for women and men. We further investigated the effect of birth weight on these associations.

**Results:** Among the 311,009 individuals (49% women) included in the study, 10,412 (41% women) were diagnosed with an ischemic stroke and 2,546 (43% women) with an intracerebral hemorrhagic stroke. We observed inverse linear and stable associations between height at all childhood ages and ischemic stroke in both sexes and intracerebral hemorrhagic stroke in men (all p < 0.002). For ischemic stroke, per unit increase in height z-score at age 7 years, the HR was 0.89 (95% CI: 0.87, 0.92) in women and 0.90 (95% CI: 0.88, 0.92) in men. For intracerebral hemorrhagic stroke, per unit increase in height z-score at age 7 years, the HR was 0.97 (95% CI: 0.91, 1.04) in women and 0.89 (95% CI: 0.84, 0.94) in men. No associations between change in height z-score from age 7-13 years were observed for ischemic or intracerebral hemorrhagic stroke among women or men. No interactions with birth weight were identified (all p > 0.07). When adjusting for birth weight the associations of childhood height with ischemic stroke in both sexes or hemorrhagic stroke among women or men were attenuated, but remained statistically significant.

**Conclusions:** Height at ages 7-13 years is inversely associated with ischemic stroke in both sexes and men and with intracerebral hemorrhagic stroke in men, independently of birth weight.

Height in childhood during this period of childhood is not associated with either of these two stroke subtypes, and thus suggests that the underlying mechanisms linking height with risk...
of stroke may exert an influence after birth but already by early childhood.

**LM3.04.08**

The prediction of adult dyslipidemia using genetic and childhood clinical risk factors: The Cardiovascular Risk in Young Finns Study

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**Background:** Dyslipidemia is a major modifiable risk factor for cardiovascular disease. We examined if the addition of novel single nucleotide polymorphisms (SNPs) for blood lipid levels enhances the prediction of adult dyslipidemia in comparison to childhood lipid measures.

**Methods:** We used 2,422 participants of the Cardiovascular Risk in Young Finns Study who had participated in two surveys held during childhood (in 1980 when aged 3-18 years and in 1986) and at least once in a follow-up study in adulthood (2001, 2007, 2011). In addition to the potential childhood risk factors of adult dyslipidemia, we examined whether a lipid-specific weighted genetic risk score (wGRS) based on 58 SNPs for low-density lipoprotein cholesterol (LDL-C), 71 SNPs for high-density lipoprotein cholesterol (HDL-C) and 40 SNPs for triglycerides (TG) associated with lipids levels improves the prediction of dyslipidemia in adulthood.

**Results:** Adjusting for age, sex, body mass index, physical activity, and smoking in childhood, childhood lipid levels and wGRSs were associated with an increased risk of adult dyslipidemia for all lipids. Risk assessment based on two childhood clinical risk factors of adult dyslipidemia, we examined whether a lipid-specific weighted genetic risk score (wGRS) based on 58 SNPs for low-density lipoprotein cholesterol (LDL-C), 71 SNPs for high-density lipoprotein cholesterol (HDL-C) and 40 SNPs for triglycerides (TG) associated with lipids levels improves the prediction of dyslipidemia in adulthood.

**Conclusion:** The inclusion of wGRSs to lipid screening programs in childhood could improve the identification of those at highest risk of dyslipidemia in adulthood, although the improvement in prediction is modest.

**LM3.04.09**

Long-term effect of early programming factors on childhood metabolism: is there an impact on the metabolome?

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**Background:** Maternal smoking, maternal pre-pregnancy BMI, delivery mode, and a higher amount of protein content in infant formula milk are among the early programming factors that modulate obesity risk later in life. The mechanisms of action involved in the lasting term programming of metabolism are unknown. We characterize and quantify the impact of a higher protein formula and other early programming factors on the metabolome of children aged 5.5 and 8 years.

**Methods:** The Childhood Obesity Project is a European multicenter, double-blind, randomized clinical trial that enrolled healthy infants. Children were randomized to receive either a higher (HP) or lower protein (LP) content formula in the first year of life. We determined 165 metabolites / 185 metabolites in the blood of children aged 5.5 years (n = 276) / 8 years (n = 235) by liquid chromatography coupled to tandem mass spectrometry. The effect of the intervention and early programming factors on metabolism was assessed in linear mixed effect models. The magnitude of the impact of each factor was evaluated using the principal component partial R-square method.

**Results:** At 5.5 years of age, plasma alpha-ketoglutarate along with the acylcarnitine/BCAA ratios were higher in the HP group. However, only alpha-ketoglutarate reached statistical significance at adjusted Bonferroni level (P = 0.031). This finding was not replicated at age 8 years. In fact, the 8y metabolome showed no significant association to the feeding group. Quantification of the impact of the early programming factors revealed that the intervention group explained 0.7% of variance in the 5.5y metabolome and 0.6% of variance in the 8y metabolome. Similarly, other early programming factors contributed similarly little to the variability of the metabolome (maximum: 1.6%). None of the effects explained considerably more variance than expected by chance. Country of residence
was the only factor that consistently explained a significant amount of variance in the metabolome (12%).

**Conclusion:** Our results suggest a programming of BCAA catabolism of infants receiving a higher protein diet during the first year of life. The effect, however, was small as was the effect of the other early programming factors on metabolome. The results might arise due to the dynamic nature of the metabolome and the proneness to influences of diet and other recent lifestyle factors which might predominantly shape the metabolic profile.

**LM3.04.10**

Characterization of breast milk macronutrient content and its association with infant body composition

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**Background and objective:** Breast milk (BM) provides the optimal nutrition for infants, but as any biological product its composition may be affected by genetic and environmental factors. Longitudinal data on BM macronutrient composition and its association with infant developmental outcomes is scarce. The objective of the present study was to quantify the BM macronutrient content in healthy mothers from 0 to 4 months postpartum, and assess its association with the physical growth of their infants.

**Methods:** Mothers (n = 370) were recruited in 13 centers across Europe, and samples from 226 subjects were analyzed. BM samples were collected during mid-morning at 2, 17, 30, 60, 90 and 120 days postpartum after complete expression of one breast. Energy content of BM was determined by MIRIS-HMA. Body weight, length and head circumference were measured in all infants. Additionally, in two of the centers (France and Sweden) infant body composition was measured at each visit using Peapod (n = 82 infants, 43 females, 39 males).

**Results:** The energy content of BM was closely associated to fat content, and it increased from 67 ± 11.63 kcal/100mL at 2 days to 52.1 ± 10.49 kcal/100 mL at 17 days, thereafter energy and fat levels remained relatively constant until 120 days. Breast milk protein levels were 2.67 ± 1.05 g/100 mL at 2 days and decreased to 1.29 ± 1.05 mg/100 mL at 120 days postpartum. Infant growth during the study period was within the WHO reference curves. From 2 to 120 days, infants gained in average 1.1 kg of body fat, going from 10.7 ± 3.6 fat % at 2 days to 22.6 ± 5.2% at 120 days. BM macronutrient content differed according to infant’s body fat accretion quartile. Interactions between gender, infant body composition and macronutrient content in BM were identified and will be discussed in detail.

**Conclusion:** Infant body composition seems to be associated to BM macronutrient content. Future longitudinal studies with long term follow up should be undertaken to better understand the impact of breast milk composition on infant growth and body composition later in life.

**LM3.04.11**

Longitudinal fetal and childhood growth patterns associated with cardiac outcomes measured by cardiac Magnetic Resonance Imaging. The Generation R Study

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**Background:** Fetal life may be critical for cardiac development and disease. We examined the effects of longitudinal fetal and childhood growth on cardiac structure and function in children, measured by cardiac MRI.

**Methods:** In a population-based prospective cohort study among 2,888 children, we estimated fetal femur length and weight by 20 and 30 weeks ultrasound, and child length and weight at birth, 0.5, 1, 2, 6 and 10 years. We performed cardiac MRI at 10 years. Cardiac outcomes included right and left ventricular end-diastolic volume (RVED and LVED), right and left ventricular ejection fraction (RVEF and LVEF), left ventricular mass (LVM) and left ventricular mass-to-volume ratio (LMVR).

**Results:** Small size for gestational age at birth, but not preterm birth, was associated with smaller RVED, LVED and LVM, relative to current body surface area (p-values < 0.05). Longitudinal analyses showed that as compared to children in the 25-75% range of RVED, LVED and LVM, those in the upper 25% had higher fetal length and weight growth from 20 weeks of gestation until birth, a normal childhood length growth and slightly lower childhood weight growth. Similarly, children with a RVED, LVED and LVM in the lower 25% had lower fetal length and weight growth, lower childhood length growth, but increased childhood weight growth. Compared to children with normal LMVR, those with high LMVR did not have different growth patterns in fetal life, but had higher weight gain in childhood. Results from conditional regression analyses suggest that both fetal life and childhood length and weight growth are all independently associated with childhood RVED, LVED and LVM. Fetal and childhood growth were not consistently associated with RVEF and LVEF.

**Conclusion:** Not preterm birth, but size for gestational age is related with left and right cardiac outcomes in childhood. Relative to current body size, children who are larger at birth, and grow to be taller and leaner in childhood have larger hearts, whereas children who are smaller at birth and who are shorter and heavier in childhood have smaller hearts with a larger...
LM3.04.12

Sexual dimorphism in the programming of altered pancreatic islet function in offspring exposed to maternal obesity

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Background: Exposure to maternal obesity contributes to an increased risk of type 2 diabetes (T2D) in the offspring. T2D results from a combination of β-cell dysfunction and insulin resistance. Thus far, studies investigating the underlying mechanisms that may explain the transmission of T2D from parent to child have mainly focused on insulin-responsive tissues. Abnormalities in β-cell function are critical in defining the risk of T2D; a key event in T2D pathogenesis is when functionally impaired β-cells can no longer compensate for insulin resistance in peripheral tissues. The aim of this study was, therefore, to elucidate whether exposure to maternal obesity (MO) during pregnancy and lactation programs changes in pancreatic islets and whether these changes are different between male and female offspring.

Methods: Female mice were fed ad libitum either a chow diet or highly palatable energy-rich obesogenic diet prior to and throughout pregnancy and lactation. Offspring were weaned onto a chow diet and remained on this diet until 8 weeks of age. Pancreatic islets were isolated from male and female offspring. Islets were stimulated with low (2.8mM) and high (16.7mM) glucose ex vivo. Insulin secretion as well as insulin and proinsulin content was determined by ELISA. Leucine/glutamine (Leu/Gtn) and potassium chloride (KCl)-stimulated insulin secretion was also determined. Mitochondrial (mt) respiration was assessed using Seahorse XF24. Expression of Ins1, Ins2, Tfam and mt encoded genes in islets was determined by qRT-PCR. Data were analysed using an unpaired t-test. A probability level of 5% was taken to be significant.

Results: Glucose-stimulated insulin secretion from islets was increased (P < 0.05) in both male and female offspring exposed to MO. In females, this was primarily due to increased mt metabolism and exocytotic capacity of islets as reflected by increased Leu/Gtn (P < 0.01) and KCl-stimulated (P < 0.05) insulin secretion respectively. There was an increase in respiration (P < 0.01) in islets from female offspring of obese dams upon exposure to glucose and a parallel increase in ATP turnover (P < 0.01). Expression of mt encoded genes mt-Nd5 (P < 0.01), Gjb (P < 0.001) and C01 (P < 0.05) was increased but the mt transcription factor Tfam was unchanged. Ins1 (P < 0.01) and Ins2 (P = 0.06) gene expression was also increased in these islets. In contrast, basal respiration was increased (P < 0.01) in islets from male offspring of obese dams. These islets failed to increase respiration to the same extent in response to glucose resulting in an overall decrease in respiration (P = 0.057) and ATP turnover (P < 0.05). Expression of mt genes and Tfam was unchanged whilst Ins1 expression was increased (P < 0.01) in these islets. Whilst islet insulin and proinsulin content was unaffected in male offspring exposed to MO, islet proinsulin:insulin content (P < 0.05) was decreased in female offspring.

Conclusion: Compensatory changes are present in the islets of female offspring exposed to MO that are not present in male offspring. This study is the first to demonstrate sexual dimorphism in the programming of altered pancreatic islet function in the offspring in response to the chronic hyperglycemic environment of MO and may explain differences in time course of the development of offspring glucose intolerance.

Wednesday October 18th Abstracts poster presentations

PO3.01 – Adiposity – Nutrition and physical activity

PO3.01.01

Adiponectin in breast milk and childhood anthropometrics and cardio-metabolic health

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Objective: Adiponectin is known for its function in glucose and lipid metabolism, and was relatively recently discovered to be present in breast milk. We assessed the association between breast milk adiponectin and childhood anthropometrics and cardio-metabolic health up to the age of 17.

Methods: In the PIAMA birth cohort, we measured breast milk adiponectin at age 3 months (n = 250). Weight and length/height were parent-reported at 3 months, annually from 1-8 years, and at 11, 14, and 17 years. BMI (kg/m²) was calculated and converted into z-scores according to national reference data. Blood pressure, HbA1c, and cholesterol were measured at age 8, 12, and 16. We used multivariable linear regression to assess associations between breast milk adiponectin (ng/ml) and anthropometric and cardio-metabolic outcomes. Associations were adjusted for exact age of breast milk collection, maternal age, presence of siblings, maternal BMI, pregnancy weight gain and child’s birth weight.

Results: In fully adjusted models, breast milk adiponectin was associated with a 0.28 lower BMI-z (95% CI: -0.60, 0.04) at 3 months. After the age of 1, there were no associations between breast milk adiponectin and BMI-z. There were no associations between breast milk adiponectin and any of the cardiometabolic outcomes in childhood.

Conclusion: Breast milk adiponectin has no long-term effect on BMI-z and cardiometabolic health in children.
PO3.01.02
Infant breastfeeding and childhood general, abdominal, liver and pericardial fat measures assessed by magnetic resonance imaging. The Generation R Study.
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Background: A longer duration of breastfeeding is associated with a lower risk of obesity and fat mass in later life. Not much is known about its effect on more specific measures of childhood fat. We examined the associations of breastfeeding duration and exclusiveness and age at introduction of solid foods with measures of general, abdominal, and organ fat at 10 years.

Methods: In a population-based prospective cohort study among 4,444 children, we obtained information about infant feeding by questionnaires. At the mean age of 9.8 years, we calculated BMI. Fat mass index (FMI, total fat mass/height²) and fat free mass index (FFMI, total fat free mass/height²) were measured by dual-energy X-ray absorptiometry and subcutaneous fat index (subcutaneous fat mass/height²), visceral fat index (visceral fat mass/height³), pericardial fat index (pericardial fat mass/height³), and liver fat fraction by Magnetic Resonance Imaging.

Results: After adjustment for age and sex, children who were never breastfed had a higher BMI, FMI, subcutaneous fat index and liver fat fraction compared to children who were ever breastfed (all P values < 0.05). Nonexclusive breastfeeding in the first 4 months of life was associated with a higher FMI, subcutaneous and visceral fat index, and liver fat fraction and with a lower FFMI, whereas a shorter breastfeeding duration was additionally associated with a higher BMI (all P values and P values for trend < 0.05). Earlier introduction of solid foods was positively associated with all fat outcomes (all P values for trend < 0.05), except pericardial fat index. After adjustment for family-based sociodemographic-, maternal lifestyle-related-, and childhood factors, only the associations of breastfeeding duration and exclusiveness with FFMI and of age at introduction of solid foods with FMI remained significant.

Conclusions: The associations of breastfeeding duration and exclusiveness and of age at introduction of solid foods with general, abdominal, and organ fat measures at the age of 10 years seem to be mainly explained by family-based sociodemographic-, maternal lifestyle-related-, and childhood factors.

PO3.01.03
Infant feeding practices and the prospective relation with childhood BMI: results from the Generation R Study
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Background: While feeding practices of parents have been implicated in childhood overweight, the long-term effects of using food to comfort a distressed infant or child remain unknown. This study examined the longitudinal association of the use of food to soothe a distressed infant with later body composition, and explored whether hedonic eating mediated this association.

Methods: This study was embedded in Generation R, a population-based birth cohort in Rotterdam, the Netherlands. Participants were 3960 mother-child dyads followed from birth until age 10 years. Using food to soothe was assessed by parental questionnaire when infants were 6 months old. The main outcome measures included body mass index (BMI), fat mass and fat-free mass, which were obtained at our research centre when children were 6 and 10 years old. Hedonic eating (food responsiveness, emotional eating) was assessed at ages 4 and 10 years with the parent-reported Children’s Eating Behaviour Questionnaire. Linear regression analyses were conducted.

Results: The use of food to soothe when infants were 6 months old predicted a higher BMI from age 6 years onwards, independently of infant weight, maternal BMI and other confounders. Specifically, frequent use of food to soothe was associated with a 0.13 higher BMI SD at age 10 years (95% CI: 0.03 to 0.22) than never use. These differences in BMI were mostly explained by differences in fat mass (B = 0.11, 95% CI: 0.03 to 0.20) and somewhat less by differences in fat-free mass (B = 0.09, 95% CI: -0.01 to 0.18). Mediation analysis showed that children’s emotional eating mediated the feeding – BMI association (e.g. at 10 years: B indirect effect = 0.04, 95% CI: 0.02 to 0.06; B direct effect = 0.14, 95% CI: 0.04 to 0.24). Using food to soothe was not associated with children’s food responsiveness.

Conclusions: The use of food to soothe a distressed infant seems to be consistently associated with obesogenic eating behaviours and the development of unhealthy body composition throughout childhood. While further studies are needed to confirm our findings, these results seem to imply that emotional feeding practices are better discouraged, while parents should be provided with adequate alternatives to soothe their infants.

PO3.01.04
Dietary glycemic load and glycemic index during infancy with growth and body composition trajectories in childhood: The Generation R Study
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Background: A high dietary glycemic load (GL) or glycemic index (GI) may increase obesity risk. However, these associations during infancy are unclear. We therefore explored associations of child’s dietary GL and GI at their age of 1 year with...
their growth trajectories up to age 9 years and body composition at ages 6 and 9 years.

Methods: We included 3,564 children of the Generation R Study, a prospective cohort from fetal life onward in the Netherlands. Energy-adjusted GL and GI were assessed at age 1 year using a food-frequency questionnaire. Height and weight were measured repeatedly between ages 1 and 9 years and body mass index (BMI) was calculated. At their age of 6 and 9 years, we measured children’s fat mass index (FMI) and fat-free mass index (FFMI) using dual-energy X-ray absorptiometry. All outcomes were standardized for sex and age. Associations of GL and GI with growth trajectories and body composition were studied using multivariable linear mixed models.

Results: In our study population of 1-year-old children, GL and GI were positively correlated with carbohydrate and sugar intake, but also with fiber, vegetable protein intake and better adherence to dietary guidelines. After adjustment for confounders, higher dietary GI was associated with higher weight up to 9 years (0.04 SDS, 95%CI:0.01,0.07), but not with height. Dietary GI was also positively associated with BMI (0.05 SDS, 95%CI:0.02,0.07), which was possibly driven by a higher FFMI (0.03 SDS, 95%CI:0.00,0.07) and not FMI. Similar findings were observed for GL and FFMI (0.03 SDS, 95%CI:0.00,0.06).

Conclusions: Dietary GL and GI during infancy seems to be positively associated with children’s FFMI in our study population. This finding should be interpreted with caution since GL and GI in our study may not only reflect refined carbohydrate intake, but also other dimensions of an overall healthy diet. Future studies should therefore further study specific types of carbohydrates, such as added sugars, rather than overall dietary GL and GI.

PO3.01.05

Association between age of introduction of complementary feeding, exclusive breast feeding duration and BMI at 5-6 years: the ABCD study

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Background: Certain maternal characteristics (such as high weight status or low educational level) have been associated with an increased risk for overweight in their children. There are differences in infant feeding practices of mothers differing in these characteristics. Timing of introduction of complementary feeding as well as duration of exclusive breast feeding may therefore have different associations with body mass index (BMI) in subgroups at varying risk for overweight.

Methods: Using data (n = 4495) from a population-based birth cohort (Amsterdam Born Children and their Development, ABCD), we studied the association between age at complementary feeding, duration of exclusive breast feeding and BMI z score (relative to WHO 2006 growth standards) at 5-6 years of age within several subgroups differing in their risk for childhood overweight based on maternal characteristics (pre-pregnancy BMI, educational level, ethnicity and neighborhood). We conducted linear regression analyses, stratified by subgroup.

Results: Compared to introduction of complementary feeding before 5 months, complementary feeding at 5 months or later was associated with significantly lower BMI z score at 5-6 years of age within the following subgroups: Dutch ethnicity (B -0.133; 95% CI: -0.215, -0.050), medium educational level of the mother (-0.191; -0.308, -0.075), normal weight of the mother (-0.081; -0.159, -0.004 ) and high-risk neighborhood (-0.160; -0.301, -0.019) (Table 1). Compared to exclusive breast feeding for 0-2.9 months, exclusive breast feeding for at least 6 months was associated with significantly lower BMI z score within the following subgroups: low- (-0.281; -0.552, -0.010) and medium educational level of the mother (-0.285; -0.455, -0.115), normal weight of the mother (-0.184; -0.288, -0.079) medium-risk neighborhood (-0.189; -0.338, -0.040) and high-risk neighborhood (-0.233; -0.439, -0.028).

Conclusions: Introduction of complementary feeding at 5 months or later and breast feeding exclusively until 6 months may provide opportunities for childhood overweight intervention in several subgroups.

Table 1. Associations between age of introduction of complementary feeding, exclusive breast feeding duration and BMI z score at age 5-6 years by risk group

PO3.01.06

Infant protein supply and adiposity risk at 6 years: secondary analysis of a randomized clinical trial

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Background: Childhood obesity has reached epidemic proportions worldwide and therefore early preventive strategies get...
more important. Infant protein supply by formula is one key driver of early weight gain which is a known risk factor for later obesity. While weight gain and obesity are widely studied, knowledge about body composition throughout early to late childhood is weak. We aimed to examine the impact of early protein supply on body composition. We investigated also discrepancies between BMI based obesity and fat mass index based adiposity in children due to the criticism that BMI generally underestimates the prevalence of fatness in children.

**Methods:** Healthy term infants (N = 1090) were randomized to different protein content infant and follow-on formula (higher protein = HP with 2.9 and 4.4g protein/100kcal; lower protein = LP with 1.77 and 2.2g protein/100kcal, respectively) in a double-blind multicentre European trial. Body composition was estimated with the Slaughter’s equation based on triceps and subscapular skinfold thickness (SF), which were measured repeatedly from 3 months to 6 years of age as were height and weight. Fat mass index (FMI [kg/m²]) was calculated and compared to European reference data from the IDEFICS study. Adiposity at 6 years was defined as FMI above the 99th percentile.

**Results:** Four-hundred forty children were examined at 6 years. We observed greater sum of SFs (Δ2yrs 0.5mm, Δ6yrs 0.7mm, P = 0.026, Δ6yrs 0.17kg/m², P = 0.006, Δ6yrs 0.17kg/m², P = 0.002) comparing HP to LP. HP is associated to a 6% increase in FMI. Adiposity risk is 2-fold in HP compared to LP (adj. odds ratio 2.13, P = 0.019). We observed adiposity based on FMI in 54 children (34 HP and 19 LP) at 6 years, whereas only 30 children (22 HP and 8 LP) were obese according to IOTF BMI criteria.

**Conclusions:** Fatness in children is influenced by early protein intake. Higher protein supply leads to increased adiposity up to 6 years. Lowering the protein content in infant formula might be an effective strategy to reduce fatness in children. BMI based obesity underestimates fatness in European children, therefore large epidemiological studies should consider the additional measurement of skinfolds to assess body composition.

**PO3.01.08**

Maternal high-fat diet during lactation programs adult offspring obesity and increased adipose tissue Stearoyl-CoA Desaturase-1 activity in a depot-specific manner


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**Background:** The prevalence of obesity and related complications has reached epidemic proportions. Increasing evidence indicates that over-nutrition during the lactation-suckling period in mothers or pups is sufficient to program later obesity risk but underlying mechanisms remain poorly characterized. Stearoyl-CoA desaturase-1 (SCD1) catalyzes the biosynthesis of the monounsaturated fatty acids (FA), palmotoleate and oleate, from the saturated FA, palmitate and stearate. SCD1 products are predominant substrates for triglyceride (TG) synthesis. Several studies have shown that white adipose tissue (WAT) expansion and TG storage capacity in adults are associated with SCD1 activation. Here, we hypothesized that early postnatal over-nutrition could program increased SCD1 activity in WAT, which could participate in establishing long term adiposity set point.

**PO3.01.07**

Perinatal exposure to sucrose or high fructose corn syrup (HFCS-55) alters adiposity and hepatic lipid composition in rat offspring

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**Background:** Perinatal exposure to excess maternal intake of added sugars, including fructose and sucrose, is associated with an increased risk of obesity and type 2 diabetes in adult life. However, it is unknown to what extent the type of sugar and the timing of exposure affect these outcomes.

**Objective:** The aim of this study was to determine the impact of exposure to maternal consumption of a 10% w/v beverage containing either sucrose or high fructose corn syrup-55 (HFCS-55) during the prenatal and/or suckling periods on offspring at 3 and 12 weeks, utilising a cross-fostering approach in a rodent model.

**Results:** Perinatal sucrose exposure decreased plasma glucose concentrations in offspring at 3 weeks, but did not alter glucose tolerance. Increased adiposity was observed in 3-week-old offspring exposed to sucrose or HFCS-55 during suckling, with increased hepatic fat content in HFS-55-exposed offspring. In terms of specific fatty acids, hepatic monounsaturated (omega-7 and -9) fatty acid content was elevated at weaning, and was most pronounced in sucrose offspring exposed during both the prenatal and suckling periods, and HFCS-55 offspring exposed during suckling only. By 12 weeks, the effects on adiposity and hepatic lipid composition were largely normalised. However, exposure to either sucrose or HFCS-55 during the prenatal period only was associated with elevated plasma free fatty acids at weaning, and this effect persisted until 12 weeks.

**Conclusion:** This study suggests that the type of sugar and the timing of exposure (prenatally or during the suckling period) are both important for determining the impact on metabolic health outcomes in the offspring.
Methods: We developed a rat model of maternal overnutrition using a high-fat (HF) diet (60% kcal from fat) exclusively during the lactation-suckling period. Offspring from control (C) and HF-fed mothers were followed until 6 month of age. We further used this model to measure SCD1 expression, activity and promoter methylation in different WAT depots of C and HF adult offspring.

Results: We showed that HF diet feeding during lactation drastically modified breast milk FA composition without altering maternal body weight. Breast milk from HF-fed mothers displayed lower levels of medium-chain FA and higher levels of long-chain FA with increased proportion of n-6 to n-3. During the lactation-suckling period, HF offspring exhibited a strong increase in body weight associated with increased mass of epididymal (eFat) and inguinal fat (iFat) depots. At 6 month of age, HF offspring were heavier and displayed a specific increase in eFat mass while iFat mass was unchanged. The eFat expansion was associated with increased SCD1 mRNA and protein expression as well as enhanced desaturation index (palmitoleate + vaccine/n-palmitate ratio) suggesting increased SCD1 activity. In contrast, SCD1 mRNA expression remained unchanged in iFat. Finally, these maternal diet-induced alterations in SCD1 expression in eFat were accompanied by differences in promoter methylation at specific CpG, suggesting that epigenetic regulation contributes to SCD1 programming in our model.

Conclusions: Taken together, we showed that maternal overnutrition exclusively during the lactation-suckling period induced adult offspring obesity which was characterized by eFat expansion and increased SCD1 levels. The depot specific nature of this programming event is of note in light of the fact that eFat develops exclusively during this postnatal period, as opposed to iFat which is already partially developed at birth. Moreover, maternal HF feeding induced drastic changes in breast milk FA composition suggesting that FA could be key metabolic programming factors in the postnatal period. Overall, our data emphasizes the importance of optimal maternal and infant nutrition in this critical window.

PO3.01.09
Monosaccharides in post-weaning diet of young mice program body composition and feeding behaviour in adulthood
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Background: The nutritional environment at various stages of early life, including the early post-weaning period, has permanent consequences affecting development and later health. However, the programming role of specific carbohydrates after lactation is largely unknown. In the present study we investigated the potential of different monosaccharides in the post-weaning diet to program adult metabolic health.

PO3.01.10
Describing objectively measured and maternal reported infant and toddler physical activity levels and patterns at 3, 6, 12, 18, and 24 months
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Background: The nutritional environment at various stages of early life, including the early post-weaning period, has permanent consequences affecting development and later health. However, the programming role of specific carbohydrates after lactation is largely unknown. In the present study we investigated the potential of different monosaccharides in the post-weaning diet to program adult metabolic health.

Data from older toddlers and children (≥3 years) has shown that physical activity is beneficial for health and growth. However, physical activity levels, patterns, and correlates have not been well described in infants and toddlers under age two. This study aimed to objectively describe levels and patterns of physical activity in a group of South African infants/toddlers.
PO3.01.11

Voluntary exercise during development can improve eating behavior and metabolism in intrauterine growth-restricted animals.

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Background: Adverse events during prenatal period, especially those related to nutrition, can lead to insufficient growth and changes in metabolism increasing the risk of chronic conditions later in life. Clinical and experimental studies demonstrated that intrauterine growth restriction (IUGR) is associated with an increased preference for foods rich in fat and sugar and altered physical activity levels. Moreover, exercise can benefit metabolic outcomes, as well as brain connectivity and neurogenesis. The aim was to investigate, in an IUGR animal model, if voluntary exercise during development improves eating behavior and metabolism in adulthood.

Methods: IUGR was induced by offering a 50% food restricted diet starting on gestation day 10 (FR group). The other group received ad libitum diet during pregnancy (Adlib group). At birth, pups were cross-fostered to Adlib dams, generating FR/Adlib and Adlib/Adlib groups (pregnancy/lactation), IUGR and Controls, respectively. Starting on postnatal day 21, all pups were exposed or not to exercise in their home cage according to the following groups: (a) unlocked running wheel, (b) locked running wheel, (c) running wheel absent. In adulthood, palatable food consumption (chow rich in sugar and fat), body weight and percentage of abdominal fat were measured in males. Analyses were conducted split by exposition to exercise.

Results: Palatable food consumption during the dark cycle was different between IUGR and Controls only in the animals without running wheel in the home cage: IUGR group had a higher number of bouts per cycle (IUGR: 28.51 ± 1.95; Control: 14.42 ± 1.95; p < 0.001) and consumed more grams in 48h (IUGR: 29.98 ± 3.15; Control: 19.29 ± 3.15; p = 0.039). Body weight at 90 days of life were higher in Controls compared to IUGR animals when there was an unlocked running wheel available (IUGR: 399.58 ± 7.34; Control: 422.0 ± 7.34; p = 0.034); unlike IUGR animals were heavier (IUGR: 411.71 ± 11.23; Control: 376.70 ± 10.59; p = 0.039) and had higher percentage of abdominal fat (IUGR: 2.10 ± 0.15; Control: 1.58 ± 0.15; p = 0.029) in the running wheel absent group.

Conclusions: The exposure to voluntary exercise throughout development was able to equalize the palatable food intake and percentage of abdominal fat between IUGR and Control animals. The higher body weight observed in Controls compared to IUGR when the animals were able to exercise in the running wheel might be explained by an increase in muscle mass, as the percentage of abdominal fat was not different between Controls and IUGR. Interestingly, the absence of difference between IUGR and Controls in all outcomes when there was a locked running wheel available showed that the locked running wheel benefited the IUGR group, probably because the animals used it to play and climb during development. Exercise during development may modulate some systems, such as the dopaminergic system, improving eating behavior in the IUGR group. This hypothesis will be tested in this animal model.
PO3.01.12  
Early nutrition and subsequent risk of overweight and obesity in 8-year old children - a MoBa cohort study

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Background: From a life-course perspective, it may be assumed that early feeding habits can influence healthy eating and weight status in later childhood. In the current project, we aim to investigate potential associations between early life adherence to the New Nordic Diet (NND) and subsequent child growth pattern. NND encompasses a concept of a potentially healthy and sustainable diet with foods that are traditionally consumed and locally available in the Northern countries, and it aims to embrace a holistic perspective of healthy eating. For this presentation, preliminary results for associations between child diet score at 6 months and subsequent risk of overweight and obesity at 8 years are shown.

Methods: This study is based on available data from the Norwegian Mother and Child Cohort Study (MoBa). The child score was constructed from 63 406 Food Frequency Questionnaire responses from parents of 6-months old children. We have previously developed a NND-score for the mother’s diet in the MoBa, and the aim was to construct child scores at various ages based on the original NND-score. The developed score is a sum of 6 subscales based on the consumption of the following compounds: 1) Homemade (HM) vs industrially produced (IP) fruit puree; 2) HM vs IP dinners; 3) HM vs IP porridge; 4) Exclusive breastfeeding at least for 4 months (yes/no); 5) Breastfeeding at 6 months (yes/no); 6) Water vs sweetened beverages. Subscales were dichotomized by the median and coded to give either 0 or 1 point. The score (0-6 points) was further dichotomized into low (0-1 points), medium (2-3 points) and high (4-6 points) NND adherence. We used cohort-specific BMI references (5-19 years) from WHO as cut-offs to the overweight/obese category (overweight > +1SD). Binary logistic regression was used to examine the association between high vs low NND category at six months and risk of overweight and obesity at 8 years. Covariates included in the model were maternal age at delivery, maternal pre-pregnancy educational level, smoking during pregnancy, parity, and maternal pre-pregnant BMI. Odds ratios (OR) with 95% confidence interval (CI) were calculated for the high-score group with low adherence as the reference group.

Results: The total sample comprised 14 844 8-year olds, of which 13.7% (n = 2085) were overweight or obese (ISOBMI > 25). Distribution according to the early diet score was as follows; low 20.2% (n = 2993), medium 56.3% (n = 8650), and high 21.6% (n = 3201). In crude analyses, high vs low early diet score was protective of overweight/obesity at 8 years (OR: 0.80; 95% CI 0.69-0.92, P = 0.003). In the adjusted model, the association weakened and was no longer statistically significant (OR: 1.05; 95% CI 0.90-1.23, P = 0.27).

Conclusion: High vs low NND adherence at 6 months was not associated with later risk of overweight/obesity. These analyses will be extended to examine the association between childhood NND adherence and growth, from birth to 8 years.

PO3.01.13  
Association of vitamin D status in pregnancy with adiposity and cardiometabolic traits in childhood: the Rhea pregnancy cohort, Crete, Greece

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Background: Vitamin D (VitD) deficiency is common in pregnant women and since the fetus relies exclusively on maternal supply, deficiency could potentially interfere with fetal development. Low maternal VitD levels have been linked to low muscle mass and to poorer bone mineral accrual in the offspring, however little is known about effects on fetal adiposity. In vitro studies have shown that VitD affects adipogenesis by inhibiting the expression of key regulators like PPARγ and suppressing the differentiation of pre-adipocytes to mature adipocytes. As a result, low maternal VitD status may increase prenatal adipocyte differentiation and adipogenesis and promote the development of later obesity. A few human studies have investigated the impact of prenatal VitD on childhood obesity and cardiometabolic risk with inconclusive results. We aimed to investigate the associations of maternal 25-hydroxyvitamin D [25(OH) D] levels during pregnancy with offspring growth and cardiometabolic risk factors in childhood, using data from a longitudinal, prospective pregnancy cohort, the “Rhea” study in Crete, Greece.

Methods: We used prospective data on 532 children participating at the four and seven years’ follow-up in the Rhea birth cohort in Crete, Greece. Maternal VitD status was estimated by measuring plasma concentration of 25(OH) D at the first prenatal visit (mean: 14 weeks, SD: 4). Outcomes included anthropometric measurements (body mass index (BMI) z-score, waist circumference, skin-fold thickness), body fat percentage, systolic and diastolic blood pressure, and serum cholesterol, HDL cholesterol, triglycerides, glucose, and plasma insulin levels. As a primary aim, we assessed the difference in mean plasma 25(OH) D concentration between those with overweight/obesity and without at the four and seven years’ follow-up. As a secondary aim, we assessed the difference in mean plasma 25(OH) D concentration between those with cardiometabolic risk factors and without at the four and seven years’ follow-up. All analyses were adjusted for maternal age, BMI, smoking, parity, ethnicity, and infant sex. The results were further adjusted for maternal and infant adiposity, physical activity, and dietary intake. An interaction term between maternal and infant 25(OH) D concentration was tested for each outcome. The study was approved by the Institutional Review Board of the University of Crete.

Results: The sample included 532 children, of which 10.9% were overweight/obese (z-score > +1SD) at the four years’ follow-up and 11.5% at the seven years’ follow-up. The mean plasma 25(OH) D concentration was significantly lower in overweight/obese children compared to non- overweight/obese children at both the four (mean: 33.1 ng/mL, SD: 19.2 vs 40.4 ng/mL, SD: 25.5, P = 0.004) and seven years’ follow-up (mean: 29.1 ng/mL, SD: 18.4 vs 35.9 ng/mL, SD: 24.2, P < 0.001). The difference in mean plasma 25(OH) D concentration between those with cardiometabolic risk factors and without was also significant at both the four (mean: 32.6 ng/mL, SD: 18.9 vs 39.8 ng/mL, SD: 25.3, P = 0.002) and seven years’ follow-up (mean: 29.3 ng/mL, SD: 18.6 vs 35.6 ng/mL, SD: 24.2, P < 0.001). The interaction term between maternal and infant 25(OH) D concentration was not significant for any outcome, indicating that the effect of maternal 25(OH) D concentration on offspring adiposity and cardiometabolic risk was independent of infant 25(OH) D concentration.

Conclusion: Our findings suggest that maternal vitamin D deficiency during pregnancy is associated with increased risk of later overweight/obesity and cardiometabolic risk factors in childhood, independent of infant vitamin D status. Further research is needed to investigate potential mechanisms and interventions to improve vitamin D status during pregnancy in order to prevent childhood overweight/obesity and cardiometabolic risk.
liped levels at 4 and 7 years of age. Adjusted associations were obtained via multivariable linear regression analyses.

**Results:** Pregnant women in Crete, Greece had low serum 25(OH) D levels (mean: 46nmol/l, SD: 16), while two thirds of women had VitD deficiency (25(OH) D <50 nmol/l). Offspings of women with very low 25(OH) D levels during pregnancy (first tertile <37.7 nmol/l) gave birth to children with higher BMI z-score (β coeff 0.2, 95% CI: 0.03, 0.37), higher waist circumference (β coeff 0.87 95% CI: 0.12, 1.63) and higher body fat percentage (β coeff 1.48, 95% CI: -0.46, 2.49) at 4 years of age, compared to women with higher VitD measurements (≥37.7 nmol/l), on covariate-adjusted analyses. The observed associations were more pronounced in girls than in boys (p for likelihood ratio test < 0.001) and persisted at 7 years of age. Maternal VitD concentrations during pregnancy were not associated with child cardiometabolic characteristics such as blood pressure or serum lipid levels.

**Conclusion:** Findings suggest that exposure to very low maternal VitD levels during pregnancy may be associated with increased central adiposity and body fat percentage in early and mid-childhood. Whether these results translate to increased risk of obesity and metabolic syndrome in later life remains to be investigated.

**PO3.01.14**

Dietary protein intake in infancy with growth and body composition throughout childhood: longitudinal cohort study

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**Background:** Protein intake in infancy promotes growth, but excessive intake may lead to obesity. However, whether these changes in body composition persist throughout childhood and are independent of later diet remains unclear. Therefore, we examined the associations of total protein intake and protein from different sources at age 1 year with repeatedly measured growth and body composition up to age 10 years, taking into account diet at age 8 years.

**Methods:** We included 3,573 children from the Generation R Study, a population-based prospective cohort study in Rotterdam, the Netherlands. Diet was assessed with food-frequency questionnaires at ages 1 and 8 years and macronutrient intakes were expressed as energy percentages (5E%). Height and weight were measured at eight time points between ages 1 and 10 years. Fat and fat-free masses were measured at ages 6 and 10 years with dual-energy X-ray-absorptiometry. We calculated body mass index (BMI), fat mass index (FMI) and fat-free mass index (FFMI). Outcomes were standardized for sex and age and expressed as standard deviation scores (SDS). Associations of protein intake with growth and body composition trajectories were examined with multivariable linear mixed models, taking into account macronutrient substitution effects.

**Results:** After adjustment for confounders, 5E% additional protein intake at age 1 year was associated with 0.11 SDS higher weight (95% confidence interval 0.05 to 0.17), BMI (0.11 SDS, 0.06 to 0.17), and FMI (0.09 SDS, 0.03 to 0.14) up to age 10 years. These associations were independent of overall diet quality or protein intake at age 8 years. Associations were irrespective of whether protein replaced dietary carbohydrate or fat and were explained by protein from animal sources and not from plant sources.

**Conclusion:** High protein intake in infancy, particularly from animal food sources, is persistently associated with adiposity up to age 10 years, irrespective of diet in later childhood. Infancy is a window of opportunity for early prevention of overweight and obesity, which can be achieved by restricting protein intake in this critical period of development.

**PO3.01.15**

Malnutrition in late-pregnancy malprograms to hyperphagia-pattern and obese-phenotype in adult rat-offspring

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**Background:** Early energy restriction, especially in intrauterine life, has been associated with disruption of metabolism control associated with the worldwide growing epidemic of metabolic syndrome. The aim of the current study was to assess lipid profile, glucose homeostasis and food intake as well as body composition of male adult rat-offspring whose mothers were undernourished during the last third of pregnancy.

**Methods:** At 70-days-old, virgin female Wistar rats were mated and the presence of spermatozoa in vaginal smear used to mark begin of pregnancy. Food was offer ad libitum until the day 14th of pregnancy, where dams underwent 50% food-restriction (FR50 group) until delivery. Control dams were fed ad libitum throughout pregnancy. At birth, rat-offspring were weighted and litter size adjusted to eight pups per dam. Rat-offspring were weaning at 21-days-old. Body weight and food intake from weaning until adulthood were assessed each two days. At 100-days-lod, the food intake during dark-cycle (from 6 PM to 11 PM and 6 PM to 6 AM) was evaluated. After that, fasted rat-offspring were euthanized to blood collection and posterior glucose and lipid profile evaluation. Body weight and visceral fat-pad were used to estimate obesity parameters.

**Results:** At birth, FR50 rat-offspring were 7.9% smaller than control ones (P<0.001). On the other hand, it was increased by +20.6% at weaning and by +13.0% at adulthood (P<0.01). When compared to control rats, the assessment of area under the curve (AUC) of body weight gain from FR50...
rats-offspring displayed an increase of 15.5% and the AUC of food intake was increased by 16.7% (P<0.05). Indeed, in relation to control rats the food intake of FR50 rats, at dark-cycle, was around 34.5% higher in the first 4h and around 6.7% higher in overnight (P<0.05). In addition, FR50 rats displayed high levels of fast glycemia (+15.2%), total-cholesterol (+21.1%) and triglycerides (+63.2%; P<0.01).

**Conclusions:** Calorie-restriction in late stage of intrauterine life malprograms long-term dyslipidemia, glucose dyshomoeostasis and a hyperphagic pattern in rats that can increase the risk factor to cardiometabolic diseases.

**PO3.02 - Genetics**

**PO3.02.01**

**Placental hypoxia-regulating network in relation to birth weight and ponderal index: the ENVIRONAGE Birth Cohort Study**

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HIF1α, miR-210 and its downstream targets ISCU, COX-10, RAD52 and PTEN are all part of the placental hypoxia-responsive network. Tight regulation of this network is required to prevent development of maternal-fetal complications such as fetal growth restriction. HIF1α expression is increased in preeclamptic placentae, but little is known about its association with birth weight in normal pregnancies. We measured placental levels of HIF1α, miR-210, ISCU, COX-10, RAD52 and PTEN in 205 mother-newborn pairs of the ENVIRONAGE birth cohort. Placental HIF1α gene expression was inversely associated with the ponderal index (PI): for a doubling in placental HIF1α expression, PI decreased by 6.7% (95% confidence interval [CI]:1.3-12.0%, p = 0.01). Placental RAD52 expression also displayed an inverse association with PI, a doubling in gene expression was associated with a 6.2% (CI: 0.2-12.1% p = 0.04) decrease in PI. As for birth weight, we observed a significant association with placental miR-20a expression only in boys, where a doubling in miR-20a expression is associated with a 54.2 g (CI:0.6-108 g, p = 0.05) increase in birth weight. The decrease in fetal growth associated with expression of hypoxia-network members HIF1, RAD52 and miR-20a indicates that this network is important in potential intrauterine insults.

**PO3.02.02**

**Association of rs11708067 polymorphism in ADCY5 with birth weight, glucose, insulin and neonatal insulin resistance**


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**Background:** The fetal insulin hypothesis proposes that the association between low birth weight, insulin resistance and decreased insulin secretion in adulthood is genetically mediated. Infants with low birth weight have increased risk for neonatal morbidity and mortality, and elevated risk to develop diseases during adulthood. However, this situation could occur not only in low birth weight infants, but also in children of adequate birth weight with genetic risk factors. Mexican population has one of the higher risk factors for T2DM in the world being 1.7 times more likely to have T2DM than non-hispanic white population. The polymorphism rs11708067 identified in ADCY5 has been associated with low birth weight, elevated risk of type 2 diabetes mellitus and lower insulin secretion in adults. However whether rs11708067 is related to fetal-neonatal insulin secretion or insulin resistance remains to be demonstrated.

**Methods:** Genotyping for rs 11708067 in ADCY5 was performed by RFLPS for 95 infants born from healthy pregnancies, recruited in the central region of Mexico. Genomic DNA was extracted from cord blood or cord tissue. Cord blood glucose and insulin were measured by glucose-oxidase and ELISE, respectively.

**Results:** The polymorphism rs 11708067 in ADCY5 is in Hardy-Weinberg equilibrium (p 0.082). Genotype and allele frequencies were: AA: 0.49, AG: 0.42 and GG: 0.09; and A: 0.7 and G: 0.3. Differences for insulin levels (p 0.001), HOMA IR (p 0.04) and HOMA B (p 0.0002) within genotypes were found with the A allele being the risk allelle, under a dominant genetic model. No differences between the genotypes for birth weight and glucose were found.

**Conclusions:** The risk allele A in rs11708067 ADCY5 could be related to fetal/neonatal insulin secretion. This is the first study evaluating umbilical cord insulin associated with rs11708067 genotype. An increase in sample size is necessary to discern if this polymorphism could be associated with birth weight in the mexican population.

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**PO3.02.03**

**Influence of known genetic variants associated with adiposity on childhood abdominal, liver and pericardial fat assessed by Magnetic Resonance Imaging**

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**Background:** Besides overall obesity as measured by body mass index (BMI), abdominal and ectopic fat depots are suggested to affect the risk of metabolic disease. The distribution and accumulation of fat to these specific fat depots may be partly explained by genetics. Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) involved in fat accumulation and distribution, mostly...
in adults. Whether these SNPs also affect abdominal and organ-specific fat depots in children is unknown.

**Methods:** In a population-based prospective cohort study among 1,995 children we tested six genetic risk scores, based on SNPs for childhood BMI, adult BMI, liver fat, pericardial fat mass, and visceral- and subcutaneous adipose tissue ratio (VAT/SAT ratio), and four individual SAT and VAT associated SNPs, for association with SAT, VAT, VAT/SAT ratio, liver fat fraction, and pericardial fat mass measured by Magnetic Resonance Imaging.

**Results:** The childhood BMI genetic risk score was associated with higher SAT (0.020 standard deviation (SD) increase in SAT per additional risk allele in the risk score, 95% confidence interval (CI) 0.009; 0.031) and higher VAT (0.021 SD increase per additional risk allele, 95% CI: 0.009; 0.032). The adult BMI genetic risk score was associated with higher SAT (0.022 SD increase per additional risk allele, CI: 0.015; 0.029), VAT (0.017 SD increase per additional risk allele, CI: 0.010; 0.025), and lower VAT/SAT ratio (0.012 SD decrease per additional risk allele, CI: -0.019; -0.006). The adult liver fat genetic risk score was associated with liver fat fraction (0.122 SD increase per additional risk allele, CI: 0.086; 0.158). Rs7185735 (SAT), was associated with SAT (0.151 SD, CI: 0.087; 0.214) and VAT/SAT ratio (-0.126 SD, CI: -0.186; -0.065), all p-values <5.00*10^{-4}. After stratification by sex the associations remained in both sexes for the adult BMI risk score with SAT and VAT, and for the liver fat risk score with liver fat fraction. Associations present among boys only were shown for the childhood BMI risk score with SAT, and the association of the adult BMI risk score with VAT/SAT ratio. Associations present among girls only were shown for the pericardial fat risk score with pericardial fat.

**Conclusions:** There is a shared genetic basis between body fat distribution in adulthood and childhood. Adiposity-associated genetic variants may regulate the distribution of fat in the body differently in boys and girls already before puberty.

**PO3.02.04**

Interaction between birth weight and the PLIN4 variant rs8887 on impulsivity at 5 years old children

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**Background:** PLIN4 is a PAT family protein acting in the lipid droplets storage. Human PLIN4 isoform encoded by the single nucleotide polymorphism (SNP) rs8887 interacts with omega-3 polyunsaturated fatty acids (n-3 PUFAs) and confers protective effect to obesity. This interaction is dependent on the A allele presence of the rs8887 SNP. Interestingly, intrauterine growth restriction (IUGR) individuals seem to be more sensitive to the protective effects of n-3 PUFAs, having less food fussiness and external eating. This study investigates whether the A allele presence of the rs8887 SNP interacts with fetal growth, influencing inhibitory control in children.

**Methods:** 254 five-year-old children taking part in a birth cohort study in Canada were genotyped and administered the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computerized cognitive battery, including the Stop Signal Task (SSRT). Birth weight ratio (BWR) was used to characterize growth during fetal life.

**Results:** There were no significant differences between the A allele carriers compared to the non-carriers for the main confounders. There was a significant interaction between BWR and the A allele presence in the SSRT task (p = 0.014), with lower birth weight being associated to poorer inhibitory control only in the non-carrier subjects (B = -586.81, beta = -1.452, t = 2.019, p = 0.045).

**Conclusions:** The rs8887 SNP appears to be an important moderator of the association between IUGR and impulsivity in children, and this has implications in primary prevention of conditions associated with inhibitory control deficits in this population.
**PO3.02.06**

The postnatal renal transcriptome is differentially affected by various intrauterine deficiencies in male rats


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**Background:** Intrauterine deficiencies may predispose to renal disease in later life. Even slight changes in gene expression during kidney development may adversely affect outcome. We aimed at identifying candidate genes and networks involved in early renal programming after intrauterine growth restriction (IUGR) in rats.

**Methods:** IUGR was induced by utero-placental insufficiency after bilateral uterine vessel ligation (LIG) or intrauterine stress by sham operation (SOP) or low protein (LP) nutrition throughout pregnancy. Offspring of dams without intervention served as controls. Kidneys were examined by transcriptome analysis on postnatal (P) days P1 and P7 (n = 5 per group and time point; n = 40 in total). Subsequently, principal component, basic molecule, upstream regulator (Ingenuity) and STRING analyses were performed.

**Results:** LIG and LP animals showed reduced kidney weight on days P1 and P7. In group LIG, expression of genes and regulators were significantly (p < 0.01) altered on P1, suggesting acute organ injury. In group SOP, however, significant alteration of overall gene expression and specific genes known to affect kidney development were primarily present on P7. In group LP, gene expression changes indicated dysregulation of PPARs on P7.

**Conclusions:** Various intrauterine deficiencies differentially affect the postnatal renal transcriptome. After utero-placental insufficiency, perinatal organ injury and regeneration may contribute to long term disease risk. Both prenatal stress and malnutrition affect gene transcription over a longer period of time, and the alterations correspond with previously described long-term sequelae. Our study may help to define targets and timing of future interventions to improve kidney outcome after IUGR.

**PO3.02.07**

Effects of cumulative childhood cardiovascular risk factor exposure on transcriptomics in adulthood: The Cardiovascular Risk in Young Finns Study

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**Background:** Cardiovascular diseases (CVD), such as coronary artery disease and stroke, are major cause of mortality and morbidity worldwide. The CVD risk factor exposure in adolescence, such as dyslipidemia, elevated blood pressure, obesity and tobacco smoke, have been shown to impact cardiovascular disease risk or intermediate CVD phenotypes in adulthood independent of adulthood risk factors. Earlier studies have linked blood transcriptomic signatures to both CVD and their risk factors. However, it is currently unclear if childhood risk factor exposure affects adult status of the transcriptome, and whether such childhood effects are irreversible. Therefore, we studied if cumulative CVD risk factor burden in childhood is...
associated with blood gene expression in adulthood independently of adulthood risk factor levels.

**Methods:** The Cardiovascular Risk in Young Finns Study (YFS) is an ongoing multicenter follow-up of Finnish subjects who were healthy at baseline in 1980. Altogether 3596 subjects (boys and girls) aged 3-18 years participated at the baseline survey. Since then, the conventional CVD risk markers have been measured repeatedly over the subsequent follow-up studies from childhood to adulthood. Using these serial data, we calculated the childhood cumulative risk factor burden for blood pressure, serum lipids, body mass index and smoking (active and passive). Adulthood genome-wide gene expression was measured using Illumina BeadChip microarrays from peripheral blood RNA samples collected within the YFS 31-year follow-up survey in 2011 (n=1650). Linear modelling was used to analyse associations between cumulative childhood CVD risk factor burden and transcriptomics in adulthood. Models were adjusted for sex, age, blood cell counts, principal component of genetic and transcriptomic data, and for corresponding adulthood risk factor variables. Transcriptome-wide associations of adulthood CVD risk factors were also studied. Transcripts with false discovery rate less than 0.05 were considered significant.

**Results:** Several childhood cumulative CVD risk factors, such as serum total cholesterol and HDL cholesterol, had associations with adulthood transcriptome. However, none of these childhood associations remained genome-wide significant after adjusting for the adulthood risk factor. In general, adulthood CVD risk factors were associated with hundreds or thousands of peripheral blood transcripts. The strongest adulthood associations were seen for body mass index and blood lipids.

**Conclusions:** Our results suggest that cumulative childhood CVD risk factor burden has no independent longitudinal functional effect on the peripheral blood gene expression patterns which have been associated with adulthood CVD risk factor levels.

**PO3.02.08**

**Cord blood leptin and insulin in association with mitochondrial DNA content in newborns**

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**Background:** According to the developmental origins of health and disease theory, a disturbance in the early life environment can contribute to disease risk in later life. Leptin and insulin are anorectic hormones involved in energy homeostasis and are crucial for fetal growth. Disturbances of these hormones contribute to obesity and diabetes. In adults, mitochondrial dysfunction is an important hallmark of metabolic disturbance, including obesity and diabetes. However, the effects of early life metabolic perturbation are unexplored. In the present study, we investigate if metabolic hormones in early life are associated with differences in mitochondrial DNA (mtDNA) content.

**Methods:** The study included 242 subjects from the FLEHS (Flemish Environment and Health Study) III birth cohort. Relative mtDNA content of cord blood leukocytes was determined using quantitative PCR as the ratio of two mitochondrial genes (MT-ND1 and MTF3212/R3319) to a single copy nuclear gene (36B4). Cord blood levels of leptin and insulin were determined using immunoassays. The association between the studied metabolic hormones and mtDNA content was assessed by use of multiple linear regression, while accounting for cord blood leukocyte and thrombocyte counts, gestational age, gender, maternal pre-pregnancy BMI, maternal age, smoking during pregnancy, parity and the highest educational level of the household.

**Results:** Leptin and insulin levels were positively associated with cord blood mtDNA content. A 25% increase in the cord blood leptin levels was associated with 3.75% (95% CI: 1.56, 5.99) higher mtDNA content in cord blood (p=0.0008). Similar, a 25% increase in the mean insulin levels was associated with a 2.48% (95% CI: 0.33, 4.67) increase in mtDNA content (p=0.024).

**Conclusion:** Neonatal metabolic hormones were associated with cord blood mtDNA content. This suggests that the variation of mtDNA content accommodate or reflect the differences in the metabolic status, already in early life.

**PO3.02.09**

**Influence of in utero metal exposure on human placental gene networks and fetal growth**

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**Background:** Fetal growth restriction has implications for health outcomes later in life, including energy balance dysregulation and neurobehavioral dysfunction. Studies, including our own, have shown that disruptions in specific genes (e.g., imprinted genes) in the placenta as well as environmental insults (e.g., metal toxicants) are associated with abnormal fetal growth. However, focusing on the independent effects of individual metals and genes fails to account for the complex interactions that likely exist among individual constituents in both multi-pollutant exposure settings as well as genomic networks. Using novel bioinformatics and biostatistics methods, we assessed metal mixture levels and profiled the placental transcriptomic network to delineate a fetal growth restriction-
related gene-environment signature in the Rhode Island Child Health Study.

**Methods:** Using weighted quantile sum (WQS) regression analysis, we assessed the influence of metal mixture exposure (16 trace metals) measured in maternal toe nails on fetal growth restriction (small for gestational age (SGA) vs. appropriate for gestational age (AGA) infants). We identified functionally-related gene-sets (modules) perturbed in fetal growth restriction following implementation of weighted gene coexpression network analysis (WGCNA) on placental RNA-Seq data (12,000 Refseq annotated genes). The first principal component of each module (module eigengene) was derived to represent average module expression, and the top 10 genes maximally correlated with each module eigengene were defined as module hub genes. To identify network modules associated with fetal growth, we assessed the association between fetal growth restriction and module eigengenes as well has hub genes using logistic regression. Associations between WQS-derived metal mixture indices and module eigengenes as well as hub genes were determined using generalized linear regression models.

**Results:** We identified a metal mixture index predominated by arsenic and cadmium that was significantly, positively associated with fetal-growth restriction. One placental network module enriched for genes functionally related to gene expression processes (GO:0010467) was significantly, inversely associated with fetal growth restriction. The fetal growth-associated metal mixture index was additionally significantly and inversely associated with the fetal growth-associated placental gene network. Out of the 10 gene expression module hub genes, 5 genes (ANKRD12, C21orf91, INO80D, MBTD1 and PHIP) were significantly, inversely associated with both fetal growth restriction and the metal mixture index.

**Conclusions:** This study provides the first comprehensive assessment of the influence of *in utero* environmental insults on fetal growth through placental genomics. Our findings suggest a combined additive effect of arsenic and cadmium on the downregulation of fetal growth, and this effect may be partially mediated by the downregulation of a network of gene expression-related genes in the placenta.

**PO3.02.10**

**Widespread prevalence of a CREBFR variant associated with weight and height in Polynesian children**

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**Background:** Investigating a large and ethnically diverse cohort from the Pacific region, we aimed to replicate and extend the recently reported findings that a CREBFR genetic variant is strongly associated with body mass index in Samoans.

**Methods:** A birth cohort of more than six thousand children was utilised. In this study, genotyping of two markers was undertaken in both Polynesian and non-Polynesian individuals in the cohort.

**Results:** We report that the CREBFR genetic variant is not confined to Samoans but is prevalent in all other Polynesian populations sampled, including Māori. We found that this variant was associated with growth from two years of age, and that the effect was more apparent in boys. On average, we observed allele-specific increases in weight (\(p = 0.008, +395\) g), height (\(p = 0.009, +0.63\) cm) and waist circumference (\(p = 0.007, +0.62\) cm) at four years of age. There was no effect on birthweight (\(p = 0.129\)).

**Conclusion:** Polynesian populations experience a disproportionally high burden of obesity, starting in early childhood. This new knowledge offers potential for more accurately targeted interventions aimed at establishing healthy growth trajectories from the earliest possible age.

**PO3.02.11**

**Perinatal over- or undernutrition programs adipogenesis: Mechanism of a common Wnt10b/PPARγ pathway mediated via differential β-Catenin signaling**

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**Introduction:** Perinatal over- or under-nutrition results in obese adult offspring with programmed enhanced adipogenesis. We have shown that increased adiposity in both offspring groups is mediated via early upregulation of adipogenic transcription factor, PPARγ, which promotes adipocyte differentiation. Induction of PPARγ and adipogenesis is regulated by factors including Wnt10b signal transduction. Activation of Wnt10b signalling inhibits adipogenesis through both canonical β-catenin dependent and non-canonical β-catenin independent pathways. We hypothesized that inhibition of Wnt10b contributes to increased PPARγ and enhanced adipogenesis in offspring exposed to maternal obesity and undernutrition. We further determined whether these effects were mediated via β-catenin pathway.

**Methods:** Female rats were fed either a high fat (HF; 60% k/cal) or control (10% k/cal) diet prior to mating, and throughout pregnancy and lactation. An additional group of dams were 50% food-restricted (FR) from pregnancy day 10 to term to produce growth-restricted newborns. After birth, HF pups were nursed by the same dam whereas FR pups were cross-fostered to Control dams. All pups were weaned to normal diet. Adipose tissue was obtained at 1 day (inguinal) and 9 months (retroperitoneal) of age from male offspring. Protein expression of Wnt10b and β-catenin were analyzed.

**Results:** As compared to controls, both HF and FR male newborn PPARγ levels were upregulated (2-fold; \(P < 0.05\)) and Wnt10b was downregulated (0.5, 0.6-fold, respectively; \(P < 0.05\)). β-catenin expression was decreased in HF (0.7-fold;
PO3.02.12
Molecular determinants of design optimality in cardiopulmonary systems: Sprouty2 coordinates airway and vascular branching programmes in mammalian lung development.

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Background: Sprouty2 (Spry2) acts as a central regulator of tubular growth and branch patterning in the developing mammalian lung by controlling both magnitude and duration of growth factor signalling. To determine if this protein coordinates airway and vascular growth factor signalling, we tested the hypothesis that Spry2 links the primary cue for airway outgrowth, fibroblast growth factor-10 (FGF-10), to genomic events underpinning the expression and release of vascular endothelial growth factor-A (VEGF-A).

Methods & Results: Using primary fetal distal lung epithelial cells (FDLE) from rat, and immortalised human bronchial epithelial cells (16HBE14o-), we utilised various molecular techniques such as western blotting, real-time PCR, chromatin immunoprecipitation and electrophoretic mobility shift assay. We identified a nuclear sub-population of Spry2 which interacted with regions of the rat and human VEGF-A promoter spanning the hypoxia response element (HRE) and adjacent 3′ sites. In FDLE cultured at the PO2 of the fetal lung, FGF-10 relieved the Spry2 interaction at the HRE region by promoting clearance of a 39kDa form and this was accompanied by histone-3 S10K14 phosphoacetylation, promoter de-methylation, hypoxia inducible factor-1α activation and VEGF-A expression. This repressive characteristic of nuclear Spry2 was relieved in 16HBE14o- by shRNA knockdown, and stable expression. This repressive characteristic of nuclear Spry2 was relieved in 16HBE14o- by shRNA knockdown, and stable expression of mutants (C218A; C221A) that do not interact with the canonical Wnt10b/β-catenin pathway in response to over-nutrition (ie, HF), the adipogenic stimulation is mediated via a non-canonical β-catenin independent pathway in response to undernutrition (ie, FR).

Conclusions: Both perinatal over- and under-nutrition promote adipose PPARγ expression via suppression of Wnt10b signalling. Whereas enhanced adipogenesis likely occurs via the canonical Wnt10b/β-catenin pathway in response to over-nutrition (ie, HF), the adipogenic stimulation is mediated via a non-canonical β-catenin independent pathway in response to undernutrition (ie, FR).
between rs602662 and gastrointestinal and respiratory illnesses, as rs602662 is in high Linkage Disequilibrium with rs601338 ($R^2 = 0.92$; Ensembl). Longer breastfeeding duration was a significant predictor for lower risk of diarrhoea independent of infant FUT2 genotype.

**Conclusions:** These results confirm the association of infant major FUT2 alleles with a higher risk of gastrointestinal illnesses in early life and additionally reveal novel strong associations with respiratory illnesses. These findings indicate that considering FUT2 locus variants would be advisable in future studies investigating risks of gastrointestinal and respiratory illnesses in infants and children.

**PO3.02.14**

**Prospective study of PPARG Pro12Ala polymorphism effect on immune system in pregnant women and their offspring: The PREOBE study**


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**Background:** Peroxisome proliferator activated receptors gamma (PPARG) is an important molecular factor participating in many metabolic pathways during pregnancy. B-lymphocyte antigen CD19 is a clinical biomarker linked to the lymphocyte B development, with relevance during early life. On the other side, the ratio CD4/CD8 $\leq 1$ is associated with immunodeficiency. We aimed to evaluate the relationship between the polymorphism of PPARG Pro12Ala and immune molecular and cellular components in 145 mothers and their offspring participants in the PREOBE study.

**Methods:** Maternal venous blood was collected at 24, 34 and at delivery plus umbilical cord samples. Immune system markers were analyzed by four-colour flow cytometry and genotyping for PPARG Pro12Ala were performed. U Mann-Whitney, Kruskal-Wallis, ANCOVA and Chi square test were performed using SPSS version 22.0, and were corrected by Bonferroni. Level of significance: $P < 0.05$.

**Results:** 125 pregnant women (86.21%) were homozygous (Pro12Pro/CC) and 20 (13.79%) heterozygous (Pro12Ala/CG). Regarding their offspring, 127 (88.47%) were homozygous with major CC genotype, 15 (11.18%) had CG heterozygous genotype, and one (0.35%) had GG genotype. Only CD19 levels in plasma were decreased in pregnant women carrying the GG and CG genotype compared to CC major homozygous one (1.63, 1.58, 1.42, respectively; $p \leq 0.05$). Only CD19 levels in plasma were modified significantly by PPARG at delivery in pregnant women carrying the CG genotype ($p = 0.0001$)

**Conclusion:** PPARG Pro12Ala polymorphism has an effect on immune parameters in pregnant women, with no apparent consequences on the immune molecules and cells in the offspring.

**PO3.02.15**

**Genetics of birth weight and other anthropometric traits and their influence on future risk of cardio-metabolic traits in Indians**

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**Background:** Phenotype at birth and early growth predict future risk of cardio-metabolic disorders. A high prevalence of low birth weight babies and emerging rise in cardiovascular diseases, type 2 diabetes and gestational diabetes stress the importance of Developmental Origin of Health and Diseases in India. Understanding the genetic basis of fetal programming will provides important insight into molecular mechanisms and how they relate to future metabolic traits. Little is known about the genetic determinants of fetal growth in Indians and how they influence later metabolic health.

**Methods:** We generated genome-wide SNP data in two Indian birth cohorts-The Pune Maternal Nutrition Study (PMNS; 658 mothers, 706 children) and The Parthenon Study (PS; 525 mothers, 564 children). We further imputed the genotype data using 1000 Genomes phase 3 reference panels. An association analysis of child genotype with anthropometric parameters at birth including weight, length, head, chest, abdominal and mid upper arm circumferences, and triceps and subscapular skin fold, was performed with residual standardized value adjusted for sex, gestational age, maternal age and body mass index (BMI) during pregnancy using linear regression with additive model. Similar association analysis was performed in adults using mothers’ genotype data. We further track genetic association with various metabolic traits in early childhood at 6 and 9.5-12 years. Association analysis was performed independently for each cohort and the results were combined by meta-analysis.
Results: The average birth weight was 2.6 kg and 2.9 kg in PMNS and PS respectively; boys were heavier than the girls. Gestational age, maternal age and BMI during pregnancy were strong predictors of birth outcomes. We identified novel variants in FBXO15 to be associated with subscapular fold, but no other variant reached GWAS significance (p < 5 × 10⁻⁸) for any anthropometric trait at birth though many variants showed suggestive association (p < 10⁻⁵). We investigated status of 60 birth weight associated variants from Early Growth Genetics Consortium and observed similar direction of association for 29 of the 42 variants present in our data. The combined effect of 42 variants showed significant association with birth weight (effect = 0.024, p = 0.003) and other birth phenotypes (Figure). Tracking analysis revealed significant positive association (p < 0.05) with anthropometric traits in children at 6 years of age (Figure). The combined effect of 42 variants showed negative association with systolic blood pressure, (effect = -0.019, p = 0.01 at 6 years; effect = -0.015, p = 0.046 at 9.5-12 years; effect = -0.025, p = 0.002 in adults), and fasting glucose (effect = -0.014, p = 0.04 at 6 years; and effect = -0.01, p = 0.05 in adults). The trends of association of maternal weight, height and cranial circumference at birth showed significant association with birth weight, height and cranial circumference at birth. We identified a novel association of adiposity at birth with FBXO15 which codes for a protein-ubiquitin ligase having a role in embryonic stem cell self-renewal. In addition, despite a small sample size, we could detect the combined effect of established birth weight associated variants with birth weight and other anthropometric traits in Indians. Further the tracking analysis revealed that the genetic effect of birth weight on cardio-metabolic traits starts in early childhood and remains consistent in adults.

Conclusions: We identified a novel association of adiposity at birth with FBXO15 which codes for a protein-ubiquitin ligase having a role in embryonic stem cell self-renewal. In addition, despite a small sample size, we could detect the combined effect of established birth weight associated variants with birth weight and other anthropometric traits in Indians. Further the tracking analysis revealed that the genetic effect of birth weight on cardio-metabolic traits starts in early childhood and remains consistent in adults.

Background: Vitamin D (VITD) is a prohormone involved in immune system, respiratory, endocrine, cardiovascular and bone metabolism. The action of the VITD are mediated by nuclear receptors, called VDR (vitamin D receptor). Changes in the composition of the VDR gene may induce to an elevated risk for development of disease linked to VITD metabolism.

Method: In a Cross-section study, there were included 106 pregnant women (37 to 42 weeks), and applied a standard questionnaire containing general health information, nutritional condition and complications during the pregnancy. Further, there were collected during the labor, 15 mL of cord blood to measurement of serum 25(OH)D and genotyping for VDR SNP.

Results: There were included 91 pregnant and newborn umbilical cords, of which 74 pairs were genotyped. The frequency of the SNP, maternal and newborn, were, respectively: Apal (30 and 22); FokI (20 and 7), BsmI (15 and 9), TaqI (23 and 13). There were no significant between the presence of any of the referred SNP and the levels of plasma maternal or cord vitamin D concentration. The mean of the age of included women were 26.2 ± 6.9 years. Most of the people self-declare brown, did not take any vitamin D supplements and only about a quarter referred sun exposure and the mean time of sun exposure were 6.0 ± 4.2 hours/week. The main complication during the pregnancy was urinary tract infection (UTI). In relation to newborns, most of them were male and the number of normal delivery and cesarian were the same. There were no association between VDR SNP with VITD concentration and weight, height and cranial circumference at birth. There is no evidence that the four SNP studied affect the vitamin D plasma concentration. Further, there is no association between VDR SNP with VITD concentration and weight, height and cranial circumference at birth.

PO3.02.17

AMPK pathway in placenta and its relationship with birth weight alterations and maternal nutrition status

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Background: Birth weight alterations have been associated with metabolic diseases during adult life. Placenta plays a central role linking maternal and fetal environment. Placenta responds with alterations in its structure and function, which can lead to changes in nutrient supply and activation of signaling molecules, such as AMPK (AMP-activated serine/threonine protein kinase). AMPK is a sensor of cellular energy status that is activated under conditions of low intracellular ATP levels following stress such as nutrient deprivation. AMPK is activated through phosphorylation by LKB1 (liver kinase B1). LKB1 is a tumor suppressor kinase that regulates multiple processes such as cell proliferation and stress responses.
Therefore, we hypothesized that alterations of birth weight and maternal nutritional status would be related to the expression and activation of the AMPK pathway in placentas.

**Methods:** Placental tissue samples (n = 60) of clinically healthy women, aged 15-45 years, with term pregnancy (37-42 SDG), were classified in three groups according to the birth weight and gestational age of the newborns: SGA (n = 20), AGA (n = 20) and LGA (n = 20) (small, adequate and large for gestational age respectively). Protein expression of AMPK pathway was evaluated (including signaling molecules AMPK, pAMPK, LKB1 and pLKB1) in homogenates of placental tissue by Western Blot. The nutritional status of the mother was analyzed according to serum levels of IGF-I evaluated by ELISA and its concentrations were interpreted together with CRP levels.

**Results:** Total AMPK protein expression in LGA group were 30% lower compared to SGA (p < 0.0013). Activation of AMPK pathway was twofold higher in SGA group (p = 0.000001) and 1.6 fold lower in LGA group (p = 0.000007) compared to AGA. Also, pAMPK of SGA group was fivefold higher compared to AGA (p < 0.000000). pAMPK/total AMPK ratio correlated with placental weight (r = -0.728, p < 0.0001) and birth weight (r = -0.841, p < 0.0001). Interestingly, pAMPK/total AMPK ratio correlated with pregestational weight (r = -0.402, p = 0.0024) but not with weight gain during pregnancy. Also, pLKB1 protein expression correlated with pAMPK/total AMPK ratio (r = 0.923, p < 0.0001). LKB1 and pLKB1 protein expression were different between groups (p = 0.013 and p < 0.0000 respectively). LKB1 protein expression in SGA showed was 35% higher than AGA, and SGA was 42% lower compared to LGA (p = 0.0274 and p = 0.0055 respectively). pLKB1 differ between SGA and LGA (3.12 vs 0.54 fold of AGA, p < 0.0000 expression respectively).

On the other hand, maternal IGF-I was correlated to CRP (r = -0.325 p = 0.0123), but not with activation AMPK pathway.

**Conclusions:** These findings suggest that LKB1 is involved in the activation of placental AMPK. As well, pregestational weight is associated with activation of AMPK pathway, and this may be related to birth weight alterations, supporting the idea of a potential role of these pathways regulating human placental and fetal growth.

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**PO3.03 – Reproduction and periconception**

**PO3.03.01**

Understanding barriers and enablers of a complex pre-conception intervention in Malaysia - preliminary findings from a process evaluation

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**Background:** Gestational diabetes mellitus (GDM) has adverse effects on pregnancy and its outcomes, and the growing prevalence of GDM globally is changing the diabetes landscape. In Malaysia the greatest increase in diabetes prevalence is reported to be amongst the younger age group (18-35 years) who have demonstrated a three-fold increase over the last two decades. The Ministry of Health leads a group of institutions in exploring the efficacy and feasibility of a pre-conception intervention among young married couples that aims to prevent GDM. The randomised controlled trial (RCT), Jom Mama, evaluates the effect of a complex intervention which comprises the usage of a personalised mobile application in combination with behaviour change counselling by community health promoters (CHP). To understand the barriers and enablers to implementing such a complex intervention, process evaluation is key, through examining implementation of the intervention, the mechanisms of its impact, and the circumstances around the intervention. A process evaluation was thus conducted in Jom Mama to assess the recruitment process, the feasibility and experiences in using the e-health platform from the perspectives of CHPs and young couples, the peer support sessions, and attrition from the intervention. The aim of this presentation is to report preliminary findings from the assessment of the feasibility and experiences in using the e-health platform and delivery of behaviour change counselling by CHPs.

**Method:** Focus group discussions (FGD), in-depth interviews (IDI) and observations by way of audio-recordings were carried out to explore the perceptions of CHPs and young couples about the intervention, specifically in using the e-health platform and on the behavioural change counselling. Data from the different approaches are triangulated. The research team conducted 9 FGD with the community health promoters, 9 IDI with the young couples, and 19 audio-recordings of the contact points. Data were transcribed and analysed using thematic analysis. Ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia.

**Results:** The CHPs welcomed the new perspective of health-care, i.e. behavioural change counselling in pre-pregnancy, different from their usual mother-and-child care. However, they were not in favour of the added work burden. The young couples preferred the face-to-face approach over telephone calls, and appreciated the counselling in motivating them towards lifestyle changes. The e-health platform has been used to its full potential by CHPs during contact points despite them admitting to being unfamiliar with the application in the early days. Good internet connectivity is key to effective use of the e-health platform, which some CHPs and young couples have complained of not always having. The young couples,
however, despite some of them not being savvy, found the phone application to be very informative.

**Conclusion:** Preliminary findings from the assessment suggest that in spite of teething problems, the e-health platform was found to be useful in facilitating lifestyle behaviour changes when paired with counselling by the CHPs.

**PO3.03.02**

**Effects of a preconception lifestyle intervention in obese infertile women on diet and physical activity: results of a randomized trial.**

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**Background:** Obesity in women of reproductive age is an increasing problem worldwide, with negative repercussions for women’s health and their future offspring. Lifestyle changes are difficult, but since women who intend to become pregnant are more susceptible for lifestyle changes, interventions during this time window might be more effective than interventions during any other period of life. The first large randomized controlled trial (RCT) of a preconception lifestyle intervention showed that the intervention was effective in reducing weight and improving cardio metabolic health. We here report the effects of a preconception lifestyle intervention on diet and physical activity in obese infertile women.

**Methods:** The current study is a secondary analysis of a multi-centre RCT, the LIFEstyle study. In total 577 obese infertile women were randomized between a six-month lifestyle intervention program (intervention group; N = 290) or prompt infertility treatment (control group; N = 287). Specific dietary behaviors were assessed using a food frequency questionnaire (FFQ). Physical activity was estimated using the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) questionnaire. Both self-administered questionnaires were filled out at baseline, and three, six and twelve months after randomization. Mixed models were used to analyze differences between groups at the various time points, during and after the intervention. All models were adjusted for baseline measurements, education level and pregnancy.

**Results:** Compared to the control group, the intervention group had statistically significantly reduced intakes of sugary drinks at three months (-0.5 glasses/day [95% C.I. = -0.8; -0.2]), savory snacks at three months (-2.4 handful/week [-3.4; -1.4]) and at six months (-1.4 handful/week [-2.6; -0.2]), and sweet snacks at three months (-2.2 portion/week [-3.3; -1.0]) and twelve months after randomization (-1.9 portion/week [-3.5; -0.3]; figure I). There were no significant differences in vegetable and fruit intake between the two groups. Women in the intervention group were more physically active than women in the control group at all time points, but these differences were not statistically significant.

**Conclusions:** Obese infertile women who followed a six-month structured preconception lifestyle intervention program decreased their intake of unhealthy, high caloric foods and beverages during the intervention and increased their total moderate to vigorous physical activity during the intervention, compared to the control group. Future research in this group will assess whether these lifestyle changes have affected maternal and offspring health.

**PO3.03.03**

**Narrative review of reviews of preconceptional interventions to prevent increased risk of obesity and non-communicable diseases in children**

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Background: Evidence for the effect of preconceptional and peri-conceptional risk factors on childhood outcomes such as obesity is growing. Insights into mechanisms that influence the early nutritional environment of the fetus have also suggested that epigenetic processes during this period can increase susceptibility to obesity and other non-communicable diseases (NCDs) in later life. Thus, if issues such as maternal malnutrition (both over and under nutrition) are not addressed before pregnancy they could lead to a passage of risk of NCDs to the next generation. Birthweight (both low and high birth weight) has been extensively studied as a risk factor for future obesity, although it is a crude marker of prenatal development. Studies have also used maternal weight and gestational diabetes (GDM) risk as proxy outcome measures for future NCDs in children, with conflicting results.

Objective: To synthesise evidence for interventions in the preconception period to prevent obesity and other risk factors for NCDs in children.

Methods: A search for systematic reviews of interventions in the preconceptional period to prevent NCDs published between 2006 - 2016 was conducted on PubMed and Cochrane Database for Systematic Reviews. Quality assessment was performed on included studies.

Results: Sixteen reviews were included in the final report. There was considerable variation in the outcomes assessed between the reviews. The reviews predominantly included observational studies, leading to an overall low quality of evidence. For the target group of this review, preconceptional women, very few studies were identified. Results from these reviews suggest that exercise and diet based interventions can significantly reduce maternal weight post-partum (Mean difference (MD) -1.93 kg [95% CI -2.96 to -0.89]). Compared to standard care, women in the intervention groups gained less weight during pregnancy (MD for gestational weight gain MD -1.66 kg [95% CI -3.12 to -0.21]). Pre-pregnancy exercise was associated with GDM risk reduction and women who received preconceptional care (PCC) had a lower mean glycosylated haemoglobin (MD -2.43 [95% CI -2.58, -2.27]) compared to women who did not receive PCC. Balanced protein energy supplementation during and before pregnancy was associated with a 32% reduction in low birthweight in the intervention compared with the control group (Relative risk 0.68 [95% CI 0.51, 0.92]), and an increase in mean birth weight (MD 73.78g [95%CI 30.42, 117.15]).

Conclusion: The quality of evidence from eligible reviews hinders development of global recommendations on the prevention of obesity and NCDs in children. Nevertheless, this review has highlighted that women who received preconception education and counselling for lifestyle modification, were more likely than those who did not receive any PCC to have improved pregnancy outcomes, such as improved control of GDM and significantly improved birthweight. Further, behavioural outcomes such as improved eating habits and increased physical activity were observed in women, which are likely to have longer-term beneficial effects on maternal and child health. The outcomes included in the results are risk factors on the pathway to obesity and NCDs in later life, and longitudinal studies with long-term follow up are needed to support these findings.

PO3.03.04

Childhood and adulthood preconception exposures influence smoking cessation during pregnancy and in midlife

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Background: Tobacco smoking among women – before, during and after pregnancy – remains a common and major preventable risk factor for immediate and long-term adverse health outcomes for both mothers and their children. Informing the development of programs that enhance smoking cessation among pregnant women and prevent relapse postpartum and beyond, requires understanding of risk factors at different life stages. In this study, we examine risk factors across the life course for smoking cessation and reduction during pregnancy, and whether this is associated with smoking status in midlife.

Methods: The National Child Development Study (NCDS) is a British national birth cohort of women born in 1958. At age 33 years, women were asked for each pregnancy whether they had smoked cigarettes in the 12 months before pregnancy. Preconception smokers were then asked if they had changed their smoking behaviour during pregnancy (quit or reduced the number of cigarettes) or continued smoking as before pregnancy. Among 1,468 women who smoked before pregnancy, we examined associations of socioeconomic, psychological, health and lifestyle risk factors reported in childhood (age 11), adolescence (age 16) and early adulthood (age 23) with change in smoking behaviour from one year before to during pregnancy using multivariable multinomial logistic regression. The association between change in smoking behaviour during pregnancy and smoking status at age 55 years was examined while adjusting for significant risk factors at each life stage.

Results: Among smokers during the preconception period (39%), 26% reduced and 35% quit smoking during pregnancy (Figure 1). Parental smoking and social class during childhood, and early adulthood social class, depression, early smoking initiation and intensity, living with a smoker, and early motherhood were associated with a lower likelihood of smoking cessation and reduction during pregnancy. Among women who smoked before pregnancy, 54% were still smokers at age 55 years (Figure 1). Compared with women who smoked before and during pregnancy, women who quit during pregnancy were three times more likely to be non-smoker at age 55 years (odds ratio 3.12, 95% CI 2.35, 4.12) after adjusting for risk factors across the life course.
Conclusion: In this population-based birth cohort study, we demonstrate that smoking cessation and reduction during pregnancy are influenced by exposures during early life, adolescence and early adulthood. These results emphasize the need for implementation of tobacco screening and cessation services that address health risks in populations experiencing disadvantages. Despite these inequalities across the life course, our findings also indicate that cessation during pregnancy may have an enduring influence on women’s smoking behavior through to midlife, highlighting that pregnancy may represent an opportunity for long-term cessation among women who smoke in the preconception period.

Prevalence and changes in smoking status among women in the National Child Development Study

PO3.03.05
Effects of Antibiotic-Disruption of the Seminal Fluid Microbiome on Male Reproductive Health and DOHaD Changes in Resulting Offspring

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Paternal environment, including diet and obesity status, can lead to detrimental developmental origins of health and disease (DOHaD) effects in resulting offspring and even future descendants. Causative factors could include: 1) Alterations in the spermatozoa as they transition from the testes to the epididymis. For instance, sperm DNA fragmentation, total sperm count, and epigenetic alterations, including sperm microRNAs and tRNAs secreted from the epididymal tubules. 2) Paternal-induced DOHaD effects that lead to modifications in the seminal vesicle fluid contents, such as metabolites and cytokines. 3) Finally, a female may perceive the compromised state of her partner and reduce her parental investment in his offspring, as has been shown to occur in mammalian and non-mammalian species. One plausible mechanism that has not been previously considered is whether paternal-induced DOHaD effects originate from alterations in a putative seminal fluid microbiome (SFM). The seminal vesicle glands secrete a slightly basic product enriched with fructose and other carbohydrates. This environment is an ideal habitat for microorganisms. Thus, we postulated the existence of a SFM that may be influenced by the male’s environmental conditions. Prior studies in men have identified several bacterial species in the semen, which were presumed to originate from the seminal vesicles. However, bacteria identified from such samples could also originate from other portions of the male reproductive system or be urinary system contaminants. We have recently confirmed the existence of a SFM and that it can be influenced by genetic status and short-term consumption of a high fat diet in mice. Further, we used a combined antibiotic approach (CUB antibiotic protocol- Clindamycin 1.4 mg, Unasyn (ampicillin/sulbactam) 40 mg/kg day, and Baytril 50 mg/kg day) designed to target the primary bacteria within the SFM to demonstrate that alteration of the SFM in mice results in metabolic changes in the seminal fluid compared to males treated with saline vehicle alone (n = 10 per group). Inosine, xanthine, and L-glutamic acid were significantly reduced in the seminal fluid of antibiotic treated males; whereas fructose was increased in this treated group (P ≤ 0.05). Pathological changes in the male reproductive system were observed, including increased Periodic acid-Schiff (PAS)+ cells in the interstitium (potentially mast cells) of the testes and epididymis and cribriform growth of epididymal tubules from CUB- antibiotic-treated males. Antibiotic-treatment also altered the bacterial composition of the SFM. Offspring derived from antibiotic-treated males paired with control females show developmental origins of adult health and disease (DOHaD) changes in postnatal ultrasonic vocalizations and increased body weight gain in later life (n = 10 per group; P ≤ 0.05). The current studies are highly pioneering and suggest disruption of the SFM leads to DOHaD effects in resulting offspring and might compromise the health of the father. Further work is needed to determine how alterations in paternal composition, environment, and treatment with antibiotics might interact to affect the SFM and possibly result in more pronounced offspring DOHaD effects.

PO3.03.07
Beneficial effects of sympathomimetics on semen quality in humans

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Background: Over 50% of the Dutch male population in reproductive age uses (non)prescribed medication. So far, potential harmful effects of medication in general on semen quality are scarcely studied. Atopy is the tendency to produce specific IgE following exposure to allergens. This is a common chronic disorder for which often sympathomimetics are used.
Therefore, the aim of this study is to investigate associations between sympathomimetics and semen quality.

**Methods:** Between 2007 and 2012 we enrolled 2,166 couples visiting the preconception outpatient clinic ‘Achieving a healthy pregnancy’ of the Department of Obstetrics and Gynecology (Erasmus Medical Centre, Rotterdam). Participants completed a general questionnaire covering details on health conditions and medication use. During this visit anthropometric measurements were performed and non-fasting blood samples were obtained for the determination of biomarkers of one carbon metabolism (folate, vitamin B12, homocysteine). Information on semen analyses was collected from medical records (i.e. ejaculate volume, sperm concentration, and motility). Data of 873 men with at least one available semen analysis were analyzed using multivariable linear regression models, adjusted for BMI, alcohol use, smoking, ethnicity, age, and folic acid supplement use.

**Results:** Characteristics of men using sympathomimetics (n = 32) and controls (n = 841) were comparable between the groups, except for folic acid supplement use. A higher percentage of included men uses folic acid supplements (24.1% vs 5.40%; P < 0.001). The use of sympathomimetics was positively associated with percentage progressive sperm (β = 10.804; 95% CI, 3.917-17.691) and adjustment for confounding by indication did not alter this association (Table). There was no association between the use of sympathomimetics and other semen parameters.

**Conclusion:** The use of sympathomimetics is positively associated with the percentage progressive motile sperm in men of subfertile couples attending a preconception outpatient clinic. Future research should focus on dose-response associations to further substantiate our findings.

**PO3.03.08**

**Insertion alternative splicing variant of androgen receptor suppresses human ovarian granulosa cells apoptosis via up-regulating miR-125b expression independent of androgen**

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**Background:** Polycystic ovary syndrome (PCOS) is a set of endocrine symptoms and one of the leading causes of infertility. The pathology of PCOS is unclear however. Androgen excess, multiple ovarian immature follicles have been proved to be critical in PCOS. Our previous study revealed the exclusive existence of androgen receptor(AR) alternative splicing variants (ASVs) including insertion type(Ins) and deletion type(Del) in ovarian granulosa cells(GCs) of PCOS patients and the predominant role of AR ASVs in the hyperandrogenism of PCOS. miRNAs are a kind of ncRNA which function as a regulator of gene expression post-transcriptionally or in an epigenetic way. Previous study showed Wt AR attenuate follicle atresia by DHT-induced transcription of miR-125b. However, it remains to be illustrated in PCOS patients with ASVs.

**Methods:** All eligible PCOS patients were recruited in the Reproductive center, National Peace Maternal & Child Health Hospital according to Rotterdam criteria. Women infertile with tubal factor or male factors seeking IVF treatment were recruited as control patients. Patients’ GCs samples were isolated. All recruited patients were divided into three groups according to their corresponding AR ASVs in GCs (Wt group with GCs solely expressing wild-type(Wt) AR, Ins group with Ins AR in GCs and Del group with Del AR in GCs). Clinical characteristics of all recruited patients were collected from clinical database. miR-125b expression was detected using RT-PCR in both patients’ GCs samples of three groups and primarily cultured GCs overexpressing ASVs. Flow cytometry and western blot were used to evaluate apoptosis of GCs. Chromatin Immunoprecipitation(ChIP) and Immunofluorescence was used to detect ability of ASVs’ nuclear translocation. CoIP and DNA Pulldown were used to explore the regulatory mechanism of Ins on miR-125b.

**Result:** ASVs were associated with higher TT level, more antral follicles and higher E2 level and larger number of follicle > 14 mm on hCG administration day by statistical analysis of clinical characteristics. Moreover, miR-125b expression was significantly up-regulated in Ins group. In vitro, GCs overexpressing Wt AR showed a significant increase in miR-125b expression with DHT trigger. However, Ins AR significantly increased miR-125b expression in a DHT-independent fashion which subsequently suppressed the apoptosis of GCs. ChIP enclosed that Wt AR bound to the promoter of miR-125b thus up-regulating miR-125b expression but this binding was not observed in Ins AR. Ins AR showed nuclear translocation dysfunction in Immunofluorescence. CoIP and DNA Pulldown suggested that Ins AR up-regulated miR-125b expression through interacting ANT2.

**Conclusion:** Ins up-regulated miR-125b expression by interacting with ANT2 in a DHT-independent way, subsequently suppressed GCs’ apoptosis.

**PO3.03.09**

**The effects of a preconception lifestyle intervention in obese women on offspring development and behavior**

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**Background:** Polycystic ovary syndrome (PCOS) is a set of endocrine symptoms and one of the leading causes of infertility. PCOS is caused by the imbalance of androgen hormones and elevated levels of insulin. The effects of a preconception lifestyle intervention in obese women on offspring development and behavior remains to be illustrated in PCOS patients with ASVs.
Background: The incidence of maternal obesity has risen dramatically over recent decades. Exposure to maternal obesity during gestation can cause alterations in fetal neuroendocrine development, neuronal proliferation and brain development and thereby may have long-term impact on offspring development and behavior. Multiple cohort studies show that maternal obesity is indeed associated with neurodevelopmental problems in the offspring, including externalizing and hyperactive problems and attention deficit hyperactivity disorder (Edlow, 2017; Rivera, 2015). A lifestyle intervention during the preconception period may offer opportunities to prevent the negative effects of maternal obesity on the offspring (Lewis, 2014). Until now, no studies have been published about the effects of a preconception lifestyle intervention on the offspring development and behavior. We have the unique opportunity to follow-up children born to obese women who were randomized to a preconception lifestyle intervention or a control group (Mutsaerts, 2010).

Methods: Women, aged between 18 and 39, with a BMI ≥ 29 kg/m² and diagnosed with infertility because of chronic anovulation, oligo- or amenorrhea or, in case of a functioning ovulatory cycle, unsuccessful conception for at least 12 months were recruited between June 2009 and June 2012 in the Netherlands. Participants were randomly allocated to a lifestyle intervention (N = 290) or to standard fertility care (N = 287). The intervention consisted of dietary counselling, increasing physical activity and an individualized behavioral modification plan. The intervention goal was a minimum of 5% weight loss or a BMI < 29 kg/m². Women who conceived within 24 months after randomization of the Lifestyle study, were approached for follow-up (N = 145 intervention group; N = 160 control group). Women filled out the Ages and Stages Questionnaire (ASQ) and the Strengths and Difficulties Questionnaire (SDQ) to assess their child’s development and behavior respectively. Mann Whitney U-tests were performed to compare ASQ and SDQ scores between the intervention and control group and between offspring of women in the intervention group who reached the intervention goal and the control group. Data collection started in January 2016 and will finish in June 2017.

Results: At time of submission we analyzed data of 34 children in the lifestyle intervention group and 55 children in the control group. Offspring of women in the intervention group did not score differently on (sub)scales of the ASQ and SDQ than offspring of women in the control group. Offspring of women in the intervention group who reached the intervention goal (N = 12) showed less conduct problems (U = 201, p < .05), less total behavioral problems (U = .210, p < .05) and a trend to less hyperactivity (U = 222.5, p = .07) than offspring of women in the control group. No differences were observed in the development of the children.

Conclusions: Preliminary analyses show that randomization to a preconception lifestyle intervention per se does not seem to affect offspring development and behavior but that successfully accomplishing a lifestyle weight reduction goal was related to a reduction in offspring conduct and behavioral problems and may be related to a reduction in offspring hyperactive problems. These findings provide insights into the opportunities to prevent adverse child outcomes related to maternal obesity.

PO3.03.10

Awareness and communication with low health literate clients in preconception care: a problem analysis

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Background: In this study a problem analysis is performed to assess health care professionals’ awareness, knowledge, attitude, and communication skills towards patients with low health literacy in offering preconception care.

Design: semi structured interviews and observations during consultations

Setting: primary midwifery practices and secondary care in around Amsterdam, the Netherlands

Population: obstetric health care professionals, general practitioners, preventive health care physicians, clients with low health literacy

Methods: We performed fourteen in-depth, semi-structured interviews with midwives, obstetricians, preventive health care physicians and general practitioners to assess their knowledge about health illiteracy. We also observed the communication skills of nine other professionals during 28 general consultations with low health literate clients. After each observed consultation we assessed clients’ opinion of the consult and determined their level of health literacy by using SAHL-Dutch.

Main outcome measures: awareness of health literacy and communication skills of professionals

Results: Reaching high-risk groups with preconception care was seen as important but difficult. Describing patients with low health literate varied among the professionals. Only a few could describe techniques how to communicate with low health literate patients. Observations showed that the least used communication techniques were: retrieving knowledge, outlining an agenda and using the teach-back method. Most clients were satisfied about the consultation and the information they received, however the understanding of the information was not always clear.

Conclusions: Awareness of health literacy is low. To improve communication skills a health literacy focused learning strategies in preconception care can raise awareness, adjust perceptions, encourage the identification of low health literacy and increase the application of communication strategies.
PO3.03.11

POHaD - Paternal Origins of Health and Disease: Paternal obesity and early embryonic development.

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Several studies showed that female obesity has a negative impact on pregnancy, embryonic development, live birth rates and offspring’s health. However, only a limited number of studies have investigated the impact of paternal lifestyle or obesity on these fertility and birth-related outcomes. In human, a link between Body Mass Index (BMI) of future fathers and the number of successful live births has been shown. Studies in animals have demonstrated that diet-induced obese males have impaired preimplantation embryo physiology and delayed embryonic development. Hence, we hypothesize that paternal periconception lifestyle and obesity can impair sperm quality and embryonic development in humans. As such, the aim of this study is to investigate the impact of paternal anthropometric characteristics on early embryonic development. We set-up a longitudinal study in Belgian couples attending the Leuven University Fertility Center (LUFC). In this “Epigenetic Legacy of Paternal Obesity” (ELPO) study we will combine three consecutive stages of human development, including the male gametes, embryos and offspring. Our aim is to include at least 120 couples between 18-45 years old. We exclude patients with a history of cancer, radiation or chemotherapy, patients with pre-implantation genetic diagnosis, patients with sub-normal sperm parameters or ICSI treatment, and use of frozen/thawed sperm samples or donor gametes. Anthropometric data, including BMI, lean and fat %, and waist circumference are measured at the time of recruitment. Socio-demographic characteristics and information regarding lifestyle and dietary/nutritional intake are collected through standardized questionnaires. Embryo growth is assessed through a computer assisted scoring system. In brief, number of blastomeres, symmetry and degree of fragmentation are recorded on day 1, day 2 and day 3, after insemination. From our preliminary data, we expect to have 60% overweight/obese men and 40% normal weight men in our study sample. Taking into account age, lean and fat mass are within the expected ranges; respectively 80% and 20%. It is our aim to explore potential associations between these anthropometric characteristics and early embryonic development, using mixed models accounting for clustering and control for potential confounding. In conclusion, this epidemiological study will improve our understanding of inheritance of paternal lifestyle factors. We believe that the current concept of the DOHaD needs an extension. Besides known maternal contributions to offspring’s health, it is important to include preconceptional paternal exposures as well. Therefore, we suggest adding a POHaD (Paternal Origins of Health and Disease) theory in this Society of DOHaD.

PO3.03.12

Pre-pregnancy dietary, lifestyle and reproductive risk factors of gestational diabetes in an Australian population-based cohort

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Background: Gestational diabetes mellitus (GDM) is one of the most common metabolic complication during pregnancy. The most well-known pre-pregnancy risk factor for GDM is being overweight or obese, but other risk factors are less well-known. The objective of this study is to identify pre-pregnancy risk factors for GDM by comparing pre-pregnancy dietary intake, lifestyle and reproductive factors between women who developed GDM and those who did not.

Methods: The Australian Longitudinal Study on Women’s Health included 4,198 women aged 25 to 30 years at baseline without pre-existing diabetes who were followed-up between 2003 and 2015. Dietary intake was assessed with a 101-item validated food frequency questionnaire at baseline in 2003. General characteristics (age, area of residence, country of birth, highest completed education, work status and marital status), family history of type 2 diabetes, lifestyle factors (BMI, physical activity level, smoking and alcohol), and reproductive factors (polycystic ovarian syndrome (PCOS), parity, weight at age ten) were assessed with self-administered questionnaires sent out every three to four years. GDM was self-reported for each pregnancy at every survey round and validated in a subsample. Risk factors between women with GDM and no GDM were tested with independent samples t-test for continuous variables, chi-square test for categorical variables and Mann-Whitney U test for dietary intake variables. Significantly different variables were included in a multivariable log-Poisson regression model using generalised estimating equations to account for correlations in repeated pregnancies contributed by a single woman and changes in risk factors over time. Prevalence of meeting nutrient recommendations were estimated using the estimated average requirements cut-point method.

Results: During 12 years of follow-up there were 335 cases of GDM (4.5%) in 7,433 pregnancies (4,198 women). Women who were overweight or obese, born in Asia, older at pregnancy, nulliparous, had a family history of type 2 diabetes, had PCOS or often drank alcohol were at higher risk of developing GDM (relative risks (95% confidence interval) ranged from 1.10 (1.08-1.16) to 2.72 (1.43-5.16), p < 0.05). Work status was associated with development of GDM in the crude analyses, but not in the adjusted model. Age at baseline, area of residence, physical activity, smoking, education, marital status

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and weight at age 10 did not differ between women with GDM and those without. Carbohydrate, sugar, fibre, vitamin C and folate intake was lower in women with GDM than those without GDM (all p < 0.05), but not for other macro- and micronutrients. Prevalence of riboflavin deficiency (2.7% in women without GDM vs. 0.8% women who developed GDM, p = 0.04), vitamin A (27.7% vs. 32.9%, p = 0.04) and calcium (54.2 vs. 60.0, p = 0.04) was lower in women with GDM than those without, but not for other micronutrient deficiencies. Conclusion: Besides overweight and obesity, older age at pregnancy, having PCOS, family history of type 2 diabetes, being Asian and nulliparous are risk factors for development of GDM. Carbohydrate, sugar and fibre intake was lower in women with GDM than women without GDM, whereas for micronutrient intake and deficiencies only small differences were found.

PO3.03.13
Reproductive parameters and oxidative stress biomarkers of male Wistar rats prenatally exposed to cigarette smoke
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Background: The negative influence of cigarette smoking on developing fetus is well documented, amongst which are retarded fetal growth, intrauterine hormonal disruption and pregnancy complications. Reports of prenatal cigarette smoking on male reproductive hormones are controversial but shortened anogenital distance has been established to be an indicator of potential male infertility. This study was therefore designed to investigate the effects of prenatal exposure to passive cigarette smoke on anogenital distance, reproductive hormones and oxidative stress biomarkers of Wistar rats. Methods: Female Wistar rats were randomly divided into two groups (n = 5) and cohabited with matured male rats. Group 1 was exposed to smoke from an idling cigarette for 30 minutes per day in an exposure chamber from day 1 of gestation till parturition while Group 2 served as control (no exposure). Morphometric variables of the litters were recorded using digital caliper on postnatal day 1 (PND1) and at the end of 6th week of postnatal life. The male offspring were then sacrificed by cervical dislocation. Blood serum was collected for assay of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) using ELISA technique. Serum levels of Catalase and SOD were determined spectrophotometrically. Results: On PND1, crown rump length and total body length of rats prenatally exposed to cigarette smoke were significantly shorter. Significantly shorter anogenital distance and crown rump length were also observed at 6th week. An apparent decrease in serum levels of testosterone, LH and FSH were observed, but these decline were not statistically significant. Serum catalase and SOD significantly declined while MDA significantly increased. Liver function biomarkers, HDL and LDL were not affected but serum levels of total cholesterol and triglyceride significantly increased. Conclusion: The observed decline in anogenital distance and precipitation of oxidative stress by intrauterine cigarette smoke exposure may predispose rats to male infertility at adulthood.

PO3.03.14
Lack of insulin response in human umbilical vein endothelial cells from pregestational maternal obesity may result from endoplasmic reticulum stress
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Pregestational maternal obesity (PGMO) is associated with adverse cardio-metabolic newborn outcome. PGMO also causes insulin-desensitization in human umbilical vein endothelial cells (HUVECs). The endoplasmic reticulum stress (ERS) has been related to the development of obesity-associated insulin resistance. However, whether ERS is present and involved in insulin-desensitization in HUVECs from PGMO is unknown. Objective: (1) To assay whether HUVECs from women with PGMO show increased ERS markers, and (2) to evaluate the involvement of ERS in insulin-induced nitric oxide (NO) synthesis in HUVECs. Methods: HUVECs were isolated from normal or PGMO pregnancies from the Hospital Clínico UC-CHRISTUS (Chile). Cells were incubated (8 hours) in absence or presence of tunicamycin (5 μmol/L, ERS inducer), tauroursodeoxycholic acid (TUDCA, 100 μmol/L, ERS reducer), or both. We evaluated the protein level of CAAT-enhancer-binding protein homologous protein (CHOP), tribbles-like protein 3.
(TRB3), and phosphorylation and total protein level of protein kinase RNA-like endoplasmic reticulum kinase (PERK), eukaryotic translation initiation factor 2-alpha (eIF2α), inositol-requiring enzyme 1-alpha (IRE1α), and c-jun N-terminal kinase 1 (JNK1) by western blot. X-box binding protein 1 (XBPI) mRNA processing was evaluated by PCR. Synthesis of NO was induced by incubation of cells with insulin (1 nmol/L, 20 min) and measured by 4-amino-5-methylamino-2', 7'-difluorofluorescein diacetate (DAF-FM) fluorescence.

**Results:** Activator phosphorylation of PERK (1.7 ± 0.3 fold) and eIF2α (1.6 ± 0.3 fold), and protein abundance of CHOP (2.5 ± 0.5 fold) and TRB3 (1.5 ± 0.2 fold) were increased (P < 0.05) in HUVECs from PGMO compared with normal pregnancies. Tunicamycin increased the levels of all ERS markers in cells from normal but not from PGMO pregnancies. Conversely, TUDCA reversed PGMO-increased levels of ERS markers, but did not alter the levels of all ERS markers in HUVECs from normal. Activator phosphorylation of IRE1α and JNK1 were unaltered, and there was not splicing of XBPI mRNA. Finally, NO synthesis was increased (2.9 ± 0.2 fold, P < 0.05) in response to insulin by HUVECs from normal, but not from PGMO pregnancies. Tunicamycin reduced insulin-increased NO synthesis in cells from normal, but not from PGMO pregnancies. TUDCA did not alter insulin-induced NO synthesis neither in normal nor in PGMO pregnancies.

**Conclusions:** HUVECs from women with PGMO show ERS by activation of PERK branch, suggesting that PERK branch-associated ERS could results in PGMO reduced insulin sensitization. The increase of TRB3 protein level suggests a potential role for this protein as inducer of insulin desensitization in this type of foeto-placental endothelium. Finally, ERS is a PGMO-associated condition that induces insulin desensitization in HUVECs.

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**PO3.04 – Maternal obesity and physical activity**

**PO3.04.01**

**Association between maternal gestational weight gain and fetal growth in Japanese underweight women**


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**Background:** In Japan, there are greater number of underweight (body mass index [BMI] < 18.5kg/m²) women, compared with other developed counties. The association between pre-pregnant underweight and fetal growth has been shown in other countries, however, there was a paucity of data on Japanese women. To investigate the association between gestational weight gain (GWG) and fetal growth in Japanese underweight women.

**Methods:** We retrospectively reviewed 391 Japanese women with singleton pregnancy who underwent perinatal care and delivered babies at term at Keio University Hospital from January 2011 to December 2015. GWG was sub-grouped into three categories based on the guideline of the Japanese Ministry of Health, Labour and Welfare (JMHFW) (Group A: GWG < 9 kg, Group B: GWG ≥ 9 kg and ≤ 12 kg, Group C: GWG > 12 kg). Birth weight was adjusted for gestational age using the guideline of Japanese Society for Obstetrics and Gynecology (JSOG). Continuous data were compared among the three groups by ANOVA, and categorical variables were analyzed by the chi-square test. The correlation between GWG and birth weight was calculated using Spearman’s correlation coefficient, and \( p < 0.05 \) was considered statistically significant.

**Result:** Of 391 women, 149 (38%) were classified as Group A, 142 (36%) as Group B and 100 (26%) as Group C (GWG: 6.1 ± 2.4kg (mean ± SD), 10.5 ± 0.9kg and 14.2 ± 2.1kg, respectively). Thirty-seven (9.5%) developed gestational diabetes mellitus (GDM) and five (1.3%) developed pregnancy induced hypertension (PIH). Maternal age at delivery, pre-pregnancy BMI and parity were not statistically different among the three groups. Birth weight was significantly different among the three groups (2976 ± 324g v.s. 2940 ± 327g v.s. 3018 ± 361g, respectively, \( p < 0.0001 \), and greater GWG was associated with increased birth weight (\( r = 0.26, p < 0.001 \)). However, the incidence of small for gestational age (SGA) was not different among the three groups (9.3%, 7.0%, 5.0%, respectively, \( p = 0.45 \)).

**Conclusions:** In Japanese underweight women, greater GWG was associated with increased birth weight. Lower GWG did not affect the incidence of SGA.

**PO3.04.02**

The joint effect of maternal smoking during pregnancy and pre-pregnancy overweight on term birth weight of the offspring

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**Background:** Maternal smoking during pregnancy is associated with decreased birth weight, and an increased risk of being born small-for-gestational age (SGA), whereas pre-pregnancy overweight is associated with increased birth weight, and an increased risk of being born large-for-gestational age (LGA). However, the effect of both maternal risk factors simultaneously on birth weight is unknown.
Methods: In the PIAMA birth cohort we studied 3,241 term infants. Maternal smoking during pregnancy and pre-pregnancy height and weight were self-reported. We used multivariable regression analysis to compare term birth weight, risk of being SGA and LGA between infants of mothers who smoked during pregnancy, who had pre-pregnancy overweight, or who had both risk factors, to infants of non-overweight, non-smoking mothers.

Results: Compared to infants of non-overweight, non-smoking mothers, infants of mothers who only smoked, had lower term birth weight (-163.8 g, 95% CI: -214.4, -113.1) and greater risk of being SGA (OR = 1.94, 95% CI: 1.39, 2.69). Infants of mothers with pre-pregnancy overweight only, had higher term birth weight (120.4 g, 95% CI: 74.1, 166.8), and greater risk of being LGA (OR = 1.81, 95% CI: 1.38, 2.37). Infants of mothers with pre-pregnancy overweight who also smoked during pregnancy had similar term birth weight (-26.6 g, 95% CI: -113.0, 59.8), SGA risk (OR = 1.06, 95% CI: 0.56, 2.04), and LGA risk (OR = 1.09, 95% CI: 0.61, 1.96) to those of mothers without both risk factors.

Conclusions: Infants of mothers with pre-pregnancy overweight who also smoked during pregnancy had similar term birth weight and risk of SGA and LGA as infants of mothers without these risk factors. Using birth weight as a health indicator in perinatal care may be misleading in infants of overweight and smoking mothers, since it may mask potential long-term health risks due to either or both maternal risk factors in those infants.

PO3.04.03

Maternal obesity in pregnancy is associated with reduced heart rate variability in neonates

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Mother-child cohort studies and investigations in experimental animals suggest that maternal obesity may adversely influence development of the central regulatory pathways controlling offspring blood pressure (BP). Non-invasive measures of heart rate variability (HRV) provide insights into development of the autonomic nervous system (ANS). Fetuses of obese mothers have decreased HRV antenatally, associated with adverse neuro-developmental outcomes in childhood. We hypothesised that there would be evidence of cardiovascular autonomic dysfunction in newborn infants of obese women. In a case-cohort study of neonates born to obese women (BMI ≥ 30kg/m², n = 34) recruited into the UPBEAT RCT, we evaluated parameters of cardiovascular function in comparison with newborn infants of lean control women (BMI, 20-25kg/m², n = 26) recruited contemporaneously, and matched for age and ethnicity. BP and continuous ECG recordings (20mins) were made in sleeping swaddled neonates after feeding and within 72 hours of delivery. ECG traces were manually edited using MediLog (SCHILLER AG, Baar CH) and LabChart (ADI Oxford UK) software and HRV, time and frequency domain parameters, were computed blinded to maternal BMI. In the HRV time domain, standard deviation of normal-to-normal R-R interval (SDNN) was significantly reduced in neonates born to obese compared to lean women (SDNN [ms]: median (IQR) 27.7 (19.9-37.8) versus 37.2 (27.4-53.0) P = 0.04). Neonatal blood pressure (SBP, DBP and MAP) correlated with the sum of triceps and subscapular skin fold thicknesses (P < 0.05) and SBP also correlated with HR (P = 0.037) and the ratio of low to high frequency bands of the power spectral analysis of beat-to-beat HRV (LF/HF, P < 0.011). BP and LF/HF ratio was not different between neonates born to obese and lean women (SBP [mmHg]: mean (SD) 68.8 (13.2) versus 69.7 (9.9) P = 0.79). Maternal obesity was associated with depressed activity of the ANS in newborns independent of neonatal adiposity. Decreased SDNN, indicative of reduced global heart rate variability, increased sympathetic tone and vagal withdrawal, is a potent cardiovascular risk factor and may contribute to the development of hypertension and systolic dysfunction in infancy. Analyses by Cardiac MRI are discussed.


PO3.04.04

Mothers’ weight before pregnancy alters newborns’ telomere-related gene expression at birth

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Background: Telomere length may be predictive of life span and is highly variable among newborns. We recently found that newborn telomere length is inversely associated with maternal pre-pregnancy BMI. Telomere transcriptome profiles might therefore be a relevant mechanism of maternal overweight/obesity on molecular ageing of the next generation.

Objectives: To unravel potential underlying molecular mechanisms in the association between maternal pre-pregnancy BMI and newborn telomere length, we investigated the influence of pre-pregnancy BMI on the expression of telomere-related genes in umbilical cord blood. Further, we examined whether differentially expressed genes were associated with cord blood telomere length.

Methods: We used cord blood microarray gene expression data of 180 newborns in the ENVIRONAGE (ENVIRONMENTal influence ON AGEing in early life) birth cohort in Belgium. Average relative telomere length in cord blood was measured using a real-time PCR method. Expression levels of 212 selected telomere-related genes were analyzed in relation to
maternal pre-pregnancy BMI and newborn telomere length using regression models adjusted for potential confounders.

**Results:** 14 out of 212 telomere-related transcripts were found to be significantly associated with pre-pregnancy BMI (false-discovery rate (FDR)-corrected P-value < 0.05). 13 genes (RTEL1, PARN, NSMCE1, RAD54L2, TELO2, NHP2, SMG1, HNRNPU, DKC1, PARP1, YLPM1, LEMD2, WRAP53) were downregulated, whereas WRN showed upregulation with increasing BMI. Expression levels of RTEL1, PARN, RAD54L2, TELO2, DKC1, and YLPM1 were positively correlated with relative telomere length.

**Conclusions:** Our findings suggest that maternal overweight/obesity before pregnancy may affect offspring health by alterations in genes involved in telomere maintenance and/or telomere damage.

**PO3.04.05**

**Psychological distress, body mass index and weight gain in pregnant women**

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**Background:** Observational studies suggest an association between psychological distress and an increased body mass index (BMI). Both are common in pregnant women and may affect maternal and offspring outcomes. We examined whether psychological distress during pregnancy is associated with BMI and gestational weight gain (GWG).

**Methods:** We performed linear regression models in a population-based prospective cohort study among 6,545 pregnant women. Information about psychological distress was obtained in the second trimester of pregnancy using the validated Brief Symptom Inventory questionnaire. The psychological distress, depression and anxiety scores were dichotomized. Pre-pregnancy BMI was assessed by questionnaire in early pregnancy. GWG was estimated as the difference between weight in the third trimester and weight before pregnancy.

**Results:** In total, 10.8% of all women experienced psychological distress. Psychological distress and anxiety were positively associated with pre-pregnancy BMI (differences in BMI were 0.65 kg/m² (95% Confidence Interval (CI) 0.28, 1.03) and 0.49 kg/m² (95% CI (0.13, 0.84) for women with psychological distress and anxiety, respectively, as compared to women without). These associations attenuated to non-significance after adjusting for confounders, mainly caused by adjustment for maternal education and ethnicity. Overall psychological distress, anxiety, and depression were not associated with GWG.

**Conclusions:** In the current study, our results suggest that socioeconomic factors may play an important role in the association between psychological distress and BMI during pregnancy. Our results do not strongly support the hypothesis that psychological distress affects BMI and weight gain during pregnancy.

**PO3.04.06**

**Pregnancy exercise and nutrition research study (PEARs) with smartphone app support**

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**Background:** Interventions focusing on changing lifestyle behaviors may improve pregnancy outcomes. Mobile health (mHealth) technologies hold potential to support such interventions. This study aimed to assess the impact of a ‘healthy lifestyle package’; an antenatal behavior-change intervention supported by smartphone-app technology, compared with usual care, on the incidence of gestational diabetes mellitus (GDM) in overweight and obese pregnancy.

**Methods:** This was a single centre randomized controlled trial conducted at a tertiary referral hospital in Dublin, Ireland. Pregnant women (BMI 25–39.9 kg/m², between 10–15 weeks) were randomized to usual care, or a ‘healthy lifestyle package’ using a computer-generated sequence in a ratio of 1:1 in sequentially-numbered, sealed opaque envelopes with said sequence. This package consisted of low glycemic index dietary advice and daily exercise prescriptions addressing behavior change, supported by a tailor-designed app. Primary outcome was the incidence of GDM (per the International Association of Diabetes in Pregnancy Study Groups criteria) at 28-30 weeks’ gestation. This trial is registered with Current Controlled trials, ISRCTN29316280. Recruitment and pregnancy outcomes are complete.
Results: Between March 2013 and February 2016, 1858 women were assessed for eligibility and 565 recruited. 278 were assigned to the intervention and 287 to usual care of which 241 and 257 women respectively, completed an OGTT. The incidence of GDM did not differ between the two groups (15.4% vs. 14.1%, RR 1.1 95% CI 0.71—1.66 P=0.71). However, the intervention group experienced a greater reduction in fasting glucose from baseline to 28-30 weeks, (-0.12 vs. 0.05 mmol/L, P=0.02), and an attenuation in mean rise in insulin (3.49 vs. 5.17 mU/L, P=0.03), and HOMA2-IR (0.41 vs. 0.54 P=0.04). The intervention group also had significantly less GWG (11.3kg vs. 12.6 kg, P=0.027), lower dietary glycemic index and higher physical activity compared to controls. No difference in mean birthweight was noted, however, the intervention resulted in fewer infants born LGA (4.1% vs. 8.7%, P=0.03). Adverse events included one neonatal death and one stillbirth in the intervention group. No maternal deaths were recorded. There was no significant difference in infants born small for gestational age (birthweight <10th centile).

Conclusions: An mHealth-supported behavioral intervention did not decrease incidence of GDM. It did, however, have a positive impact on maternal GWG, glycemic index, physical activity, glucose homeostasis, and the number of infants born LGA.

PO3.04.07
Exercise before and during pregnancy alters the microbiome and glucose intolerance in females born growth restricted fed a high-fat diet
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Intrauterine growth restriction programs adult metabolic disease, which is reported to be alleviated by exercise. Additional physiological challenges, such as pregnancy and obesity, reveal and exacerbate metabolic disease, respectively, in females born small. The gut microbiome has also been implicated in modulating metabolic health. This study aimed to determine whether exercise before and during pregnancy is more beneficial in preventing metabolic dysfunction than exercise initiated during pregnancy alone and whether these outcomes are exacerbated with high-fat feeding. We additionally characterized the maternal gut microbiome to elucidate the role it may play in the metabolic phenotype in females born growth restricted. Uteroplacental insufficiency was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery on E18 in Wistar-Kyoto rats. Female offspring were fed a standard chow or high fat diet (HFD; 23% fat) from 5 weeks and mated at 20 weeks. Rats either exercised on treadmills for 4 weeks before and throughout pregnancy, during the final two thirds of pregnancy only or were Sedentary. A glucose tolerance test was performed (E18) and pancreatic β-cell and islet mass measured at E20. Rats were individually placed in metabolic cages for 24 hrs (E18) and feces collected for 16S rRNA microbiome profiling. Control and Restricted female rats exposed to a HFD were heavier with greater adiposity compared to Chow-fed rats, irrespective of exercise interventions. HFD exacerbated pregnancy-induced glucose intolerance in Restricted Sedentary rats. Exercise before and during pregnancy, prevented the development and exacerbation of glucose intolerance in Restricted and HFD rats. HFD rats exercised before and during pregnancy had increased β-cell and islet mass. Metabolic dysfunction was unchanged with exercise during pregnancy alone. Diet was the major driver of changes to the gut microbiome, with bacterial communities from HFD rats exhibiting a higher Firmicutes:Bacteroidetes ratio. Exercise had the largest impact on Chow-fed Restricted rat microbiota. Gut microbiotal communities from Chow-fed Control and Restricted rats were taxonomically and structurally indistinguishable in Sedentary mothers. However, exercise initiated prior to and during pregnancy specifically affected microbial communities in Chow-fed Restricted rats. Exercise altered community beta-diversity and decreased the abundance of bacterial orders (Lactobacillales and Enterobacteriales) and several genus of the order Clostridia. Additionally, correlations between the abundance of microbial taxa and glucose intolerance measures were detected in Restricted, but not Control rats. In conclusion, females rats born growth restricted are at an exacerbated risk of glucose intolerance when exposed to a HFD, which is prevented by exercise prior to and during pregnancy associated with improved β-cell mass. Our observation that identical microbial communities from Control and Restricted rats respond differently to exercise suggests that there is an interaction between exercise, the microbiome and physiological changes in mothers born growth restricted, which may be linked to metabolic disease. This study also suggests that exercise prior to and during pregnancy is more beneficial in preventing metabolic disease and dysbiosis than exercise during pregnancy only. Our findings have implications for maternal metabolic and microbiome dysfunction in growth restricted females, which may impact offspring health.

PO3.04.08
Gestational weight gain and its relationship with the birthweight of offspring
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Objective: To explore the appropriate weight gain in pregnancy and its relationship with the birthweight of offspring.
Methods: A total of 16 460 healthy pregnant women who delivered in Beijing Obstetrics and Gynecology Hospital and Haidian Maternity and Child Health Care Hospital in 2010 were recruited. All are singleton pregnancies. Conditions of babies and mothers were recorded, including maternal age, height, prepregnant weight, pregnant weight, gestational weeks
on delivery, delivery mode and new born birthweight. All the pregnant women were divided into underweight, normal weight and overweight group according to their prepregnant body mass index and the criteria of overweight and obesity for Chinese adults. Birth weight between 2500 g and 4000 was defined as normal birthweight, and 2900 g to 3499 g was defined as appropriate birthweight. Logistic regression model and receiver operating characteristics (ROC) curve analysis were used to explore the recommended gestational weight gain (GWG).

**Results:** (1) The average of GWG of the 16460 women was (17.1 ± 4.9) kg, and the average birthweight of the babies was (3406 ± 400) g. Prevalence of low birthweight and macrosomia was 0.92% (152/16460) and 7.55% (1242/16460), respectively. GWG of underweight (n = 3089), normal weight (n = 11478) and overweight group (n = 1893) was (17.4 ± 4.6) kg, (17.3 ± 4.8) kg and (15.6 ± 5.3) kg, respectively. And GWG was positively related with the birthweight of the offspring (P < 0.01). The differences of GWG, neonatal birthweight and macrosomia prevalence among the three groups are statistically significant (P < 0.01). (2). There are 8449 appropriate birthweight babies in the three groups. For their mothers in the underweight, normal weight and overweight group, the recommended GWG for all the three groups. For their mothers in the underweight, normal weight and overweight group, the recommended GWG for all the three groups. (3) According to the recommended GWG, low GWG will increase the risk of low birthweight (OR = 1.589, 95% CI: 1.085-2.326) and reduce the risk of macrosomia (OR = 0.200, 95% CI: 0.102-0.624). Excessive GWG will increase the risk of macrosomia (OR = 2.031, 95% CI: 1.789-2.306), but will not lower the risk of low birthweight (OR = 1.168, 95% CI: 0.774-1.764). (4) For the underweight, normal and overweight group, the range of GWG obtained by the receiver operating characteristics (ROC) curve analysis were 16.3-16.7 kg, 15.6-17.8 kg and 14.6-15.1 kg. For all the three groups, the range was 15.6-16.7 kg. The ranges obtained by the ROC curve were all within the recommended range.

**Conclusion:** The GWG was positively associated with the birthweight of offspring, and the appropriate GWG was around 16.0 kg.

**PO3.04.09**

**Can voluntary exercise in rat offspring reverse renal changes caused by maternal obesity?**

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**Background and aims:** Maternal nutrition is implicated in the development of adult metabolic diseases, and children of obese mothers have 22% increased risk of developing kidney disease. This suggests that impairments in kidney function may be programmed prenatally. However the link between maternal obesity and offspring kidney disease remains unclear. We studied whether running wheel exercise impacted kidney changes in rats born to lean or obese mothers.

**Methods and results:** Adult female Sprague Dawley rats were fed either normal chow or HFD ad libitum for 5 weeks, then mated with chow fed male rats. Dams continued on their assigned diet during lactation. Female offspring were weaned onto either chow or HFD and half of the offspring were exercised from 10-15 weeks of age prior to cull. Body weight, kidney mass, and kidney triglyceride levels were measured and kidney mRNA extracted for gene expressions. Offspring of obese mothers had significantly increased body weight and fat mass which were reduced by offspring exercise. Kidney weight was significantly increased by both maternal and offspring HFD. Maternal obesity was associated with increased renal triglyceride in both chow-fed (20%) and HFD-fed (28%) offspring (P < 0.01). It was also increased in offspring consuming HFD from both lean and obese mothers (P < 0.01). However, exercise increased renal triglyceride accumulation across all groups and reached significance only in HFD fed offspring from both mothers (P < 0.01). This accumulation was associated with altered renal expression of genes involved in lipid metabolism induced by maternal and postweaning HFD. Significant upregulation of the kidney injury markers Kim 1 and Ngal suggests evidence of early renal injury.

**Conclusions:** Our study suggests that exposure to maternal and postnatal obesity may alter offspring kidney function which might not be reversed by voluntary exercise.

**PO3.04.10**

**Influence of maternal obesity during pregnancy on offspring cardio-metabolic health and disease**

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Maternal obesity during pregnancy is a major public health problem worldwide. In Western countries, obesity prevalence rates in pregnant women are estimated to be as high as 30%. In addition, it is estimated that in these countries approximately 40% of women gain an excessive amount of gestational weight. Accumulating evidence strongly suggests a long-term impact of maternal obesity and excessive weight gain during pregnancy on adiposity and cardio-metabolic related health outcomes in the offspring throughout the life course. Stronger associations tend to be present for maternal prepregnancy body mass index than maternal weight gain during pregnancy. Thus far, it remains unclear whether these associations are explained by causal underlying mechanisms, or reflect confounding by various family-based socio-demographic, nutritional, lifestyle-related and genetic characteristics. The underlying mechanisms have mainly been assessed in animal studies and small human studies, and remain to be further explored in large human studies. Further research to explore the causality, underlying mechanisms and potential for prevention of cardio-metabolic
Maternal obesity, pro-inflammatory cytokines and offspring blood pressure and obesity


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Background: Approximately one third of women of childbearing age in the United States are obese and ~ 20% of conceptions occur in obese women. Among women with an ideal pre-pregnancy weight, ~ 40% gain excessive weight during gestation. Both pre-pregnancy obesity and excessive gestational weight gain (GWG), collectively referred to as gestational obesity, are risk factors for childhood obesity and other cardiometabolic dysfunctions. While chronic systemic inflammation is hypothesized to be a link from gestational obesity to cardiometabolic dysfunction in affected offspring, empirical data are limited in humans.

Methods: Logistic regression models were employed to examine associations between maternal systemic inflammatory cytokines/chemokines involved in inflammatory (TNF-α, IL-6, IL-8, IL-1β) and adaptive immune response (IL-4, IFNγ, IL-12 p70, IL-17) and pre-pregnancy obesity (BMI > 30), excessive GWG, and indicators of offspring cardiometabolic function in 356 mother-infant pairs. Maternal obesity, child blood pressure, and obesity at 5 years were ascertained via questionnaires and medical records. Child obesity status was determined using growth charts from the Centers for Disease Control. Blood pressure percentiles were calculated according to the National Education Program Working Group on High Blood Pressure in Children and Adolescents and then dichotomized at > 90th percentile. Cytokines/chemokines were measured in maternal first trimester plasma using human cytokine EMD Milliplex MAP kits and then dichotomized by the top third as well as top two thirds compared to the rest of the distribution. Models were adjusted for: maternal smoking, age, race, and education, with the addition of child sex for child obesity and blood pressure.

Results: The majority (89%) of participants were less than 35 years of age and a little over half were African-American. Among African Americans but not Caucasians, women with a pre-pregnancy BMI ≥ 30 had more TNF-α levels in the top third of the distribution (OR = 2.72, 95% CI = 1.38-5.38) compared to those with a BMI < 30 (Figure 1a). Maternal TNF-α levels in the top third of the distribution were also associated with pre-hypertension in African American offspring (OR = 1.32, 95% CI = 1.04-1.66, Figure 1d). Maternal IL-4 levels in the top two thirds of the distribution were associated with excessive GWG (OR = 2.88, 95% CI = 1.20-6.94) in African Americans (not shown). IL-4 in the top two thirds of the distribution was associated with a lower risk of obesity at age five years, associations being somewhat stronger in male offspring (not shown). In addition to IL-4 and TNF-α, there is evidence of associations between levels of other cytokines, including IL-8, IL-6, and IL-12, during the first trimester and risk of childhood obesity or blood pressure (Figures 1c and 1d).

Conclusions: Despite a limited number of cytokines/chemokines examined, these data are consistent with an influence of pre-pregnancy obesity on immune responses, with race and sex-specific effects. It is also possible that the affected immune responses are distinct from those influenced by excessive GWG. Confirmation of these findings will require replication with larger sample sets.
Background: Maternal gestational weight gain (GWG) seems to have an impact on offspring’s body weight. We aimed to analyse the influences of maternal GWG on their infants' growth during the first 18 months of life.

Methods: 170 healthy term infants between 0-2 months of age were randomized in a double-blind study to receive either standard infant formula (F1: n = 85) or formula supplemented containing LC-PUFAs, milk fat globule membrane components and synbiotics (Nutriexpert factor) (F2: n = 85). As control, a cohort of 50 breast-fed infants (BF) was also enrolled. Anthropometric data and percentiles were obtained and z-scores were calculated based on WHO standards of growth; the infants were classified as: risk of deficit, possible risk of deficit, normal, possible risk of excess and risk of excess regarding anthropometric measurements. Mothers were classified into 3 groups depending on their compliance with the American Institute of Medicine (IOM) recommendations for GWG according to pre-conceptional body mass index (BMI) (underweight: 12.5–18.0 kg; normal weight: 11.5–16.0 kg, overweight: 7.0–11.5 kg; obese: 5.0–9.0 kg), being classified as below, comply or exceeded the IOM recommendations. Normal distribution was assumed using Kolmogorov-Smirnov, and Chi-Square test and ANOVA test were performed using SPSS 22.0.

Results: No differences were found in maternal GWG according to the 3 infants-fed study groups. There were differences in anthropometric measures in the offspring during the first 6 months of life depending on their maternal GWG, but these differences disappeared at 18 months of age.

Conclusions: Worse growth trajectories were observed in the first months of life in infants born to mothers who didn’t reached the recommended GWG according to their pre-conceptional BMI, in comparison to those infants whose mothers complied the recommended GWG. Abnormal growth trajectories have been found that are important predictors for the onset and development of a wide range of later diseases.

Research question: The duration for which infants are exclusively breastfed (exBF) and the total duration for which infants are breastfed (exBF plus supplemented breastfeeding or TBF) influence numerous health outcomes over the lifetime. In particular, a growing body of epidemiological evidence indicates that shorter durations of exBF and TBF are associated with increased risks of developing obesity-related non-communicable diseases such as diabetes and heart disease in adulthood, making the promotion of appropriate exBF and TBF durations a public health priority. The available evidence, derived almost entirely from industrialized, state-level populations with strong socio-cultural stigmas against overweight and obesity, indicates that bigger mothers are less likely to breastfeed at all and are likely to end exBF and TBF earlier, compared to other mothers. It is currently unclear whether this is a general human pattern with a physiological explanation or whether it is unique to industrialized populations in which overweight and obese mothers breastfeed less for cultural reasons (e.g. stigmatization, lack of body confidence, lack of help with infant care).

Methods: With this in mind, we used published data from anthropological literature to investigate whether population mean durations of exBF and TBF are associated with coarse indicators of maternal adiposity and amount of help with infant care across a sample of 21 small-scale human populations from 16 countries on four continents; adult female adiposity is not stigmatized and is even viewed as desirable in most of these populations. Our adiposity indicator was population’s mean adult female Body Mass Index (BMI; weight/height²). Our infant care help indicator was a dummy score of whether or not mothers in a given population were generally reported to be helping their infants at least 65% of the time during infants’ first year of life. We fit linear mixed models by maximum likelihood to the data, allowing intercepts to vary randomly among continents.

Results: We found that population’s mean duration of exBF was longer in populations in which mothers received relatively little help with infant care; exBF duration was not associated with population’s mean adult female BMI. In contrast, population’s mean duration of TBF was not associated with amount of help mothers received but was significantly negatively associated with population’s mean adult female BMI. Specifically, each one-point increase in BMI was associated with approximately 1.6 months reduction in TBF duration.

Conclusions: Our results suggest that the negative association between duration of exBF and maternal adiposity reported in epidemiological studies may be socio-culturally driven and unique to industrialized, state-level populations. They further suggest that the previously documented negative association between TBF duration and maternal body size likely reflects a more general human pattern. These findings imply that promotion of extended exBF duration should perhaps focus on cultural factors (e.g. reducing stigma, improving self-efficacy).
and body confidence for bigger mothers in industrialized populations; considering the role of infant care structure in small-scale populations). Promoting longer durations of TBF may require deep understandings of the physiological tradeoffs it involves for mothers of all sizes and in a wide variety of contexts.

PO3.04.14

Low physical activity is associated with lower birth weight among rural pregnant women in Central Malaysia.

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Physical activity (PA) among pregnant women has been attributed to help improve birth outcomes. Living in different sociodemographic settings may contribute to differences in types of PA performed daily. Hence, this study was planned to identify the differences in types of PA between urban pregnant women (UPW) and rural pregnant women (RPW) in Central Malaysia. In addition, physical activity factors associated with birth weight was also studied. A prospective cross sectional study design was carried out among 498 pregnant women (at 24 weeks gestation and above) attending government maternal clinics in urban and rural districts. A validated Pregnancy Physical Activity Questionnaire was utilized for physical activity assessment meanwhile anthropometric measurement was determined using Tanita SC-330. Mean (SD) age of UPW and RPW was 29 (4.76) and 29 (5.23) years old, respectively. Most pregnant women in both counterparts fall into the overweight and obese pre-pregnancy body mass index category with RPW (52.6%) having higher percentage than UPW (45.3%). RPW were found to significantly conduct more light intensity PA (p = 0.04) and household/caregiving PA (p = 0.03) while UPW were significantly more sedentary (p < 0.05) than RPW. Prevalence of low birth weight was higher among RPW (10%) as compared to UPW (2%). Meanwhile, the prevalence of high birth weight was 4% for UPW and 1.5% for RPW. Multivariate analysis showed that sedentary PA (β = 0.23, p = 0.03) was positively associated meanwhile occupational PA (β = -0.29, p = 0.01) had inverse association with infants’ birth weight among RPW. No significant association was found for the UPW. In conclusion, sedentary activity among rural pregnant women may contribute to higher infant birth thus, recommending physical activity should be advocated during pregnancy.

PO3.04.15

Breastfeeding and exclusive breastfeeding are associated with maternal body mass index and social status among Norwegian mothers


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Background: Exclusive breastfeeding is recommended to secure adequate nutrition for infants. Long-term benefits from breastfeeding include reduced risk of noncommunicable diseases as obesity and diabetes type 2 in later life. The Norwegian Health authorities recommend exclusive breastfeeding the first 4 to 6 months of life, followed by a gradual introduction of food with continued breastfeeding. Despite a long paid maternity leave, exclusive breastfeeding rates at six months are low in Norway. In the latest national cross-sectional study on infant nutrition (2013), only 17% were exclusively breastfed at 5.5 month.

Previous studies have shown that mothers with higher socioeconomic status breastfeed longer than mothers with lower SES. This contributes to maintaining the social gradient in health. There is also a negative association between high maternal BMI and breastfeeding/exclusive breastfeeding, which is worrying considering the growing epidemic of overweight. We wanted to explore whether there is a social gradient in length of exclusive breastfeeding among Norwegian mothers in 2016, and if there is any association with maternal body mass index.

Methods: In 2016, a total of 715 infant/mother-dyads in the Norwegian randomized controlled trial Early Food for Future Health, completed the baseline questionnaire when the child was between 5 and 6 months. The baseline data were used to explore associations between length of breastfeeding/exclusive breastfeeding and socioeconomic factors and maternal body mass index during the first 5 months of life. Data concerning breastfeeding were collected by a Food Frequency Questionnaire. Predictor variables were selected based on earlier studies, and socioeconomic variables that were thought to affect breastfeeding and exclusive breastfeeding were included. Univariate tests with p-value less than 0.1 were considered candidate for the adjusted model. These were included: Maternal age, maternal education, marital status, parity, maternal BMI, degree of urbanization, geographic region, ability to pay an unforeseen expense of 3000 NOK, difficulties with running expenses and smoking status. Binary logistic regression analyses were used to examine factors that contributed to breast feeding and exclusive breastfeeding. A two tailed 5% level of significance was used.

Results: 16.4% of the infants were exclusively breastfed at 5 months of age. Infants of mothers with overweight or obesity had reduced odds of being exclusive breastfed the first 4 months of age. Infants of mothers with high parity had higher odds of being exclusively breastfed the first 5 months of age. Infants with higher educated mothers had increased odds of being breastfed at 1.2 and 5 months of age, compared to infants with lower educated mothers. Infants of mothers with overweight or obesity had lower odds of being breastfed at 3 and 4 months of age.

Conclusions: Our results confirm the negative trend in exclusive breastfeeding after 4 months of age and the social inequalities in breastfeeding/exclusive breastfeeding duration in Norway. Norwegian health authorities aim to increase the duration of breastfeeding. Targeting low SES-groups and
PO3.05 - Microbiome

PO3.05.01

Dairy lipids and probiotic L. fermentum in infant formulas differently program gut microbiota and physiology in a minipig model

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Even though breast milk is the gold standard in neonatal nutrition, most infants are at least partly formula-fed. Improving infant formulas (IF) to better approach the physiologic effects of breast milk is therefore of great importance. Human milk contains lipids with a very specific and complex structure and a diversified bacterial ecosystem that may be key factors in nutritional imprinting. However, very few IF contains dairy lipids (DL) rather than plant lipids (PL), or a probiotic component. Whereas short-term benefits of DL and Lactobacillus fermentum CECT 5716 (Lf) have previously been demonstrated on gut physiology, their long-term effects remain unknown. We hypothesized that the addition of DL and Lf in IF may impact gut microbiota and physiology in the neonate and that these early changes may have long-term consequences. The objective of this study was therefore to investigate, in a Yucatan minipig model, the short- and long-term effects of the addition of both DL and Lf in IF on gut physiology and microbiota. Forty-eight male and female piglets received a formula containing as lipids, only plant lipids (PL), a half-half mixture of PL and DL (DL), or a half-half mixture of PL and DL supplemented with Lf (DL + Lf) from postnatal day (PND) 2 to 28. Twenty-two piglets were euthanized at PND28 to investigate the short-term effects on digestion, gut microbiota (16S rRNA sequencing, ¹H NMR metabolomic analysis) and lipid metabolism. Twenty-six pigs were weaned on a standard diet for 1 month, then challenged with a hyperenergetic diet for 3 months and euthanized at PND140 to investigate the long-term effects on gut microbiota, intestinal barrier, immune and endocrine functions, and glucose metabolism. On the short-term (PND28), the addition of DL and Lf led to an increased gastric proteolysis, jejunal density of goblet cells and ileal lipolysis compared to PL. DL (± Lf) piglets displayed lower free fatty acids and triglycerides plasma concentrations compared to PL piglets. Gut microbiota composition was different between groups, the top 5 differentially impacted bacterial families being Ruminococcaceae, Lachnospiraceae, Bacteroidales S24-7 group, Prevotellaceae and Porphyromonadaceae. According to microbiota metabolism differed by 20 metabolites such as short-chain fatty acids, carbohydrates and amino acids. These early effects were associated with long-term consequences (PND140). Gut microbiota composition was different between groups, implicating the same top 5 families but with more differentiating families induced by Lf. DL + Lf increased intestinal GLP-1 basal and meal-stimulated secretory capacities, ileal trans- and paracellular permeabilites and decreased jejunal passage of LPS. DL (± Lf) decreased LPS-induced pro-inflammatory cytokine (TNFα and IL-8) secretions of ileal explants. The metabolic adaptations to the HE diet were similar between groups. This work clearly demonstrates a long-term programming effect of the addition of DL and Lf in IF, mainly targeting gut physiology and microbiota. DL have a beneficial impact on intestinal immune function whereas Lf is mainly of benefit to the endocrine function and impacts intestinal permeability. The role of the early gut microbiota modulation will be highlighted with integrative approaches that are currently underway.

PO3.05.02

Birth mode and infant gut microbiota sequentially mediate the association of maternal overweight with childhood overweight

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Background: Childhood overweight is a global public health concern. In Canada, over 20% of preschool children are overweight. Also on the rise is maternal obesity during pregnancy. Although children born to obese mothers are at higher risk for obesity, the mechanisms behind this association are not fully...
delineated. The transmission of obesogenic microbiota is recently hypothesized as a novel possible pathway. The current study examined whether birth mode and infant gut microbial diversity are sequential mediators in the association between maternal and childhood obesity.

**Methods:** The study population comprised a large sub-sample of 999 infants enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) population-based birth cohort. Maternal BMI [body mass index = weight (kg)/height (m²)] was calculated from data taken from hospital records or pre-pregnancy recall, or measurements taken at 1 year if the former were not available. Maternal overweight/obesity was classified as > BMI 25.0. Gut microbial diversity and composition of 3-month old infants was assessed using high-throughput 16S rRNA sequencing. At age 3 years, age-gender BMI-z scores were generated from measured weight and height according to WHO criteria. Child overweight/obesity was defined as >97th centile BMI z score. Data on maternal smoking, birth mode, breastfeeding and antibiotic exposure were retrieved from administered questionnaires or birth charts. A multiple mediator path model was evaluated to examine the indirect effects of birth mode (M1) and infant gut microbial diversity (M2) as mediators of the maternal–childhood obesity association. Statistical analyses were performed in SAS V9.4.

**Results:** One in 5 toddlers born to overweight/obese mothers were overweight at age 3 years versus 5% of children born to normal weight mothers. This translated into a 5-fold increased risk of overweight/obese at age 3 years (OR: 4.9, 95%CI: 2.8-8.7). Maternal overweight was associated with increased infant gut microbial indices at 3 months of age including total microbiota species richness, Firmicutes richness and diversity (P < 0.01). Increases in these indices elevated risk of overweight in toddlers more than two times. Moreover, overweight mothers were more likely to give birth by CS (OR 1.4, 95%CI: 1.1-1.9). CS-delivered infants had high total microbiota species richness but low Firmicutes richness and diversity at 3 months (P < 0.05). The multiple mediator path model revealed that birth mode and infant gut microbiota (especially total species and Firmicutes richness) sequentially mediated the association of maternal overweight with childhood overweight (P < 0.05).

**Conclusion:** This study provides evidence of a novel sequential mediator pathway involving mode of delivery and infant gut microbiota for the association between maternal overweight and childhood overweight.

**PO3.05.03**

**Absence of intestinal microbiota in early life does not critically affect cholesterol metabolism in mouse offspring**

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**Background:** Microbiota influences the development of the metabolic system and impacts on efficiency of food uptake, diet-induced obesity, cholesterol absorption and excretion and bile acid composition. Antibiotic treatment during early development of mice perturbs the microbiota only transiently, but nevertheless causes long-lasting metabolic changes. We aimed to identify potential mechanisms underlying such long-lasting changes in metabolism. Therefore, we determined the effects of a germ-free versus conventional state during gestation and lactation on cholesterol metabolism in the offspring at adult age.

**Methods:** We used germ-free C57BL/6J mice and germ-free mice that were conventionalized 5 weeks before mating them for breeding. Male and female offspring of the germ-free group were conventionalized at weaning. At weaning, offspring originating from the germ-free (former GF) and the conventional (CV) group were individually housed. Between age 10 and 30 weeks, mice were challenged with a Western-type diet. We repeatedly measured body weight and performed glucose and insulin tolerance tests (GTT and ITT) before and after the dietary challenge. At age 28-30 weeks, we assessed the following cholesterol homeostasis parameters: dietary cholesterol intake, intestinal absorption, *de novo* synthesis, biliary secretion rate, and finally, bile composition and fecal excretion rate. We terminated mice at 30 weeks and harvested blood and organs.

**Results:** Surprisingly, body weight did not differ between CV and Former GF mice for both males and females over their whole lifetime. Similarly, the germ-free condition in early life did not affect either the GTT or the ITT, before and after the dietary challenge with Western-type diet. Interestingly, liver weight, lipoprotein distribution, food intake, fecal neutral sterol excretion, total biliary bile acid concentration, and intestinal cholesterol homeostasis were similar between the former GF and CV group. Former GF mice had a lower bile flow than CV mice (males -19%, p < 0.05; females -23%, p < 0.01), while lower biliary cholesterol secretion was only observed in Former GF males compared to CV males (-56%, p < 0.05). However, a consistent and strong gender effect was found for many of the parameters studied: males had a higher body and liver weight, plasma lipoprotein-cholesterol content, and fecal neutral sterol excretion; females had a higher cholesterol absorption and biliary bile acid concentration.

**Conclusions:** This study demonstrates that complete absence of intestinal bacteria in mother and offspring during gestation...
and lactation does not influence glucose and cholesterol metabolism of the offspring in adulthood. The present germ-free and previous antibiotic results indicate that, in early life, a germ-free condition or administration of antibiotics differently affect adult metabolism. We hypothesize the presence of a specific microbiota composition mediates these programming effects.

PO3.05.04
Role of breastmilk microbiome in colonisation of the infant gut: a systematic review

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Background: Characterisation of the human gut microbiome has led to much interest in its role in the development of chronic diseases from obesity and cardiovascular disease to inflammatory and neurological diseases. Early colonisation of the infant gastrointestinal tract is likely to be a key determinant in the establishment of the gut microbiome in later life. The breastmilk microbiome may contribute significantly but it is unclear how the bacteria detected in human milk are derived and if they are transferred to and survive in the infant gut. A systematic review was carried out to evaluate the published evidence.

Methods: Searches were carried out using PUBMED, OVID, LILACS and PROQUEST and search terms included: (“Microbiota”[Mesh] OR “Metagenome”[Mesh] OR “Dysbiosis”[Mesh]) AND “Anti-Bacterial Agents”[Mesh]) AND (“Infant”[Mesh] OR “Infant, Extremely Premature”[Mesh] OR “Infant, Extremely Low Birth Weight”[Mesh] OR “Infant, Low Birth Weight”[Mesh] OR “Infant, Very Low Birth Weight”[Mesh] OR “Infant, Small for Gestational Age”[Mesh] OR “Infant, Premature”[Mesh] OR “Infant, Postmature”[Mesh] OR “Infant, Newborn”[Mesh] OR “Infant, Premature, Diseases”[Mesh]) and (microbiota OR bacteria OR microflora OR microbes) AND (dysbiosis) AND (infant OR neonate OR baby) AND (health) AND (disease) AND (birth OR parturition) AND (breastmilk OR breast milk OR human milk) AND (bacteria OR breast feeding OR breastfed) AND (formula OR infant OR formula OR bottle fed OR breast feed) AND (lactation). After initial removal of duplicates and not-relevant papers, sixty six papers were scrutinised by three authors before final evaluation of the evidence. Papers were considered for information on sample collection, avoidance of contamination procedures, specified bacterial analysis methods and kits used, and if they discussed maternal and infant events that may influence colonisation including mastitis and antibiotic use.

Results: Many studies considered the breastmilk microbiome and a small proportion of these considered the transfer of the bacteria to the infant and measured populations in infant faeces. Some studies followed transfer of probiotic organisms in interventional trials. Collection of breastmilk samples varied in timing (from colostrum to samples collected up to 6 months after birth) and in the method of collection (manual expression vs pump). Breasts were cleaned before sampling in many different ways including with water only, soap, saline, iodine, or chlorhexidine or some rejected foremilk before main sampling. The numbers of samples collected per study ranged from 5 to 220 and some studies looked at the whole bacterial profile whereas other concentrated on individual species. The sample storage conditions and times varied between studies along with the methods and kits used for DNA extraction and bacterial identification. In many studies there was little information on maternal health and antibiotic use.

Conclusions: Many studies reported a range of different bacteria in breast milk, however, the variation in methodology may have influenced the results. Standardisation of techniques would enhance the reliability of breastmilk microbiome research. More research is required to establish the factors determining the composition and impact of the microbiome of human milk on the colonisation of the infant gastrointestinal tract.

PO3.05.05
Diet-induced cholestasis modifies the maternal gut metabolome and microbiota, resulting in offspring metabolic impairment, altered intestinal metabolites and bacteria.

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Background: Pregnancy is associated with a change in the gut microbiome by the third trimester. Gut microbiota influence enterocyte signals that impact susceptibility to metabolic disorders, for example diabetes mellitus. Bile acids influence microbial growth, thus intestinal bile acid exposure in pregnancy may contribute to metabolic impairments observed in cholestatic pregnancy. The initial offspring microbiota is largely determined by the maternal microbiota, with inheritance in utero, at delivery, via lactation and in the shared environment of early neonatal life.

The offspring of cholestatic pregnancies demonstrate metabolic impairments; in a mouse model of cholestasis, female pups had
impairred glucose tolerance and dyslipidaemia when challenged with a Western diet. Similarly, the 16 year old children of mothers with intrahepatic cholestasis of pregnancy had raised BMI and fasting insulin (boys), higher hip and waist girth (girls), and lower fasting HDL cholesterol (girls) than the children of uncomplicated pregnancies in the North Finland Birth Cohort. We hypothesise that the offspring of cholestatic pregnancies develop an abnormal gut microbial and metabolite composition secondary to maternal alterations, contributing to phenotype of the offspring.

**Methods:** C57BL/6 female mice were fed normal chow or 0.5% cholic acid-supplemented diets and subsequently mated. Their offspring were fed normal chow or Western diets. Ultra-performance liquid chromatography – mass spectrometry was used to assess the caecal metabolome. 16S rRNA sequencing was performed to determine the caecal microbiota. Results were compared using OPLS-DA, PCA, NMDS, and t-tests with Benjamini-Hochberg correction for multiple measures.

**Results:** Supplementation of the maternal diet with cholic acid significantly alters the maternal microbiota with a similar effect to that of normal pregnancy, enhancing the abundance of Bacteroidetes and sulphur-utilising bacteria, with an associated reduction in microbial richness and diversity. Adult offspring of cholic acid fed mothers, when challenged with a Western diet, had increased susceptibility to obesity, impaired glucose tolerance, dyslipidaemia and hepatosteatosis. This phenotype was more marked in the female offspring. The offspring microbiota was significantly affected by maternal and neonatal diet, with a gender difference in the microbial composition revealed in the pups of mothers fed cholic acid when fed a Western diet. The female offspring of cholic acid fed mothers had a higher abundance of Alistipes, a bile-resistant member of the Bacteroidetes phylum, than males. Interestingly, this group had lower caecal bile acids (p = 0.036) than from normally-fed mothers when challenged with a Western diet, particularly deoxycholic acid, cholic acid and o-muricholic acid.

**Conclusions:** Pregnancy and cholic acid feeding have similar impacts upon the composition of the gut microbiome and metabolome. Maternal cholic acid feeding results in increases in bile-resistant bacteria in the caecum of female offspring. A gender difference in the microbiome and bile acid content of the caecum is revealed by a Western diet.

Together, these findings demonstrate how the establishment of the offspring gut microbiome, and associated metabolome is influenced by an altered maternal environment, contributing to an increased long-term risk of metabolic impairment.

**PO3.05.06**

**Gut microbiota and overweight at the age of 3 years**

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**Background:** Intestinal microbiota has been associated with overweight in adults, but the evidence with children is limited. The objective of the study was to explore whether composition of the gut microbiota at the age of 3 years is associated with overweight and obesity in children in this cross-sectional data set.

**Methods:** Children, who participated in the Vitamin D Antenatal Asthma Reduction Trial (VDAART), underwent standardized height and weight measurements, and collection of stool samples three years of age. 16S rRNA sequencing (V4 region) of the stool samples were performed with Illumina MiSeq. Overweight or obesity was defined as body mass index z-scores greater than the 85th percentile.

**Results:** Out of 502 children, 146 (29%) were categorized as overweight or obese. Maternal pre pregnancy BMI, high birth weight and length, formula feeding during the first year, high frequency of fast food consumption, and time watching TV at 3 years were the risk factors for overweight or obesity. From the top of the 20 abundant genera, high relative abundance of Parabacteroidetes (Bacteroidetes; Bacteroidales) (aOR 0.69, 95%CI 0.53, 0.90 per interquartile increase) and unassigned genus within Peptostreptococcaceae (Firmicutes; Clostridiales) (aOR 0.83, 95%CI 0.69, 0.99 per interquartile increase) were inversely associated with overweight or obesity, whereas high relative abundance of Dorea (Firmicutes; Clostridiales) (aOR 1.23, 95%CI 1.05, 1.43 per interquartile increase) was positively associated. None of the associations were significant after multiple testing corrections. No associations were found with Shannon index or richness and overweight or obesity.

**Conclusions:** Our data suggest that gut composition of microbes at the age of 3 years are starting to show similar effects on the development of overweight as have been found in adults. Further follow-up is needed to discover long-term effects.

**PO3.05.07**

**Males born growth restricted and fed a high-fat diet have altered microbiome and metabolic dysfunction**

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Obesity is associated with an increased risk of developing diseases including diabetes. One subset of the population who are at an increased risk of obesity are individuals who were born
growth restricted. Growth restricted males have reduced pancreatic β-cell mass and are prone to developing diabetes, which may be exacerbated if they become obese. The gut microbiome has also been suggested to modulate metabolic health. This study investigated the effect of obesity on metabolic health and the gut microbiome of growth restricted male rats. Uteroplacental insufficiency was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery in Wistar-Kyoto rats on embryonic day 18 (term = 22 days). Male Control and Restricted offspring were randomly allocated to a Chow or high-fat diet (HFD; 43% kcals from fat) from 5 weeks. Rats at 4-5 months underwent an insulin challenge (IC), intraperitoneal glucose tolerance testing (IPGTT), were individually placed in an indirect open-circuit calorimeter chamber (CLAMS for 36h) to determine their energy expenditure and spontaneous physical activity, and placed in a metabolic cage for 24h (feces collected for 16S rRNA microbiome profiling). Restricted males were born small but reached a similar size to Control males by 6 months. Consumption of a HFD increased body weight from 3 months, irrespective of birth weight. HFD males had increased basal insulin, insulin area under the curve (AUC), first phase insulin secretion and homeostatic model assessment of insulin resistance (HOMA-IR) during IPGTT, despite no changes in basal glucose and glucose AUC. Glucose AUC following IC was increased in Restricted HFD males compared to Chow-fed, indicating insulin resistance. Restricted males had a higher VO2, VCO2, and produced more heat during the dark cycle despite lower activity demonstrated by fewer stereotypy movements such as grooming and scratching. A HFD reduced VO2, VCO2 and also reduced stereotypy. There were no changes in rearing or jumping movements across any groups. Neither diet nor Restriction altered the operational taxonomic unit (OTU) richness of gut microbial communities, however diet altered the structure and OTU composition of gut communities. In both Control and Restricted rats, HFD increased the abundance of the phylum Proteobacteria and decreased the phyla Bacteroidetes and Candidatus Saccharibacteria. Although Restriction did not impact OTU richness of community structure, Restricted microbial communities had phylum-level increases in Desferribacterales.

These data suggest that growth restricted male rats, whose body weight caught up to Control, have an increased resting metabolic rate despite being less active, which may protect them from developing glucose intolerance and insulin resistance on a Chow diet at 6 months of age. Restricted males have an altered baseline gut microflora which may contribute to, or be an indicator of, their altered metabolism. HFD results in insulin resistance, which may be linked to the major changes observed in the gut microbial community. Aging Restricted rats further or challenging them with an greater HFD may promote metabolic dysfunction. Our findings may indicate an association between metabolic and microbiome function, which may benefit from interventions to improve metabolic health.

**PO3.05.08**

Vitamin D dietary intakes is among the most potent modifiers of gut microbiota in pregnant women- the prospective NoMIC cohort

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**Background:** Although diet is known to have a major modulatory influence on gut microbiota, knowledge of the specific roles of particular vitamins, minerals and other nutrients is limited. Modulation of the composition of the microbiota in pregnant women is especially important as maternal microbes are transferred during delivery and initiate the colonization process in the infant. We study the associations between intake of specific dietary nutrients during pregnancy and gut microbiota composition.

**Methods:** Utilizing the Norwegian NoMIC cohort, we examined the relations between intakes of 28 dietary macro- and micronutrients during pregnancy, derived from food frequency questionnaires administered to 60 women in the second trimester, and observed taxonomic differences in their gut microbiota four days after delivery (assessed through Illumina 16S rRNA amplicon analysis).

**Results:** Higher dietary intakes of fat-soluble vitamins, especially Vitamin D, were associated with reduced microbial alpha diversity (p-value < 0.001). Furthermore using recently developed statistical methodology, we discovered that the variations in fat-soluble vitamins, saturated and mono-unsaturated fat, and cholesterol intake, were associated with changes in phyla composition. Specifically, Vitamin D, mono-unsaturated fat, cholesterol and Retinol were associated with relative increases in Proteobacteria, which is a phyla known to encompass multiple low-pathogens and to have pro-inflammatory properties. In contrast, saturated fat, Vitamin E and protein were associated with relative decreases in Proteobacteria.

**Conclusion:** The results in this article indicate that fats and fat-soluble vitamins, and especially Vitamin D, are among the most potent dietary modulators of gut microbiota in mothers. These results are supported by a recent Nature paper, where genome-wide association analysis identifies variation in vitamin D receptor influencing the gut microbiota. The shifts in microbiota due to diet need to be further studied to understand their implication for health.

**PO3.05.09**

Gut microbiota in healthy Japanese infants and young adults born by C-section

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Our intestinal microbiota plays a fundamental role in numerous aspects of our health and many diseases. The bacterial colonization in human gut starts heavily immediately at birth or perhaps even before that i.e. in-utero, and the array and magnitude of this colonization which can influence several aspects of infant’s long-term health is impacted by many factors such as birth mode, feeding type etc. The frequency of cesarean delivery is increasing worldwide and this upsurge has been speculated to partly underlie the concurrent rise in the prevalence of diseases such as allergy, obesity, diabetes etc. among young population. However, quantitative and longitudinal data on this early-life gut microbiota spectrum is relatively limited and disparate. Herein, using a highly sensitive analytical approach based on reverse-transcription-quantitative-PCR targeting bacterial rRNA molecules, we examined the dynamics of the gut microbiota development in more than 150 healthy term infants from birth till 3 years of age. About 95% of babies were found to carry one or more bacteria in their first intestinal discharge i.e. meconium obtained within 24h after birth. Interestingly, a comparable array of bacteria including Bacteroides fragilis group, enterobacteria, enterococci, staphylococci and bifidobacteria was observed in the meconium of both vaginally- and cesarean-born infants, suggesting that several bacteria might be already present before birth in term infants’ gut. However, the meconium of cesarean-born babies were significantly less often colonized with Lactobacillus genus (6% vs. 37%) and L. gasseri subgroup (6% vs. 31%), as compared to vaginally-born counterparts, and this difference persisted up to 3-6 months of life, suggesting that the primary source of lactobacilli in infant gut is mainly from maternal vaginal/ perianal flora during vaginal delivery and that cesarean-born infants might experience deprived/ delayed colonization of some important Lactobacillus species. Further analyses revealed that cesarean-born babies also had significantly lower carriage of B. fragilis group, bifidobacteria and lactobacilli and lower fecal organic acids concentration and alternatively showed higher carriage of alpha-toxigenic Clostridium perfringens and a higher fecal pH at one or more time-points from day 7 to 6 months of age, thereby indicating a state of gut dysbiosis in cesarean-born babies. Intriguingly, in a concomitant study, we analyzed the gut microbiota of healthy young adults (n = 165) wherein we found significantly lower detection rate of Bacteroides fragilis group, Lactobacillus sakei subgroup and fecal propionic acid in subjects that were born via C-section as compared with vaginally-born counterparts, suggesting that several birth mode-related differences in gut microbiota might persist even beyond teenage. Further studies should evaluate and validate these findings in different population cohorts. Overall, the data clearly demonstrate that early-life gut microbiota is significantly influenced by birth mode and that the elements of cesarean-mediated gut dysbiosis might persist much longer than previously believed. Studies are clearly needed to probe the precise sources/ significance of various gut bacteria in the neonatal gut as well as to scrutinize the connection, if any, of these early life bacterial encounters with host’s long-term health and diseases.

PO3.05.10

Differences in breast milk microbiomes between HIV-infected women on ART and non-infected women living in South Africa

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Background: The human breast milk (HBM) microbiome is known to vary according to several factors such as genetics, maternal health (including HIV status) and nutrition, mode of delivery, lactation stage and geographic location. Globally, more than 1 million HIV-exposed, uninfected infants are born annually. Given that HIV-infected mothers on ART are encouraged to exclusively breast feed their infant for the first 6 months of life, a disrupted infant gut microbiota may ensue, resulting in increased morbidity and mortality of HIV-exposed, uninfected infants. Little is known about the effect of HIV infection combined with the use of antiretroviral treatment (ART) on the HBM microbiome, however it has been shown to cause significant shifts in the rectal microbiome and the function it carries out. Nested in The Drakenstein Child Health Study, our study embarked on an investigation into any changes in the compositional and functional components of the HBM microbiome of South African women infected with HIV currently on ART.

Methodology: This was a cross sectional study of 128 HBM samples: HIV-infected women on ART (n = 64) and HIV-uninfected women (n = 64). Breast milk samples were collected 7 – 10 weeks postpartum. Nucleic acids were extracted on the QIAasympol SP instrument using the QIAasympol® Virus/Bacteria mini kit (Qiagen, Hilden, Germany). HBM microbiome profiles were determined by Illumina MiSeq (Illumina, Inc. Madison WI) sequencing of bacterial 16S rRNA gene amplicons at the Centre for Proteomic & Genomic Research (CPGR, Cape Town, South Africa) and the function profile inferred using PICRUST.

Preliminary Results: Changes in the HBM microbiota are associated with maternal physiological status, including obesity, celiac disease and HIV status. González et al. (2013) showed that HIV-infected women in Mozambique had higher bacterial diversity and higher prevalence of Lactobacillus spp. in their HBM compared to the non-infected women. However, this study did not take into account the use of ART. In addition, this study used culture-dependent methods for the microbiota description. Another study by McHardy et al. (2013) showed significant functional and compositional shifts in the rectal microbiota between HIV-infected subjects on ART and healthy controls and concluded that HIV infection altered the rectal ecosystem and selected for different microbial metagenomic functions.

Conclusion: We hypothesize that there will be significant shifts in the HBM microbiota composition and imputed...
function between HIV-infected women on ART compared to their non-infected controls. This work may lead to targeted therapeutic supplementation of breast feeding. HIV-infected mothers. The lactation period may provide a new target for devising novel dietary and nutritional tools to modulate the milk microbiota and thereby reduce the risk of non-communicable diseases, while at the same time promoting breast feeding. We will have our results available by the end of May 2017.

PO3.05.11
Delivery type is associated with microbiota composition and body adiposity in young adults of the Nutritionists Health Study
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Background: Studies have reported that eutrophic and obese adults have diverse histories of early life events and microbiota composition. The association of caesarean delivery with obesity in adulthood raised a hypothesis that the newborn gut colonization might be an underlying mechanism favoring the body fat accumulation. Despite the observation that delivery type and characteristics of gut microbiota were associated, investigations in young adults who became or not obese are scarce. The Nutritionists Health Study – NutriHS is a cohort of undergraduates and graduates from Nutrition College, and represents a unique opportunity to identify early cardiometabolic risk markers. We hypothesized that microbiota composition established in early postnatal life persists until adulthood with impact in body adiposity. We examined the association of gut microbiota composition in young adults, with or without weight excess, according to their delivery type.

Methods: The current cross-sectional analysis was conducted in 151 healthy participants (90% women, 18-40 yrs) of the NutriHS. After completing self-administered questionnaires (e-NutriHS), they were invited to a clinical visit for physical examination and lab procedures. The profile of the fecal microbiota was obtained by sequencing the V4 region of the 16S rRNA gene (Illumina® MiSeq platform). Participants were stratified by BMI (≤ 25 kg/m²) and by delivery type; cardiometabolic variables and bacterial abundances were compared using Student t test or Mann-Whitney U test.

Results: Mean age(SD) of the participants was 24.8(5.9) years; 28.5% had BMI ≥ 25 kg/m². Similar proportions of normal-weight (48%) and excessive-weight individuals (49%) reported a cesarean delivery. As expected, individuals with BMI ≥ 25 kg/m² had greater mean (SD) values of abdominal circumference [91.7(11.3) vs. 71.9(5.1) cm, p < 0.001], systolic blood pressure [115(11) vs. 106(13) mmHg, p < 0.001], fasting plasma glucose [84.0(10.4) vs. 80.1(8.4) mg/dl, p < 0.001] than those with BMI < 25 kg/m², but they did not differ regarding insulin, HOMA-IR, C-reactive protein and lipopolysaccharides values, and microbiota composition. The comparison of these variables after sub-stratification of BMI groups by delivery type showed no differences within groups. Comparing the microbiota composition according to delivery type within the BMI < 25 kg/m² group, genera abundance rates did not differ. However, within the BMI ≥ 25 kg/m² group, lower abundance of Blautia (p = 0.016) and a higher of Bacteroides (p = 0.024) were found in individuals who had cesarean delivery compared to those born by natural delivery.

Discussion and conclusion: Differences in abundances of certain genera in gut microbiota of cesarean-born overweight participants are in agreement with literature: Blautia genus was more abundantly reported in children who had early gut colonization after exposure to vaginal delivery. These results favors the hypothesis that microbiome, defined early in the cycle of life, can persist until adulthood. On the other hand, Bacteroides genus includes gram-negative bacteria with lipopolysaccharides in their outer surface, which are able to trigger inflammation. Since low-grade inflammation represents a pathophysiological basis for cardiometabolic diseases, our findings help understanding how early life event could confer risk in adulthood mediated by the gut microbiota.

PO3.05.12
Gut microbiota composition in children and adults: Ruminicoccaceae vs Lachnospiraceae
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Introduction: In the past decades we have begun to realize the importance of trillions of microbes living in our guts, collectively termed gut microbiota. It is known that microbiome is dynamic through the life course and is still in developing phase during the childhood, but it was not studied yet in large population-based cohort studies. In order to examine the shifts in gut microbiome in children and elderly in relation to health and disease, we profiled the gut microbiome of two extensively phenotyped cohorts: the Rotterdam Study (RS, elderly) and the Generation R birth cohort (GenR).

Materials & Methods: Over 1,700 faecal stool samples in the RS cohort (n = 14,000 elderly; mean age = 57; range = 46 to 88) and over 3,000 in the multi ethnic GenR cohort (n = 9,000 children; mean age = 10; range = 9 to 12) were collected through regular mail and stored at -20°C. The 16S ribosomal RNA gene (variable regions V3 and V4) was amplified and sequenced using Illumina MiSeq technology. Reads were clustered into Operational Taxonomic Units (OTUs). Comparative analysis of microbiome diversities of the two cohorts was done in R and R packages vegan and MaAsLin. In both cohorts only samples from subjects with North-European ancestry were considered for analysis. In RS cohort only samples with age range of 51-62 years were considered in analysis.
During analysis we adjusted for age, sex, technical covariates, and multiple testing by FDR (q < 0.05).

**Results:** In total, 1,081 RS and 1,463 GenR samples were included in the analysis (n = 2,544). After quality filtering 770 genus-level OTUs were obtained. Our results showed significant clustering of both cohorts based on Bray-Curtis dissimilarity metric (PERMANOVA, p = 0.001) and a higher alpha diversity (Shannon Index) in RS (Mean = 4.01) than in GenR(Mean = 3.8; ANOVA, p < 2.2e-16). Our analysis revealed that 175 OTUs were more abundant in RS as compared to GenR, while 137 OTUs were more abundant in GenR as compared to RS (q < 0.05). Largest differences were observed for genera from family Lachnospiraceae including Anaerostipes and Blautia that were more abundant in RS, and genera from family Ruminococcaceae including Faecalibacterium and Subdoligranulum that were more abundant in GenR.

**Conclusion:** Comparing the gut microbiome compositions in Subdoligranulum and observed for genera from family Lachnospiraceae GenR as compared to RS (q < 0.05). The normalweight group didn’t present a significant over-abundance in a specific group at phylum level. On the other hand, regarding metabolic performance, gut microbial functionality in children from obese mothers was significantly enriched in Carbohydrate transport and metabolism, within this category, we observed an over-representation of proteins belonging to glycosidases, β-glucuronidase and α-galactosidase compared to overweight group, which presented a significant enrichment in cell wall membrane envelope biogenesis category and the normalweight group, which presented significant enrichments in more diverse pathways.

**Conclusions:** These results suggest that the composition and metabolic performance of the gut microbiota in the child may depend on maternal metabolic state during pregnancy. Children born to obese mothers, may present a gut microbiota community specialized in getting greater energy from foods compared to children born to healthy normalweight or overweight mothers.

**Funding:** This study was funded by Spanish Ministry of Innovation and Science. Junta de Andalucía: Excellence Projects (P06-CTS-02341); Spanish Ministry of Economy & Competitiveness (BFU2012-40254-C03-01); and MyNewGut FP7 EU Project (n° 613979).

**References**


**PO3.05.13**

**Functionality and structure of neonatal gut microbiota community depend on pre-pregnancy maternal weight**

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**Background and objectives:** The human gut microbiota has become the subject of extensive research in recent years and our knowledge about its influence in different diseases is rapidly growing. Until now, studies focused on the origins of obesity were oriented towards dietary excesses (processed sugars, fat, and proteins) or host genes. But recent studies have shown changes in gut microbiota associated to different diseases, like obesity. The aim of this study was to analyze the gut microbial community composition and functionality in children born to mothers with different body mass index (BMI) at 6 months old.

**Methods:** The PREOBE project is an observational cohort study on healthy normo-, overweight and obese women. We analysed associations between the gut microbiota of 46 children of 6 months old, assessed by 16S rRNA gene sequencing and metaproteomics, with mother’s BMI.

**Results:** We analyzed the gut microbiota structure using UniFrac distance and we observed three different clusters depending on whether the mother was normalweight, overweight or obese. The obese group presented a significant over-abundance of Firmicutes compared to overweight group, which presented a significant over-abundance of Proteobacteria. Conversely, the normalweight group didn’t present a significant over-abundance in a specific group at phylum level. On the other hand, regarding metabolic performance, gut microbial functionality in children from obese mothers was significantly enriched in Carbohydrate transport and metabolism, within this category, we observed an over-representation of proteins belonging to glycosidases, β-glucuronidase and α-galactosidase compared to overweight group, which presented a significant enrichment in cell wall membrane envelope biogenesis category and the normalweight group, which presented significant enrichments in more diverse pathways.

**Conclusions:** These results suggest that the composition and metabolic performance of the gut microbiota in the child may depend on maternal metabolic state during pregnancy. Children born to obese mothers, may present a gut microbiota community specialized in getting greater energy from foods compared to children born to healthy normalweight or overweight mothers.

**Funding:** This study was funded by Spanish Ministry of Innovation and Science. Junta de Andalucía: Excellence Projects (P06-CTS-02341); Spanish Ministry of Economy & Competitiveness (BFU2012-40254-C03-01); and MyNewGut FP7 EU Project (n° 613979).

**References**

Results: We observed an important shift in gut microbiota composition from 6 to 18 months old, with a significant enrichment in Bacilli, Proteobacteria and Actinobacteria at 6 months, and a significant enrichment in Clostridia, Bacteroidetes and Verrucomicrobia at 18 months. We also observed differences on infants gut microbiota structure based on mothers’ BMI using Unifrac distance. Moreover, at 6 months, we found significant group differences in cognition composite language, expressive language and composite cognitive scores being higher in the obese group, compared to children born to normal weight mothers. These higher scores were related to a higher abundance of Flavonifractor and Clostridium XIVa. At 18 months, the offspring born to obese mothers had lower scores in language composite and the previous differences in language and cognition was replaced by a suggestive trend of lower gross motor scores in the obese groups. Lower motor scores were associated to a significant overabundance of Lactobacillus. These results suggest that there are clear differences in the offspring gut microbiota composition between 6 to 18 months and depend on maternal metabolic status. Flavonifractor and Clostridium XIVa were related to better language development in offspring born to obese mothers at 6 months. Lactobacillus seems to be related to better language and cognitive development in offspring born to obese mothers at 18 months.

Conclusions: In the present study, significant associations between gut microbiota and neurodevelopment (language, cognition, motricity and socioemotional development) have been demonstrated; these associations are different depending on mother’s pre-pregnancy BMI.

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PO3.06 – Neurodevelopment - Nutrition

PO3.06.01

Early diet with improved LCPUFA content protects the brain against the early-life-stress induced deficit by modulating hippocampal neurogenesis and microglia

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Early-life stress (ES) affects brain function for life. Clinical and pre-clinical evidence shows that ES, malnutrition and infection can lead to cognitive impairment and increased vulnerability to develop psychopathologies later in life. We have previously shown that chronic ES exposure induces cognitive decline in mice, which correlates with a reduction in hippocampal neurogenesis in adulthood. Also, ES affects neuroimmune cell function, as ES-exposed mice display more IBA1 and CD68 expressing hippocampal microglia compared to control mice. Given the high nutritional demand of Wound infections often cause harmful and costly clinical complications to our health care systems. Infected wounds impose a significantly negative effect on patient care and recovery as infection hinders wound healing, resulting in increased patient morbidity and mortality. We screened 212 wound specimens from patients in some health institution in Buea municipality and analyzed for common bacteria pathogens using standard microbiological and biochemical methods. Antimicrobial susceptibility of isolates was determined using the disc diffusion assay.

A total of 169 (79.9%) samples were infected. The frequencies of isolation from various sources were as follows; Burns 100%, Ulcers 86.7%, Postoperative wounds 79.3% and Open wounds 78.8%. Twelve bacteria species were identified; Staphylococcus aureus, Escherichia coli, Enterobacter cloacae, Enterobacter aerogenes, Proteus mirabilis, Klebsiella pneumoniae, Hafnia alvei, Pseudomonas aeruginosa, Serratia marcescens, Serratia rubideae Serratia sakazakii and Streptococcus sp. Results of antibiotic sensitivity tests revealed the most active drugs against these infectious agents to be oxofacin (100%) and perflinoxacin (100%), followed by ceftriaxone (94.2%) and gentamicin (92%). Isolate exhibited complete resistance to oxacillin (100%). Multi-drug resistance (resistance to five or more drugs) was exhibited by over 71.7% of isolates. Multi-drug resistance was commonly encountered in Staphylococcus aureus with 31.5% of this organism being resistant to seven drugs.

PO3.05.15

Prevalence of pathogenic bacteria in open and surgical wounds of patients attending hospitals in Buea municipality

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the brain during development, the quality of early nutrition is critical. Long-chain polyunsaturated fatty acids (LCPUFA’s) provided by the diet are crucial building blocks for brain development and function, and also have metabolic and immunomodulatory properties. We hypothesised that an early dietary intervention with an improved LCPUFA quality is protective against ES-induced functional deficits. We investigated if a dietary intervention with essential LCPUFA’s can modulate ES-induced effects and which are the neurobiological substrates for the beneficial effects of the diet. ES exposed C57BL/6J mice dams and their offspring were exposed to a diet with either low or high n-6/n-3 LCPUFA ratio (accomplished with modulating LA/ALA content of the diet) from postnatal (P) 2 to P42. At P42 all offspring was switched to a semisynthetic rodent chow (AIN93-M), and mice were tested for cognitive function at 4 month. At 6 months of age mice were sacrificed and we assessed how ES w/wo diet affected fatty acid composition, levels of neurogenesis and microglia in the hippocampus. We found that early life exposure to a diet with low n-6/n-3 ratio is able to prevent ES-induced cognitive decline. This dietary rescue was accompanied by restoration of ES-induced reductions in hippocampal newborn cell survival and increased hippocampal CD68 expression, suggesting that the beneficial effect of the diet could, at least in part, be mediated by modulating hippocampal neurogenesis and microglia functioning. To what extent altered neurogenesis and microglia activity contribute to the beneficial effects of the diet is currently under investigation. In conclusion, ES-induced cognitive decline can be prevented by an early postnatal dietary intervention with an improved LCPUFA quality, and affects neurogenesis and neuroimmune cell function. The current data may provide useful insights for the development of targeted dietary interventions in vulnerable populations.

The aim of this study was to examine the associations between maternal seafood intake during pregnancy and neurodevelopmental outcomes in the offspring.

**Methods:** We used data from the Norwegian Mother and Child Cohort Study (MoBa), a prospective nationwide pregnancy cohort. Maternal food intake during the first half of pregnancy was assessed by a validated food frequency questionnaire (FFQ). The exposure variables comprised: i) total seafood and ii) subcategories of lean and fatty fish. The exposure variables were examined both as continuous and categorical variables.

Child neurodevelopment was assessed by a selection of questionnaire items from the Child Behavior Check List (CBCL) and Ages and Stages Questionnaire (ASQ) at child’s age 18 months, 36 months and 5 years. These outcome variables comprised: i) emotional problems (internalizing behavior) ii) behavioral problems (externalizing behavior), iii) communication skills, and iv) motor skills. Externalizing and internalizing behavior scores (range 0-1) were extracted using exploratory factor analysis, and communication and motor skills scores were mean item scores (0-1). Lower scores reflect less cognitive, motor and behavioral difficulties. In total, 46,423 mothers were eligible for inclusion, i.e. had delivered singleton, term babies, had answered the baseline questionnaire and provided valid dietary information from the FFQ and had data for at least one of the outcomes. For the children, outcome data were available for 36,850 at 18 months, 30,447 at 36 months, and 25,142 at 5 years. We examined associations between seafood exposure and the neurodevelopment outcomes at each of the time points with regression models and adjusted for the following covariates: maternal age, parity, education, BMI, Hopkins score for maternal depression, n-3 fatty acid supplement use, and total energy intake. Models with continuous exposure variables included a quadratic term to account for non-linear associations. Mixed models were used to check for interaction with sex.

**Results:** Median maternal seafood intake was 235 g/week (5th, 95th percentile: 55, 520), of which lean fish constituted 56% and fatty fish 34%. Fourteen percent of the mothers had low intake (<100g seafood/week), 75% had moderate intake (100-400g/week) and 11% had high intake (>400g/week). Increasing maternal seafood intake, whether modelled as a continuous variable or by categories, was associated with reduced difficulties on all outcomes, but the effect estimates were small. Figure 1 illustrates associations between maternal seafood with internalizing and externalizing behaviour scores at 18 and 36 months, and 5 years. Associations did not differ between boys and girls. When examining lean and fatty fish separately, the associations were stronger for lean than for fatty fish.

**Conclusions:** In this large cohort of mothers and children, maternal intake of seafood during pregnancy, and particularly lean fish, was consistently associated with reduced symptoms of neurodevelopmental problems in children at 18 months, 36 months and 5 years.
Maternal seafood intake (g/week), internalizing and externalizing problems in children. Cubic splines from GAMs; \( y = \text{change in score (range 0-1)} \)

PO3.06.04

Maternal use of iodine containing supplements in pregnancy is associated with increased risk of child attention-deficit/hyperactivity disorder

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Background: Mild- to moderate iodine deficiency is highly prevalent in pregnant women worldwide, including in several European countries. Iodine supplements are recommended for pregnant women in many countries, also by the WHO if diets are insufficient in iodine. However, little evidence exist on the potential effects of supplemental iodine for pregnant women in populations characterized with mild- to moderate iodine deficiency. The aim of this study was to explore the association between maternal iodine supplement use and risk of child ADHD in a population with high prevalence of inadequate iodine intakes in pregnant women and with no official recommendation for supplementation.

Methods: This study includes 75,832 mother-child pairs participating in the Norwegian Mother and Child Cohort Study (recruited 2002-08). Maternal iodine intake was assessed using an extensive and validated food frequency questionnaire covering food and supplement intakes during the first half of pregnancy. Inclusion criteria comprised available data on exposure and covariates, singleton birth, no reported use of thyroid medication in pregnancy, and child living in Norway by December 2015. Participants who reported a very high intake of iodine from supplements (>250μg/day) were excluded (1.7%). Outcomes were i) ADHD diagnosis registered in the Norwegian Patient Registry by Dec. 2015 (\( n = 1696 \) (2.2%) children, mean age at diagnosis: 8.3y; interquartile range (IQR): 7.0, 9.5), and ii) Symptom score >1.5SD (in a subsample of \( n = 27,509 \) on maternally reported child ADHD symptoms at age 8y (nine items on inattention and nine on hyperactivity/impulsivity from the ADHD Rating Scale). Associations were explored by multivariable Cox and logistic regression, and models included interaction terms between iodine from food (below/above the estimated average requirement for pregnant women by the Institute of Medicine; 160μg/day) and iodine from supplements. Covariates were maternal age, BMI, parity, education, energy intake, fiber intake, n-3 fatty acids EPA and DHA from food and supplements, folic acid supplement use, smoking in pregnancy, birth season, and child sex.

Results: Use of iodine-containing multisupplements was reported in 30% of pregnancies (median supplemental iodine: 86 μg/day; IQR: 54-150; range 0.7-250), and only nine women reported taking an isolated iodine supplement. Use of supplemental iodine in pregnancy was associated with an increased risk of child ADHD diagnosis, both when the maternal diet was low in iodine (<160μg/day) (HR: 1.13; 95% CI: 1.00, 1.29 compared to children of non-users), and when maternal diet contained ≥160μg iodine/day (HR: 1.47; 95% CI: 1.17, 1.85)(Table 1). The negative impact of supplemental iodine on ADHD diagnosis was primarily seen in participants who initiated use of iodine-containing supplements in the first trimester of pregnancy. The results were in agreement with associations with high levels of maternally reported ADHD symptoms at child age 8y, both for >1.5SDs symptoms of inattention, and of hyperactivity. Adjusting for any maternal supplement use did not change the results.

Conclusions: In this large pregnancy cohort, iodine supplement use in pregnancy was associated with an increased risk of child ADHD. The negative impact was most pronounced in children of women who initiated iodine supplement use in the first trimester of pregnancy.
Maternal iodine supplement use and risk of child ADHD by maternal iodine intake from food (<160μg/day or ≥160μg/day)

PO3.06.07
Micronutrients during pregnancy and child psychomotor development: opposite effects of Zinc and Selenium
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Background: Studies on the impact of micronutrient levels during different pregnancy periods on child psychomotor functions are limited. The aim of this study was to evaluate the association between maternal plasma concentrations of selected micronutrients, such as: copper (Cu), zinc (Zn), selenium (Se), and child neurodevelopment.

Methods: The study population consisted of 539 mother-child pairs from Polish Mother and Child Cohort (REPRO_PL). The micronutrient levels were measured in each trimester of pregnancy, at delivery and in the cord blood. Psychomotor development was assessed in children at the age of 1 and 2 years using the Bayley Scales of Infant and Toddler Development.

Results: The mean cord plasma Zn, Cu and Se concentrations were 1.1 ± 0.3 mg/l, 0.6 ± 0.3 mg/l and 31.1 ± 8.2 μg/l, respectively. There were no statistically significant associations between Cu levels and any of the analyzed domains of child development. A positive association was observed between Se level in the 1st trimester of pregnancy and child language abilities at one year of age (β = 0.2, p = 0.03 and β = 0.3, p = 0.005, respectively) at one year of age. Motor score among one-year-old children decreased along with increasing Zn levels in the 1st trimester of pregnancy and in the cord blood (β = -12.1, p = 0.003 and β = -6.5, p = 0.03, respectively). A similar pattern was observed for the association between Zn level in the 1st trimester of pregnancy and language abilities at one year of age (β = -7.4, p = 0.05).

Conclusions: Prenatal Zn and Se status was associated with lower and higher child psychomotor abilities, respectively, within the first year of life. Further epidemiological and preclinical studies are necessary to confirm the associations between micronutrient levels and child development as well as to elucidate the underlying mechanisms of their effects.

PO3.06.08
Effect of early life dietary supplementation with prebiotic and omega-3 poly-unsaturated fatty acids on behaviour and immunomodulation in healthy mice
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Introduction: Prebiotics and omega 3 poly-unsaturated fatty acids (n-3 PUFA) have microbiota modulating properties that can lead to immunoo- and neuromodulation. The objective of this study was to evaluate the dietary effect of a combination of short chain galacto- and long chain fructo-oligosaccharides (scGOS:lcFOS) and n-3 PUFA on behaviour and the immune system in mice.

Method: Postnatal dietary supplementation with 3% scGOS:lcFOS (9:1) and/or n-3 PUFA was tested in healthy male BALB/c mice. Explorative behaviour and anxiety were assessed by an open field and a marble burying test, respectively, at 4, 6 and 8 weeks of age (n = 8-10 per group). In addition, caecal short chain fatty acids (SCFA) and splenic and mesenteric lymph node (MLN) levels of CD4+ subsets (Th1, Th2, Th17 and regulatory T cells) were measured. All dietary groups including a control diet were compared using two-way or one-way ANOVA analysis.

Results: At 6 weeks of age scGOS:lcFOS and n-3 PUFA separately did not significantly change explorative behaviour of mice. Combination of scGOS:lcFOS with n-3 PUFA resulted in reduced explorative behaviour of mice when compared to the scGOS:lcFOS diet alone. At 8 weeks of age all enriched dietary groups showed a trend towards more explorative behaviour compared with the control group. In addition, the scGOS:lcFOS group buried less marbles compared with the control. In the n-3 PUFA and in the combination diet groups no differences in number of buried marbles were observed compared with the control group. Caecal SCFA levels were only significantly increased in the scGOS:lcFOS group compared with the control group. Although no significant difference was detected in caecal iso-SCFA levels in the scGOS:lcFOS and the n-3 PUFA groups compared with the control group, the levels were decreased by the combination diet. Furthermore, the levels of Th1, Th2, Th17 and regulatory T cells in the spleen and in the MLN were not significantly different between the dietary groups.

Conclusions: Early life dietary supplementation with scGOS:lcFOS had the highest beneficial effect on explorative behaviour and reduction of anxiety. In addition, only scGOS:lcFOS enhanced the levels of caecal SCFA and none of the diets showed significant differences in the levels of Th1, Th2, Th17 and regulatory T cells in spleen and MLN in healthy mice. Further studies are needed to investigate the possible interaction between the dietary components.

PO3.06.09
Does DHA supplementation in preterm infants in the neonatal period improve attention at 18 months' corrected age?
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Background: Docosahexaenoic acid (DHA) is an omega-3 (n-3) long chain polyunsaturated fatty acid that is essential for the development of the brain and the central nervous system. DHA is particularly concentrated in the frontal lobe of the brain that controls higher order cognitive functions, including attention. Preterm infants, particularly those born very preterm (<29 weeks’ gestation) miss out on the peak period of DHA accretion into the brain in the last trimester of pregnancy, and this may contribute to the higher incidence of attention-related disorders in children born preterm. The objective of this study was to determine the effect of DHA supplementation in infants born very preterm in the early postnatal period on attention measures at 18 months’ corrected age.

Methods: This study was a follow-up study of children who participated in the N3RO (N-3 fatty acids for improvement in Respiratory Outcomes) trial. In N3RO, infants born <29 weeks’ gestation were randomly assigned to receive either a DHA-rich emulsion (60 mg/kg/day DHA) or soy-oil emulsion (control group) within three days of their first enteral feed until 36 weeks’ post menstrual age (PMA) or discharge, whichever occurred first.[#_ENREF_1].

A subset of N3RO infants enrolled in Adelaide were invited to participate in the attention follow up study, and to attend an assessment at 18 months’ corrected age. Three assessment tasks were administered: a single object task, a multiple object task and a distractibility task, all of which required the child to maintain attention on specific toy/s for 3 or 5 minutes in either the presence or absence of a distractor. Each test session was video-taped. The key outcomes assessed in these tasks included the percentage of time spent looking at the toy, the number of times attention shifted between toys and the average latency to turn to the distractor (primary outcome).

Results: 116 families were approached and 78 agreed to participate in the N3RO attention follow up study at 18 months’ corrected age. A total of 77 children (57% males and 43% females), completed the attention study at 18 months’ corrected age. These children had a mean gestational age of 26±1.3 weeks. In the N3RO cohort, total blood DHA concentrations were higher in the intervention group compared to the control group. All 77 assessments have been scored and final analysis is nearing completion when group analysis and unblinding will occur. In the single object task, children spent 86% (95% CI, 83% - 89%) of the 5 minutes assessment looking at the toy. In the multiple object task the children shifted their attention between the 5 different toys 40±14 times (range 2 – 83 times).

Conclusions: There is a wide variation in the attention parameters assessed in this population between individual children. Unblinded group analyses are in progress and will be presented.

PO3.06.11
Cord serum concentrations of 25-hydroxy vitamin D with growth and neurodevelopment during infancy
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Background: Vitamin D deficiency in the newborn has been proposed as a risk factor for multiple chronic conditions. Whether umbilical cord serum 25-hydroxyvitamin D3 (25(OH)D3) deficiency is associated with infant growth and neurodevelopment is unclear.

Methods: We examined the associations of 25(OH)D3 measured using the liquid chromatography tandem mass spectrometry (LC-MS/MS) with weight-for-age, length-for-age, body mass index (BMI)-for-age, head circumference-for-age z-scores (World Health Organization Standard) and neurodevelopment assessed from Ages and Stages Questionnaire using linear or logistic regressions in the Shanghai Allergy Cohort study (n = 1,030).

Results: 25(OH)D3 deficit (< 20 ng/ml) was associated with higher weight-for-age z-score (mean difference = 0.217, 95% confidence interval (CI) (0.022 to 0.412) and BMI-for-age z-score (mean difference = 0.278, 95% CI (0.078 to 0.480), but not length-for-age z-score, head circumference-for-age z-score or neurodevelopment at 2 years, adjusted for sex, socio-economic position, parents' age at birth, gestational age, season of birth, and Vitamin D supplementation.

Conclusion: In a population from a non-Western setting, 25(OH)D3 deficit is associated with higher weight and BMI z-score during infancy. More evidence is warranted to determine the role of 25(OH)D3 in the early origins of adiposity.

PO3.06.12
Maternal Nutritional Status and Fetal Brain Development

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Background: Maternal health during pregnancy can influence fetal brain development and subsequently the cognitive-emotional outcomes in offspring. Despite the importance of antenatal environment in neurodevelopment, the origins of inter-individual variation in fetal brain development are largely unknown. In the present study we assessed the relative importance of several maternal factors such as the maternal mental health, metabolism and nutritional status in defining individual variation in fetal neural development.

Methods: MRI and DTI measures of 9 brain regions were obtained from 189 neonates from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort. Linear regression models were used to determine associations between 61 measures of the intrauterine environment (reflecting maternal stress, metabolism and nutrition) and inter-individual variation in fetal brain development.

Results: Our findings suggest profound, region-specific influence of maternal nutrition over maternal metabolism and mental health on neonatal brain structure and organization.

Conclusions: This study gives an overview of how different maternal variables influence in utero brain development and emphasizes the importance of maternal nutrition.

PO3.06.13
Associations between maternal diet during pregnancy and early childhood development in urban South Africa: A proposal
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Background and rationale: Approximately 250 million children in low- and middle-income countries are at risk of not reaching their developmental potential. This is worrisome as suboptimal development concludes to less productive adults earning less in wages, exaggerating an intergenerational cycle of poverty. As the trajectories for later health and development are determined during the first 1000 days of life, both the World Health Assembly Nutrition Targets and the Sustainable Developmental Goals call for action to, amongst others, improve maternal, infant and young child nutrition in an effort to ensure sustainable social and economic progress. The South African government has, as part of the country’s National Development Plan 2030, equally committed to reducing poverty by ensuring adequate nutrition during pregnancy to enhance early childhood development (ECD). Nutrition support for pregnant women in South Africa is, however, solely provided as iron, folic acid and calcium supplementation. Although information of the dietary intake of this vulnerable group is limited, the levels of food insecurity, even in urban areas, remain high. Little is yet known of the association of the maternal diet with foetal growth, and how this translates to fine- and gross motor, and social-emotional development during early childhood. Research in this area is thus warranted.
**Aim:** To assess associations between the maternal diet during pregnancy and early development of their offspring in urban South Africa.

**Objectives:** To (1) describe the maternal diet throughout pregnancy in terms of nutrient intake and dietary patterns; (2) assess ECD by means of foetal growth, anthropometrical measurements, and fine- and gross motor, and social-emotional development; (3) assess the associations of maternal diet during pregnancy with foetal growth, as well as development at age six months; and (4) determine the associations of maternal diet-related factors, including food security, with ECD.

**Design/ Methods:** This study forms part of the Nutrition in Pregnancy and Early Development (NuPED) study (NWU-00186-15-A1; NWU-00049-16-A1), which is a longitudinal cohort study. A minimum of 250 women (18–39 years, living in Johannesburg, South Africa) with a singleton pregnancy, not using illicit drugs or smoking, and with no known non-communicable disease or other serious illnesses, are currently being enrolled prior to 18 weeks’ gestation. Maternal follow-up and data collection takes place at weeks <18, 22 and 36 gestation, as well as at birth. Data collection of offspring occurs at birth and 6 months of age. Figure 1 depicts data collection and collection time-points.

**Conclusion:** Understanding the associations between maternal nutrition during pregnancy and ECD will contribute to the knowledge base informing gestational interventions to ensure optimal childhood development.

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**PO3.06.14**

Association of psychomotor development with feeding practices and nutritional status of 6-month-old infants in a peri-urban community of South Africa

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**Background:** Inadequate nutrition during the first thousand days has long-term effects on growth and cognitive development. Stunted children usually experience delayed cognitive development, increased morbidity and mortality. Anaemia and iron deficiency as a result of micronutrient undernutrition remain problems of public health importance worldwide as it effects mental, motor and socio-emotional development

**Methods:** This study used baseline data of a randomized controlled trial to evaluate psychomotor development in relation to feeding practices and nutritional status of 6-month-old infants (n = 750) from a peri-urban community of South Africa. Psychomotor development was assessed by Kilifi Developmental Inventory and a South African parent rating scale. The weight-for-length (WLZ), length-for-age (LAZ) and weight-for-age z-scores (WAZ) were based on the WHO classification. Blood samples were analysed for haemoglobin (Hb), plasma ferritin (PF), and soluble transferrin receptor (sTfR). Socio-economic, breastfeeding and complementary feeding practices were assessed by questionnaire.

**Results:** Stunting was prevalent in 28.5%, of infants. Multivariable binary logistic regression showed that lower birth weight (OR 0.12, 95%CI 0.07 to 0.20, P < 0.001) and shorter maternal height (OR 0.94, 95%CI 0.91 to 0.98, P = 0.001) were inversely associated with stunting. The other factors associated with stunting were higher sTfR (mg/L) concentrations, lower Hb (g/dL) and low education level of the mother/caregiver. Anaemic infants (36.5%) had lower scores for both eye-hand coordination (P < 0.001; d = 0.497) and locomotor activities (P < 0.001; d = 0.463). Scores for eye-hand coordination activities were also lower for infants suffering from iron deficiency anaemia. Stunted infants had significant lower parent rating scores (P = 0.001; d = 0.231).

**Conclusions:** Multi linear regression analysis showed a significant positive correlation between haemoglobin concentration and eye-hand coordination, locomotor and combined psychomotor scores. Psychomotor development in relation to nutritional status and growth provide a more conclusive representation of infant psycho-motor development.

**Funding:** This study was sponsored by GAIN with co-funders DSM and UNilever.

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**PO3.06.15**

Exposure to maternal high fat diet programs reward behavior in the offspring

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**Background:** Offspring of Sprague-Dawley rat dams fed a 60% high-fat (HF) diet during gestation and lactation (HF offspring) display increased body weight and adiposity compared to offspring of dams fed chow diet (CH offspring). Furthermore, male and female HF offspring have a greater preference ratio for HF diet, display a blunted locomotor response to amphetamine (2mg/kg, i.p.), and do not develop a conditioned place preference (CPP) for food reward compared to CH offspring. Collectively, these data suggest that dysregulation of the reward system results in changes in reward-
motivated behaviors. Here, we assessed their behavioral response to cocaine using a CPP paradigm, as well as their cocaine-induced locomotor response. Next to determine a potential mechanism which may contribute to the manifestation of these behaviors, we assessed ΔFosB immunoreactivity in the nucleus accumbens (NAc) as it has been shown to be elevated after exposure to drugs of abuse and natural rewards.

Methods: Timed-pregnant Sprague-Dawley rat dams were placed on either standard laboratory CH diet (Purina 5001) or a purified HF diet (60%, Research Diets) on gestation day 2 and remained on these diets throughout gestation and lactation. On P21, all offspring were weaned onto CH diet and behavioral testing began at 6 weeks of age. For the CPP paradigm, male and female offspring (n = 8/diet/sex) were trained to associate a chamber with cocaine (10 mg/kg, i.p.) or saline. Initial preference was determined prior to conditioning, and the non-preferred chamber was paired with cocaine treatment. After the 8 day conditioning period, rats were tested for their preference during a 15-min test. Two-days later we assessed locomotor activity in response to an injection of cocaine (10 mg/kg, i.p.). For the assessment of cocaine-induced ΔFosB in the nucleus accumbens (NAc) as it has been shown to be elevated after exposure to drugs of abuse and natural rewards.

Results: Male HF offspring did not develop a CPP for cocaine compared to male CH offspring, though both dietary groups displayed a cocaine-induced locomotor response. In contrast, both female CH and HF offspring preferred the cocaine-associated chamber. Furthermore, female HF offspring displayed increased ΔFosB immunoreactivity in both the NAc core and shell after 5 days of cocaine treatment, compared to HF controls, but cocaine-treated CH offspring did not.

Conclusions: While both male and female HF offspring are hypo-responsive to amphetamine, CH and HF female offspring do not differ in their response to cocaine. Therefore, behavioral impairments may be dependent upon the rewarding stimuli, suggestive of different mechanistic changes to the reward system. Taken together, these data demonstrate that exposure to HF diet during early life results in long-term behavioral deficits to drugs of abuse and natural rewards.

PO3.06.16

The effect of maternal vitamin D depleted diet during gestation on the behaviour and activity of young adult mouse offspring.

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Background: The fetus is reliant on maternal vitamin D, and vitamin D deficiency (VDD) affects a substantial proportion of the population. Maternal pregnancy VDD is linked to altered offspring brain development, impaired skeletal muscle structure and function, and to increased risk of being overweight in early postnatal life. We hypothesised that a maternal VDD diet would impair activity in young adult mouse offspring.

Methods: Female C57BL/6J mice were fed a control (C; 1 IU/g vitamin D₃) or VDD (0 IU/g vitamin D₃) diet 6 weeks prior to mating and throughout pregnancy and lactation. Offspring were weaned onto the C diet. 25-hydroxyvitamin-D₃ concentration ([25(OH)D₃]pl) was measured by HPLC tandem mass spectrometry in maternal E16 (C, n = 6; VDD, n = 6), maternal weaning (C, n = 5; VDD, n = 6), and 15wk offspring (C, n = 5; VDD, n = 7) plasma. Open-field activity was assessed for five minutes in female 15wk offspring (C, n = 5; VDD, n = 7). Distance travelled, time ambulatory (crossing more than three photo-beams in two seconds), vertical counts (rearing onto hind limbs) and number of jumps were recorded. Data were analysed by independent t-test.

Results: Maternal E16 and weaning [25(OH)D₃]pl was significantly lower in the VDD group compared with C group (P < 0.001). There was no difference in [25(OH)D₃]pl between groups in 15wk offspring. VDD group female offspring displayed a reduction in distance travelled (P < 0.001) and time spent in ambulatory behaviour (P < 0.01) compared with C group offspring. Vertical counts and number of jumps in this time period were also significantly lower in the VDD group compared with C group offspring (P < 0.01).

Conclusions: The reduction in offspring activity with a maternal VDD diet may reflect altered brain function or hind limb strength. Underlying mechanisms could include impaired neurological development and altered skeletal muscle fibre type composition, respectively. These changes could impact on offspring adiposity in a subsequently obesogenic postnatal environment or age-related degeneration in neurological function and skeletal muscle strength.

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PO3.07 – Neurodevelopment – Population health

PO3.07.01

Hearing loss among 9- to 11-year-old children in the Netherlands: the Generation R Study

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Background: Adequate hearing is essential for communication, and accordingly for development of any growing child. Perceptive, permanent hearing loss can occur due to a variety of factors, including factors that are modifiable, such as exposure to noise. As a condition without primary treatment options – only hearing aids or cochlear implantation so far – primary prevention is of great importance, and should start as early as possible. To develop optimal prevention strategies, knowledge of the current epidemiology of childhood permanent hearing

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Background: According to the World Health Organization (WHO) Brazil is the country with the largest number of people with Anxiety Disorder in the world. This means that 18.6 million Brazilians presented some form of anxiety disorder in 2015. Depression affects approximately 5.8% of the Brazilian population; what means 11.5 million people in Brazil. The first 2 years of life are essential for the child to establish an affective bond with parents, mothers and / or caregivers. A strengthened affective bond is expected to decrease the risk of neurological or psychiatric disorders in the future.

Methods: The Welcome Baby Project, the first virtual cohort in Brazil, aims to demonstrate that a social network can be used as a tool to promote health, clarify important issues and encourage the need to stimulate child development in the first 2 years of life. We are following 642 women and their babies since the first trimester of pregnancy, in a closed group within Facebook, which is the social network used. Participation was on a voluntary basis. The children are now about 2 years old. All women who were interested, accepted the terms and conditions, and filled out an online form. Every day we provide online behaviour-changing health information about many issues, reinforcing the importance of the affective bond between parents and caregivers. The instrument used to assess the risk of psychiatric disorders in childhood was the IRDI, (Indicadores Clínicos de Desenvolvimento Infantil, witch means, in portuguese language, Clinical Indicators of Risk for Child Development), developed by Kupfer in 2009.

Results: The questionnaire with questions refers to the Clinical Indicators of Risk for Child Development was answered by 148 mothers. We observed that in our sample 16.2% of children between 0 and 4 months old (group 1) were at risk for child development; 25% of children aged between 4 and 8 months (group 2) ; 32.7% between 8 and 12 months (group 3) and 37.2% aged between 12 and 18 months old (group 4). These children received a score compatible with risk for infantile development. In the Brazilian population studied by Kupfer this risk was around 40% in all groups. We did not find a relationship between higher or lower risk for child development and maternal level of education or socioeconomic level in groups 1, 2 or 3 (Pearson > 0.05). However, in group 4, mothers with lower educational level had an Odds Ratio of 2.3 of having a child at risk and mothers whose family income was 5 minimum wages or less had an Odds Ratio of 2.2 of having a child at risk for child development.

Conclusion: this is an innovative project in its form and content. The social network can be used as a tool to promote health, clarify important issues and promote neurodevelopment in all educational and social groups.

PO3.07.03
Perinatal vulnerability leads to multiple poor health and development outcomes in the first 1000 days of life.

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Background: New Zealand is regarded as a “great place to raise kids”, but international rankings of child health tell a different story. New Zealand children rank bottom of 24 OECD countries for non-intentional injury, infant mortality and immunisation rates. Hospitalization rates for respiratory and skin infections are twice those of Australian children. Overall population statistics hide large health inequalities, with Māori and Pacific children most vulnerable to a poor start to life.

Method: Growing Up in New Zealand is the contemporary longitudinal cohort study that tracks the health and development of 6853 NZ children from born in 2009 and 2010, in the context of their diverse families and their wider social environments. The longitudinal study was explicitly established to provide population relevant evidence to inform new cross-sectorial policies that could improve population wellbeing and reduce inequalities in health and development from birth. Information is currently available from children, families and routine record linkage over their first five years of life. Factor analysis and stepwise multivariable regression were used to
examine the capacity of twelve routinely available antenatal maternal factors to define population sub-groups of NZ children most vulnerable to poor health and development from before they were born. Risk factors included teenage motherhood, lower socioeconomic status, partnership status for mothers, antenatal maternal depression and maternal smoking.

**Results:** Risk factors for vulnerability clustered with no single risk factor being sufficient alone to efficiently identify vulnerable population sub-groups of pregnant mothers. Three common clusters occurred however which together explained just less than 50% of the population distribution of all factors. Using longitudinal exposure data over the first 1000 days of life we noted that cumulative exposure identified vulnerability more efficiently than any single time point, and also that Māori and Pacific mothers and children experienced the greatest cumulative burden of adversity. Exposure to a greater cumulative exposure in the perinatal period in particular was associated with lower birth weight, reduced breastfeeding duration more childhood infections and admissions to hospital as well as with more likelihood of abnormal behaviours in the pre-school period.

**Conclusions:** Identifying vulnerable children effectively from before their birth using clusters of routinely available maternal risk factors offers an opportunity to optimise life course well-being and give all NZ children the best start in life. Using multi-disciplinary population relevant evidence on a cohort of almost 7000 NZ pre-school children it is clear that cumulative exposure to disadvantaged environments from before birth leads to some population subgroups in New Zealand falling behind before they can even begin life’s race. Additionally the information from the cohort about “what works” for children who are resilient in the face of this cumulative adversity can provide us with novel ways to support all NZ children and families better right from the start.

**PO3.07.04**

**Risk factors for social-emotional development and behavior problems at age two: Results from the All Our Families pregnancy cohort**

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**Significance:** Research has demonstrated that early social-emotional delays and behavioral problems at preschool age are associated with ongoing behavior problems at school age (Briggs-Govan & Carter, 2008; Lavigne, Cicchetti, Gibbons, & Binnns, 2001), psychiatric disorders (Campbell, Shaw, & Gilliom, 2000; Campbell, Speiker, Burchinal & Poe, 2006) and poorer academic achievement (Campbell et al., 2006; Gray, Carter, Briggs-Govan, Jones, & Wagnmiller, 2014). The development of social-emotional competencies have important social outcomes for young children, including the ability to make friends, friendship maintenance and friendship quality (Dunn & Cutting, 1999; Rubin, Bukowski, & Parker, 1998; Walden, Lemerise, & Smith, 1999) and social acceptance among peers (Coie, Dodge, & Kupersmidt, 1990). Understanding modifiable risk factors for sub-optimal development requires consideration of contemporary family circumstances, including demographics, birth outcomes, mental health, social support, parental relationship, parenting and engagement with community to determine areas for effective early intervention to optimize development. This study sought to identify risk factors for delayed social-emotional development and behavior problems at age two among a contemporary population based cohort.

**Methods:** The All Our Families (AOF) study is a population based pregnancy cohort in Calgary, Alberta, Canada. Women were recruited in 2008 and 76% (n = 1595) completed five comprehensive questionnaires from mid-pregnancy to two years postpartum. At age two, social-emotional competence and behavioral problems were measured using the Brief Infant Toddler Social and Emotional Assessment (BITSEA). Chi-square analysis and multivariable logistic regression modeling was used to identify key risk factors for delayed social-emotional development and behavior problems at age two.

**Results:** At age two, 13% (n = 210) of children had delayed social-emotional development and 15% (n = 236) had behavior problems. Risk factors for delayed social-emotional development included maternal depression (OR 2.46 95% CI 1.63-3.72), lower parenting self-efficacy (OR 2.76, 95%CI 1.51-5.06), the child not being engaged in daily imitation play (OR 1.43, 95% CI 1.02-1.99), the child experiencing sleep onset delays (OR 1.58 95% CI 1.05-2.37) and not attending an informal play group (1.43 95% CI 1.03-1.99). The probability of socio-emotional delay at age 2 is 65% for children exposed to all risk factors. Risk factors for behavior problems included lower maternal optimism (OR 2.02 95% CI 1.36-2.99), maternal depression (OR 2.19 95% CI 1.46-3.27) having a mother who reported more difficulty balancing responsibilities (OR 2.32 95% CI 1.55-3.47), the child being exposed to a second language (OR 1.88 95% CI 1.37-2.58), the child experiencing sleep onset delays (OR 1.55 95% CI 1.06-2.26), the child experiencing frequent night wakings (OR 2.95 95% CI 2.13-4.10) and the child having daily screen time of at least one hour (OR 1.85 95% CI 1.34-2.54). The probability of behavior problems at age 2 is 88% if a child is exposed to all 6 risk factors.

**Conclusions:** Strategies that enable parents of newborns in establishing healthy sleep habits, engagement in daily play, attending informal playgroups and limiting screen time show promise as preventative strategies to positively impact children’s psychosocial development. Strategies aimed at identifying and supporting mothers of young children experiencing poor mental health may also improve children’s development.

**PO3.07.05**

**The role of perinatal essential fatty acids in attention deficit and hyperactivity disorder symptoms**

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Background: A balanced level of omega-6 (n-6) and omega-3 (n-3) fatty acids during pregnancy is critical for foetus brain development. Deficient n-3 intake may be associated with neurodevelopmental disorders in a long-term, such as Attention Deficit and Hyperactivity Disorder (ADHD). In the general population, these deficiencies can be linked to subclinical ADHD symptoms. This study aims to explore a potential longitudinal association between perinatal n-6:n-3 ratio concentration and child ADHD symptom scores at four to five years old.

Methods: This study is based on INMA project, a population-based birth cohort in Spain. The sample size was of 523 children, based on biomarker availability and ADHD symptom measured. The n-6 and n-3 concentrations were measured in cord blood samples. ADHD symptoms were reported by preschool teachers through the ADHD DSM-IV checklist. Child and family general characteristics were prospectively collected through parental and in person questionnaires during yearly clinical visits. For the association models, pooled zero-inflated negative binomial regressions and inverse probability weighting were applied. All the analyses were stratified by child sex.

Results: We found associations between n-6:n-3 ratio and ADHD symptom score [Incidence Rate Ratio (IRR) = 1.20; 95% Confidence Interval (CI) = 1.01, 1.42] in child males, but not in females (IRR = 0.89; 95% CI = 0.74, 1.08). After specifying the type of symptoms, the associations were observed both in Inattentive-subtype symptoms (IRR = 1.21; 95% CI = 1.03, 1.42) and Hyperactivity-subtype symptoms (IRR = 1.18; 95% CI = 0.96, 1.44) in males.

Conclusions: Each n-6:n-3 ratio unit in cord blood concentration increased a twenty percent the ADHD symptom score in child males. These findings represent a proof of concept for the prevention of subclinical symptoms of neurodevelopmental disorders in the general population by reinforcing the importance of having a fatty acid balanced diet during pregnancy.

PO3.07.06

Children’s leisure activities are associated with their behavioural characteristics aged Five: Lifeways Cross-Generation Cohort Study, Republic of Ireland

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Background: Mental and behavioural disorders not only affect adults’ wellbeing, but also present serious social and public health concerns for children and young people. The effect of traditional leisure-related activities such as drawing, reading books or socialising with other children has been less studied in relation to children’s behavioural problems in early childhood, in an era of a more online-connected activities and technologies. The present analysis aimed to examine the relationship between the time spent by five-year-old children in traditional leisure activities and their social behavioural patterns.

Methods: Participants were 461 children and their mothers from a prospective cohort study, followed from pregnancy. Children’s factors at birth and when five years old, as well as maternal circumstances during the first-second trimester of pregnancy, were also included in the analysis. Six domains from the Preschooler Social Behaviour questionnaire, Physical Aggression, Opposition, Hyperactivity, Inattention, Anxiety and Prosocial behaviour, as reported by the mother, were the main outcomes. The average daily time (hours(hrs)) spent on each of the following activities were considered as main predictors and analysed separately, using multivariate linear regression models: time spent in a car/bus, reading/looking at books, drawing or making constructions, watching television (TV), being in the company of other children, and playing alone.

Results: The mean score (± SD) for the behavioural patterns in the children aged 5 were: Physical Aggression: 1.79(1.37); Opposition: 1.79(1.36); Inattention: 1.38(1.43); Anxiety: 1.36(1.31); Prosocial: 4.22(1.66). Regarding leisure activities, children spent an average (per day) 0.84(0.56) hrs in a car/bus, 1.04(0.66) hrs reading/looking at books, 1.44(0.78) hrs drawing/making constructions, 1.63(0.76) watching TV, 2.37 (0.77) with other children, and 1.19(1.19) hrs playing alone. After adjustment for child’s and maternal characteristics at birth and pregnancy respectively, as well as child’s sleep disruptions and region of residence, time spent on a car/bus was positively associated with anxiety behaviour (Linear Coefficient (β) (95% CI): 0.25(-0.01, 0.49)); time spent reading/looking at books was inversely associated with both physical aggression (β: -0.25 (-0.43,-0.06) and inattention (β: -0.29 (-0.47,-0.10)).

Conclusion: Children spending greater time on positive activities were in general less likely to have reported behaviour problems, employing a standardised scale. Maternal parity and socioeconomic circumstances during the pregnancy were also associated with their offspring’s behaviour problems. Positive
parenting strategies are appropriate from pregnancy period onwards, based on these findings.

PO3.07.07

Differential effects of maternal and postnatal obesity on activity, anxiety and memory in adult mouse offspring

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Background: Obesity during pregnancy is becoming more common in many populations, which has implications for the health and wellbeing of offspring. Maternal obesity influences offspring behaviour such as activity, anxiety/stress and memory in adult life, which may be due to the effects of low-grade inflammation on the developing brain. This study investigated behaviour in adult offspring from high fat-fed obese mothers, who were themselves also challenged with a postnatal high fat diet.

Methods: Female C57BL/6 mice were fed either a high fat diet (HF; 45% kcal fat) or control diet (C; 7% kcal fat) 6 weeks before mating, throughout pregnancy and lactation. Offspring were fed C or HF diet from weaning onwards creating 4 groups of male and female offspring: (CC, n = 8–12; CHF, n = 7–13; HFC, n = 10–12; HF, n = 10–11). In 15-week-old offspring, activity was assessed by open field (OF) testing, anxiety behaviour was assessed using the elevated plus maze (EPM) and short-term memory was tested by novel object recognition (NOR). Data were analysed by ANOVA.

Results: Male, but not female, offspring activity (distance travelled and number of ambulatory episodes) was increased (P < 0.05) following exposure to prenatal HF diet then postnatal C diet (HFC group), but not in the pre- and postnatal HF exposed (HFHF) group. Prenatal HF diet also tended to reduce short-term memory in male offspring (P < 0.1), as shown by reduced discrimination between novel and familiar objects in the NOR test. Offspring fed a postnatal HF diet, regardless of prenatal diet, particularly males, tended (P < 0.1) to exhibit reduced anxiety behaviour, spending more time in the open arms of the EPM. In addition, postnatal HF diet tended to reduce time spent resting (males, P < 0.1), reduced velocity (males, P < 0.07) and reduced number of jumps (both sexes, P < 0.05) during OF testing.

Conclusions: This study has shown differential effects of exposure to high fat diets in either pre- or postnatal life on offspring behaviour and memory, in a sex-specific manner. Maternal high fat diet did not increase offspring anxiety at this age, in contrast to other studies, but tended to reduce memory and was associated with hyperactivity in males, a feature of attention deficit hyperactivity disorder (ADHD) in children that has been observed following maternal obesity. Long-term exposure to a postnatal high fat diet reduced locomotor activity, modifying the effects of maternal high fat diet on offspring activity. Behavioural studies of these offspring at 52 weeks will determine whether these effects persist and/or worsen with age and are associated with inflammation in key brain regions.

PO3.07.08

Maternal lipid profiles during early pregnancy and eating behaviour in the offspring

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1Academic Medical Centre, AMSTERDAM, The Netherlands; 2Department of Clinical Epidemiology, Biostatistics and Bioinformatics, AMC, AMSTERDAM, The Netherlands; 3Swammerdam Institute for Life Sciences, Centre for Neurosciences, UvA, AMSTERDAM, The Netherlands

Background: Maternal obesity is an important risk factor for overweight and obesity in the offspring. As the foetus is completely dependent on maternal nutrient supply, the maternal diet has a substantial influence on foetal development. Several animal studies have shown that a maternal diet rich in fat and sugar permanently alters the offspring’s eating behaviour; decreased satiety and increased food responsiveness caused increased food intake and consequently obesity in the offspring. A possible underlying pathway could be the maternal lipid profile. Intra-uterine exposure to adverse lipids, negatively influenced by an unhealthy maternal diet, could program foetal brain structures and thereby program satiety and food responsiveness. Human studies have already shown associations between in utero starvation and altered eating behaviour in the offspring. However, human research on maternal overnutrition and offspring’s eating behaviour is scarce. This study therefore aims to investigate whether there is an association between the maternal non-fasting prenatal lipid profile and eating behaviour of the offspring at age 5.

Methods: This study is part of the Amsterdam Born Children and Their Development (ABCD) study. 2318 nondiabetic women with singleton pregnancies were eligible for further analysis. A maternal non-fasting blood sample was taken during early gestation (mean;13 weeks) to determine total cholesterol (TC), triglycerides (TG), free fatty acids (FFA), Apolipoprotein A1 (ApoA1) and Apolipoprotein B (ApoB) levels. Eating behaviour of the offspring was measured at age 5, using the maternally reported Children’s Eating Behaviour Questionnaire (CEBQ). High scores on the food responsiveness scales (food responsiveness, enjoyment of food) and low scores on the satiety scales (satiety responsiveness, slowness of eating) suggest increased food intake. Associations were analysed using multivariable linear regression, adjusting for covariates in different models. Missing values of covariates (<19.7%) were imputed by multiple imputations (20 datasets). Model 1 included the potential confounders maternal age, ethnicity, educational level, prepregnancy BMI, smoking, parity and offspring's sex. In model 2, additional adjustments were made for postnatal factors (exclusive breastfeeding, accelerated postnatal...
growth). In model 3, maternal weight gain since pregnancy was added to indicate the child’s family environment. Effect modification by child’s sex was considered.

Results: In all models, a high maternal TC level was associated with lower enjoyment of food ($\beta$ = -0.039 [95%CI: 0.065;-0.021]) and higher satiety responsiveness (0.040 [0.013;0.067]), and slowness of eating (0.051 [0.020;0.081]) in the offspring. ApoB showed similar associations (-0.139 [-0.274;-0.004]), however, not all models yielded significant results. A high ApoA1 was associated with lower enjoyment of food (-0.103 [-0.205;-0.001]). Increased TG was associated with higher scores on food responsiveness (0.055 [0.012;0.098]) and enjoyment of food (0.068 [0.025;0.112]). Maternal FFA was not significantly associated with eating behaviour in the offspring. Interactions with gender were not significant in the models ($p > 0.10$).

Conclusion: The results indicate a significant association between the early maternal prenatal lipid profile and offspring’s eating behaviour at the age of 5. TG results were showing a positive association as expected, however, other associations were contrarily inversed to expectations. Further research is needed to confirm these results and investigate underlying mechanisms.

<p>| Table 3: Association between prenatal maternal lipid profile and offspring’s eating behaviour at age 5 |
|-------------------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>TC (mmol/L)</th>
<th>ApoA1 (g/L)</th>
<th>ApoB (g/L)</th>
<th>ApoB (g/L)</th>
<th>TG (mmol/L)</th>
<th>FFA (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>code</td>
<td>-0.067</td>
<td>-0.104</td>
<td>0.028</td>
<td>0.058</td>
</tr>
<tr>
<td>HF</td>
<td>code</td>
<td>0.040</td>
<td>0.017</td>
<td>-0.121</td>
<td>0.100</td>
</tr>
<tr>
<td>control</td>
<td>code</td>
<td>-0.067</td>
<td>-0.104</td>
<td>0.028</td>
<td>0.058</td>
</tr>
<tr>
<td>HF</td>
<td>code</td>
<td>0.040</td>
<td>0.017</td>
<td>-0.121</td>
<td>0.100</td>
</tr>
</tbody>
</table>

Association between prenatal maternal lipid profile and offspring’s eating behaviour at age 5

PO3.07.09

Longitudinal study of the effect of maternal and postnatal obesity on motivation for appetitive reward in male and female offspring

C.A. Hawkes, L.C. Contu, C.J. Heath

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Background: Increasing numbers of children are born to overweight and obese women and are themselves at greater risk of developing metabolic and related diseases in early adulthood. Increased risk of obesity in the offspring may be due to prenatal changes that increase motivation for consumption of palatable food. However, few studies have tested this hypothesis in the context of both pre- and postnatal obesity. Moreover, there is currently no data about how obesity impacts on motivation in aged animals. The purpose of this study was to investigate the impact of maternal and postnatal obesity on the motivation of young and aged offspring for appetitive reward.

Methods: Female C57BL/6 mice were fed a control (C, 10% fat) or high fat (HF, 45% fat) diet for 4 weeks before mating and during gestation and lactation. At weaning, male and female offspring were fed a C or HF diet, generating 4 experimental groups: C/C, C/HF, HF/C and HF/HF (n = 11/group) representing the pre- and postnatal diet respectively. The rodent touchscreen apparatus was used to assess the motivation of the offspring for strawberry milkshake reward using the progressive ratio task. All offspring were assessed at 6 months of age and a subset of male offspring were re-evaluated at 12 months of age. Statistical analyses were carried out using the Kruskal-Wallis test with Dunn’s post-hoc test.

Results: Dams and offspring fed the HF diet weighed significantly more than animals fed the C diet. 6-month old male C/HF and HF/HF offspring had significantly lower breakpoints and fewer total presses compared to C/C mice. No differences in breakpoints were observed between C/C and HF/C or between HF/C and HF/HF offspring groups. A similar pattern of response was observed for young adult female C/HF and HF/HF offspring. Female offspring also showed lower breakpoints compared to male offspring in all diet groups except those born to obese mothers. Preliminary comparisons of breakpoint in young vs. aged male offspring suggest an increase in the total presses and a higher breakpoint of C/HF and HF/HF, but not C/C or HF/C offspring at 12 months of age compared to their performance at 6 months of age.

Conclusions: These results suggest that post-natal obesity, irrespective of exposure to gestational obesity, significantly decreased motivation of young adult animals for an appetitive reward. This effect was observed in both male and female offspring, although females had a lower motivation for the reward. Interestingly, the motivation for appetitive rewards seems to increase in obese, but not lean male offspring with age, suggesting that reward pathways may be differentially affected by obesity over the life-course.

PO3.07.10

Developmental paths of healthy term infants in the I-Chat study. Is plagiocephaly causing developmental delay?

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Background: Infant physical development emerges through a continuous series of dynamic interactions between innate characteristics, environmental conditions and the experiences of daily interactions with others. Non-synostotic plagiocephaly
(NSP) has become one of the most prevalent developmental conditions reported in healthy children. Despite universal parent education programs, the pervasiveness of NSP in healthy, low risk infants continues to create resource distribution issues for public health services. Increased awareness and reports linking NSP with potential adverse developmental outcomes accentuates parental and clinician anxiety about the risk the condition poses and heightens the need for prospective birth cohort studies to determine if NSP causes developmental delay or developmental delay causes NSP. The purpose of this study was to examine the developmental profiles of typical healthy term infants and the influence of parent handling in the first 10 months of life on these developmental trajectories.

Methods: A prospective longitudinal study design was used to observe 52 (26 male) healthy, term (37-41 weeks) infant-mother dyads at infant’s age one, three and ten months within their home. Head shape was measured by plagiocephalometry and motor development was assessed using the Test of Infant Motor Performance at 1 and 3 months, Alberta Infant Motor Scale and the Peabody Developmental Motor Scale at 1, 3 and 10 months. Parent handling was assessed by the Infant Handling Score, a valid and reliable tool developed specifically for the project. The infants were classified into 4 groups as typical development (TD), suspect motor delay (SMD), atypical head shape (AHS), or both (SMD-AHS) based on the cut scores of the motor measures and plagiocephalometry.

Results: Of the 52 infants, 36 (69.2%) demonstrated developmental concerns (13, SMD, 16, AHS, 7, SMD-AHS). Developmental concerns were more likely in first born infants (n = 24, 66.7%) (TD First born = 25%; SMD = 76.9%; AHS = 62.5%; SMD-AHS = 57.1%). Male gender distribution varied within groups (TD = 56.25%; SMD = 46.2%; AHS = 37.5%; SMD-AHS = 71.4%). Of the 23 infants with AHS, resolution of head shape occurred for 15 (65.2%) including 6 (85.7%) of the SMD-AHS group by 10 months. Mothers of SMD infants had lower recall of handling education than those with TD infants (p = .015). Significant differences for infant handling scores were found at 1 month between TD and AHS (p = .007) and SMD-AHS (p = .001). At 10 months, 8 (15.4%) infants still demonstrated motor delay, 3 (23%) within SMD and 5 (71.4%) within SMD-AHS groups.

Conclusions: Typical term infants demonstrate variations in motor and head shape development over time. For most infants, SMD and NSP are transient in nature and resolve with time. Even though a proportion of infants with SMD developed NSP, there is probably not a causative link. Infant handling techniques appear important. Powered birth cohorts of diverse socio-educational backgrounds are required to validate these results and identify the key parent handling behaviours that prevent NSP. Revision of early parenting programs is recommended to develop parent confidence, enhance infant handling abilities and improve the developmental outcomes for all infants.

PO3.07.11
Antecedents of worry in mothers of children who are choosy at 15 months of age

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Background: Picky eating is a common problem in childhood which is sometimes associated with low intake of some important dietary components and often concerns parents. The peak age for picky eating is at around 3 years, but parents can worry about it well before that age. In a previous analysis in the Avon Longitudinal Study of Parents and Children (ALSPAC) 56% of children were described as choosy with food at 15 months, and these children were three times more likely than non-choosy children to be picky eaters at 3 years. Many mothers expressed worry about their child’s choosiness at 15 months and this was associated with an enhanced likelihood of the child being picky at 3 years. The aim of the present study was to identify areas where support to parents may be effective in reducing the level of maternal worry and subsequent picky eating behaviour in children.

Methods: Children who were choosy with food (n = 3210) were identified from a questionnaire completed by the caregiver (usually the mother) when the child was 15 months old. The mother was asked if this behaviour worried her greatly, a bit or not at all. Questionnaires during pregnancy and the early life of the child covered many aspects of feeding the child as well as symptoms of anxiety and depression in the mother.

Results: At 15 months of age, 5.0% of mothers of children who were choosy with food were greatly worried about this behaviour, with 27.1% a bit worried. The mother was twice as likely to be worried if the child was first-born compared with third-born or more (Table 1). The worry of the mother at 15 months postpartum was associated with the child refusing solid foods (mother 92% more likely to be greatly worried) and being difficult to feed (53% more likely) by 6 months of age. There were also associations between worry and feeding practices. If the child was introduced to lumpy foods from 10 months onwards compared with between 6 and 9 months the mother was 2.3 times more likely to indicate that she was greatly worried about the child’s choosiness at 15 months. Mothers who had fed vegetables to their child daily at 6 months were 49% less likely to be greatly worried at 15 months. There was no association between the presence of maternal depressive or anxiety symptoms (during pregnancy or the first year of the child’s life) and worry about the child’s choosiness at 15 months postpartum.

Conclusion: The strongest associations with maternal worry about child choosiness at 15 months were the child being first-born, and the child refusing solid foods and the mother finding the child difficult to feed in the first 6 months. Maternal worry was associated with the later introduction of lumpy/chewy foods and less vegetables being fed to the child. Supporting parents, particularly of first-born children, during the stage at which solid foods are introduced is likely to be beneficial in...
reducing maternal worry and may allow avert picking eating behaviour during later childhood.

### PO3.07.12

**Prenatal programming by maternal age: Fetal neurobehavior and birth outcomes**

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**Background:** According to the prenatal programming hypothesis, aspects of the intrauterine environment play a critical role in shaping offspring development that persist into later life. Maternal age is predictive of both developmental and outcomes; advanced maternal age is a risk factor for a number of developmental disorders, yet young maternal age is associated with heightened risk for adverse birth outcomes such as preterm birth. Identifying variation in fetal development across the maternal age span would be beneficial for prenatal programming research. Demographic differences between younger and older mothers make specifically isolating effects of maternal age challenging. The aim of this study was to assess the role of maternal age in fetal neurobehavioral development, as well as infant birth outcomes.

**Methods:** Data were drawn from two cohort studies conducted in the same setting in New York City. Participants were healthy pregnant women (n = 487) recruited during either first or second trimester of their pregnancies from antenatal clinics. Ages of mothers ranged from 14 to 45 (M = 22), with teenage women specifically over-sampled as this was the targeted population of one study. Fetal behavioral monitoring sessions occurred in a laboratory twice: in weeks 24-27 (session 1), and 34-37 of pregnancy (session 2).

**Results:** Higher levels of stress were independently associated with reduced fetal movement across all subjects in session 1 (r = -0.304, p < 0.001) but not session 2. Maternal age showed inverse associations with maternal prenatal stress and with fetal neurobehavior: older age was associated with lower perceived stress in sessions 1 (r = -0.354, p < 0.001) and 2 (r = -0.219, p < 0.001) and increased fetal movement in sessions 1 (r = 0.510, p < 0.001) and 2 (r = 0.485, p < 0.001). Finally, older age was also associated with higher birth weight (r = 0.035, p < 0.05). Some sex differences in fetal development by maternal age were observed: in female fetuses only, older maternal age was associated with lower mean fetal heart rate during (r = -0.239, p < 0.05) and after (r = -0.239, p < 0.05) lab-induced stressor tasks in session 2; and older age was associated with a greater degree of correlation between fetal heart rate and movement (an indicator of more advanced neurodevelopment) in session 1 (r = 0.238, p < 0.05).

**Conclusions:** Paradoxical associations between maternal stress, maternal age, and fetal neurobehaviour were observed: higher stress was associated with reduced fetal movement, yet older pregnant women had both lower levels of perceived stress throughout pregnancy, and greater fetal movement. Fetal motor activity is thought to be a positive indicator of overall fetal well-being, and is positively associated with measures of emotional and behavioural regulation in early childhood. Older age also was associated with higher birth weight. Taken together, these data suggest that babies born to younger mothers have a more at risk profile: reduced movement and lower birth weight, suggesting the increased risk for behavioral problems in offspring of young mothers may have early origins, even before birth.

### PO3.07.13

**Sex of older siblings and cognitive function**

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²Clinical Epidemiology and Biostatistics, Örebro University, ÖREBRO, Sweden; ³School of Health Sciences, Örebro University, ÖREBRO, Sweden

**Background:** Number of older siblings is associated with lower cognitive function, possibly as marker of material disadvantage. Sex differences may signal an influence of inter-sibling interactions.

**Methods:** The study used a national Swedish register-based cohort of men (n = 644,603), born between 1970 and 1992 who undertook military conscription assessments in adolescence that included cognitive function measured on a normally-distributed scale of 1-9. Associations with siblings were investigated using linear regression.

**Results:** After adjustment for numbers of younger siblings, year of conscription assessment, age/year of birth, sex, European socioeconomic classification for parents and maternal age at delivery; the regression coefficients (and 95% confidence intervals) for cognitive function are -0.26 (-0.27, -0.25), -0.42

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**Table 1. Factors associated with maternal worry about her child being choosy with food at 15 months of age.**

<table>
<thead>
<tr>
<th>Variable (Reference category)</th>
<th>Mother generally worried at 15 months</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Party (third-born or more)</td>
<td>1st-born</td>
<td>2.14</td>
<td>1.25-3.06</td>
</tr>
<tr>
<td>2nd-born</td>
<td>0.75</td>
<td>0.42-1.35</td>
<td>0.34</td>
</tr>
<tr>
<td>Weak matching at 15 (yes)</td>
<td>0.85</td>
<td>0.38-1.11</td>
<td>0.31</td>
</tr>
<tr>
<td>Choking at 15 (yes)</td>
<td>1.51</td>
<td>0.69-3.07</td>
<td>0.27</td>
</tr>
<tr>
<td>Slow feeding at 15 (yes)</td>
<td>1.51</td>
<td>0.69-3.07</td>
<td>0.27</td>
</tr>
<tr>
<td>Small quantities at 15 (yes)</td>
<td>1.26</td>
<td>0.81-1.91</td>
<td>0.27</td>
</tr>
<tr>
<td>Difficult to feed at 15 (yes)</td>
<td>1.04</td>
<td>0.55-1.91</td>
<td>0.87</td>
</tr>
<tr>
<td>Age siblings outnumber (months or more)</td>
<td>1.04</td>
<td>0.42-2.41</td>
<td>0.58</td>
</tr>
<tr>
<td>Falls on demand at 15 (yes)</td>
<td>0.84</td>
<td>0.32-1.34</td>
<td>0.57</td>
</tr>
<tr>
<td>Difficult to feed at 6 mo (yes)</td>
<td>1.53</td>
<td>0.48-2.99</td>
<td>0.027</td>
</tr>
<tr>
<td>Slow feeding at 6 mo (yes)</td>
<td>1.53</td>
<td>0.36-2.87</td>
<td>0.018</td>
</tr>
<tr>
<td>Small quantities at 6 mo (yes)</td>
<td>1.11</td>
<td>0.31-1.09</td>
<td>0.59</td>
</tr>
<tr>
<td>Choking at 6 mo (yes)</td>
<td>0.43</td>
<td>0.21-0.90</td>
<td>0.035</td>
</tr>
<tr>
<td>Refused solid food at age 6 mo (yes)</td>
<td>0.43</td>
<td>0.21-0.90</td>
<td>0.035</td>
</tr>
<tr>
<td>Duration of breast feeding (mo &gt; 0)</td>
<td>0.40</td>
<td>0.21-0.79</td>
<td>0.041</td>
</tr>
<tr>
<td>Baby food at 6 mo (none)</td>
<td>No answer</td>
<td>0.30</td>
<td>0.15-0.65</td>
</tr>
<tr>
<td>1st produced</td>
<td>0.30</td>
<td>0.15-0.65</td>
<td>0.001</td>
</tr>
<tr>
<td>2nd produced</td>
<td>0.30</td>
<td>0.15-0.65</td>
<td>0.001</td>
</tr>
<tr>
<td>Vegetables eaten at 6 mo (none)</td>
<td>No answer</td>
<td>0.28</td>
<td>0.14-0.58</td>
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<tr>
<td>Fruity eaten at 6 mo (none)</td>
<td>No answer</td>
<td>0.28</td>
<td>0.14-0.58</td>
</tr>
<tr>
<td>Age introduced to foods (6-9 mo)</td>
<td>No answer</td>
<td>0.28</td>
<td>0.14-0.58</td>
</tr>
</tbody>
</table>

Reference: Mother not worried about child being choosy with food at 15 months

Model explains 13.8% of the variance (n=210)
(-0.44, -0.40), and -0.72 (-0.76, -0.67) for one, two and three or more male older siblings, respectively, compared with none; and -0.22 (-0.23, -0.21), -0.39 (-0.41, -0.37), -0.62 (-0.67, -0.58) for one two or three and three or more female older siblings, respectively, compared with none. A larger number of younger siblings is not associated with lower cognitive function in the adjusted model.

**Conclusions:** Family size is associated with cognitive function: older male siblings may have greater implications than females due to their demands on familial resources or through inter-sibling interactions.

**PO3.07.14**

**Neurodevelopmental delay associated with infancy weight gain among Chinese term-born infants**


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**Background:** Infancy is one of the foremost periods of neurodevelopment, and early development plays a key role on health status in later life, which is partially irreversible. Studies focusing on term-born infants did not reach a consensus on the association between early growth and neurodevelopment. Absolute weight gain as an indicator of infancy growth is easily available and understandable for parents. This study aimed to investigate the association in Chinese population in order to generate advices easy to access.

**Methods:** 5244 term-born children born from 1 February, 2012 to 31 December, 2015 in Guangzhou, China were included in the analyses. Neurodevelopment examinations of children were conducted at one year old at child care clinics in Guangzhou Women and Children Medical Center using the Chinese revised Gesell Developmental Schedule (GDS) including 5 developing domains: adaptive behavior, gross motor, fine motor skills, language, and social function. The association between infancy weight gain and neurodevelopmental delay (defined as Gesell score < 85) at one year old was assessed in generalized linear mixed models with logit functions adjusted for potential confounders. Analyses were further stratified by infant sex.

**Results:** A U-shaped relationship was found between weight gain from birth to one year old and neurodevelopmental delay in gross motor and social domain among term-born infants. Regarding development delay in gross motor at one year old, compared with less than 5kg weight gain in infancy, 5-6kg [effect estimate (95% CI): 0.64 (0.48,0.85)], 6-7kg [0.54 (0.41,0.72)] and 7-8kg[0.63(0.46,0.87)] was associated with a lower risk, while this association disappeared if the children gained more than 8kg[1.04(0.74,1.46)] were at same risk level as less than 5kg. Furthermore, we found that female infants tended to be more sensitive than males to the effect of weight gain on developmental delay in the domain of language although the interaction was not statistical significant.

**Conclusions:** This study suggests that either too slow or too fast infant growth may increase the risk of development delay, which partially differs from conventional perspectives that only limited growth influence early neurodevelopment. So far, most previous studies employed standardized indicators such as Z score or SD score to investigate the association between infancy weight gain and neurodevelopment. For the reason that parents in developing areas may have limited access to healthcare and hardly understand the meaning of standardized values, also standardized indicators have their own limitations, we employed absolute weight gain itself as the main indicator though children diverse in respect of sex and gestational weeks. In the future, further studies are needed to verifying the accuracy of this method considering application on clinic.
PO3.07.15
Developing brain function for age curves from birth using novel biomarkers of neurocognitive development: The BRIGHT Study

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Background: In Sub-Saharan Africa one third of children fail to reach their full cognitive potential by three years of age. This is hypothesized to be due to poverty, disease and malnutrition. However, there is a lack of data from such settings to explain the neural basis leading to these outcomes. The BRIGHT project will longitudinally examine associations between cognitive function, behavioural performance and physical growth in infants from the Gambia, West Africa and the UK over the first two years of life.

Methods: Pregnant women are recruited in late gestation and infants seen at 1, 5, 8, 12, 18 and 24 months of age. At each time point brain function is measured by an optical imaging (fNIRS), electrophysiological markers (EEG, at months 1, 18 and 24) and behavioural assessments. Information on parental mental health, maternal and infant diet, infant sleep and home environment is collected to supplement the assessments of infants’ development.

Results: Recruitment into the BRIGHT commenced in May 2016 and the study will be completed in late 2019. We aim to recruit 200 mother-infant pairs in rural Gambia and 60 mother-infant pairs in the UK (Cambridge). The detailed, longitudinal data we will collect will allow us to chart typical and atypical brain development. With the larger sample size in the Gambia we will additionally investigate the impact of undernutrition during the first two years of life on infant brain development.

Conclusion: The BRIGHT study is the first ever longitudinal brain imaging study of infants in sub-Saharan Africa. The use of novel brain imaging methodologies in this setting will enable us to establish brain function for age curves of infants in both settings. This will offer insight into the effects that malnutrition, social or environmental factors and increased risk of disease have on infant cognitive development, which will be the first step towards targeted interventions.

PO3.07.16
Pregnancy risk factors in autism: a sibling matched case-control study in Italy

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Background: Autism Spectrum Disorder (ASD) is a multifactorial disease, where a single risk factor unlikely can provide comprehensive information. Recent epidemiological studies have pointed out a number of pregnancy and peri-post natal factors which, contributing to focal brain inflammation, predispose to ASD development. In a previous study we have shown a significantly higher prevalence of six potential risk factors in autistic group in comparison with external control group. The aim of this study was to assess the frequency of 12 potential environmental risk factors derived from a careful interview about pregnancy and peri/post history of mothers having had both one child with autism and one or two typically developing siblings observed in two Institutions in Italy adopting the same protocol.

Methods: The clinical sample included a cases group of 35 autistic children and adolescents (mean age 8.22, S.D. 6.35) compared to an internal control group formed by 42 siblings (mean age 8.98 years, S.D. 6.66). It is important to note that the latter group represented all the siblings available. Mothers of autistic children who met the inclusion criteria were invited to an individual structured interview about early risk factors in separate sessions (two or three) each dedicated to a specific pregnancy after having signed an informed consent. The first interview was always dedicated to the child with the disorder. Twelve risk factors were taken into account: solvents/paints exposure during pregnancy; living in apartments with PCV flooring; drinking tap water during pregnancy; pregnancy complications; dystocic delivery; cesarean delivery; perinatal complications; low gestational age at delivery; no breast feeding; child early antibiotic therapy; number of life stressful events during pregnancy; use of pharmaceutical drugs during pregnancy.

Results: A higher prevalence of environmental risk factors was observed in 11 out of 12 risk factors in autistic group in comparison with siblings control group (sign test: p < 0.003). For seven of them the odds ratio was higher than 1.5: solvents/paints exposure/pregnancy (OR 2.56); drinking tap water (OR 2.19); pregnancy complications (OR 1.81); cesarean delivery (OR 2.75) perinatal complications (OR 1.94); low gestational age (OR 1.96) and early antibiotic treatment after delivery (OR 2.03).

Conclusions: Pregnancies related to autism development show a different pattern of pregnancy risk factors in the same mother, with an higher prevalence in 11 out of 12 of them. This suggest that environmental and incidental phenomena can influence pregnancy outcome in predisposed subjects.
**Background:** Various types of circulating fatty acids affect the functioning of the immune system. For example, long-chain polyunsaturated fatty acids (PUFAs) modulate inflammatory responses of the immune system via signal transduction, gene expression and modulation of cell membrane fluidity. The development of the immune system starts prenatally. Because maternal fatty acids are transferred to the fetus via the placenta, we hypothesized that maternal blood fatty acid levels in pregnancy affect blood T cells in the infant. Hence, we studied the association between maternal fatty acid compositions during pregnancy and the child’s T lymphocyte numbers between birth and two years of age.

**Methods:** In this prospective cohort study, embedded within the Generation R Study, we included a subgroup of 350 mother-child pairs. At the second trimester of pregnancy three maternal circulating fatty acid patterns were identified using principle component analysis: (1) A pattern high in n-6 PUFA, with the highest factor loadings for C22:4-n6, C22:5-n-6, C18:3-n6; (2) A pattern high in mono-unsaturated fatty acids (MUFA) and saturated fatty acids (SFA), with the highest factor loading for C16:0, C16:1-n7, C20:4-n6; (3) A pattern high in n-3 PUFA; with the highest factor loading for C20:5-n3, C22:5-n3, C22:6-n3. At birth, 6 months, 14 months and 24 months 6-color detailed immune-phenotyping of naive and memory T lymphocytes was performed. We used linear mixed effect models to estimate the association between maternal fatty acid patterns and circulating blood T lymphocytes over the first two years of life, independent of maternal and child confounders.

**Results:** Over the first two years of life, the maternal fatty acid pattern high in n-3 PUFA mainly affected child CD4+ and CD8+ effector memory RA+ T lymphocyte (TemRA) numbers over time, as illustrated in figure 1. No significant effects of maternal fatty acid patterns were observed for average T lymphocyte numbers at baseline. Overall, the trend was observed that children exposed to relatively high maternal n-6 PUFA patterns had higher absolute numbers of T lymphocytes than children exposed to relatively low maternal n-6 PUFA patterns over the course of two years. In contrast, for children exposed to high maternal n-3 PUFA or high maternal MUFA and SA patterns, a trend of higher absolute T lymphocyte numbers was observed than for children exposed to low maternal n-3 PUFA or low maternal MUFA and SA patterns.

**Conclusion:** The dynamics of T lymphocytes in the first two years of life are affected by specific maternal fatty acid patterns during pregnancy. A maternal fatty acid pattern high in n-3 PUFA was associated with lower CD4+ and CD8+ TemRA cells in children over time. This suggests a potential anti-inflammatory effect of the maternal fatty acid pattern high in n-3 PUFA. Further studies are necessary to relate our findings to the onset of inflammatory diseases.

**Effect of maternal FA patterns high in n-3 PUFA during pregnancy on effector RA+ T cells in children during the first two years of life.**

**PO3.08.03**

**Protocol to determine effects of maternal iron and n-3 fatty acid deficiency on the epigenome and gut microbiome in rats**

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**Background:** Both iron and n-3 fatty acids (FAs) are crucial nutrients for optimal early childhood development. Nutrient deficiencies seldom occur in isolation and many women of reproductive age are likely to suffer from both iron deficiency (ID) and inadequate n-3 FA status due to poor-quality diets. Maternal ID and n-3 FA deficiency (n-3 FAD) may irreversibly affect offspring neurodevelopment. Studies using rat models of perinatal ID or n-3 FAD have resulted in persistent neuroanatomical and neurochemical changes, accompanied by cognitive and behavioural impairments. Recent studies highlight the influence of maternal nutrition on the offspring’s epigenome, which may result in neurodevelopmental deficits and increases the vulnerability to neuropsychiatric manifestations later in life.

There is increasing evidence for the role of nutrition in altering the gut microbiota, which in turn was shown to cross-talk with the brain – also referred to as the microbiota-gut-brain-axis. Both, dietary iron intake and n-3 FA status were shown to modulate the host’s gut microbiome. It was further suggested that the modulation of the gut microbiota by dietary factors...
may influence epigenetic regulation of gene expression. Our previous rat study suggests that combined deficiency in iron (induced post weaning) and n-3 FAs disrupts brain neurotransmitter metabolism to a greater extent and leads to more severe deficits in cognitive performance than ID or n-3 FAD alone. Currently we are executing a rat model with the primary aim to investigate the consequences of maternal ID and n-3 FAD, alone and in combination, on offspring neurodevelopment and function. The proposed study serves to elucidate molecular mechanisms underlying the functional outcomes.

Objectives: 1) To determine the effects of ID and n-3 FAD, alone and in combination, during gestation and lactation on the epigenome and gut microbiome of the offspring in the context of neurodevelopment; 2) to investigate whether effects are sex-specific; and 3) to explore potential associations between the offspring’s epigenome and gut microbiome.

Methods: Using a 2 × 2-factorial design, 32 female Wistar rats will be randomly allocated to one of four diet groups: Control, ID, n-3 FAD, or ID + n-3 FAD. Female rats will be maintained on allocated diets throughout the periconceptional period, pregnancy and lactation. At weaning [post-natal day (PND) 21], offspring (n = 24/group; male:female = 1:1) will receive a control diet for three weeks until euthanasia at PND 42–45 (adolescence). From PND 34–40, offspring will undergo cognitive and behavioural testing. Iron and n-3 fatty acid status, as well as kynurenine pathway metabolites will be determine in blood samples. Neurotransmitter analysis will be performed in different brain areas, and epigenetic effects will be assessed in brain and liver tissue using genome-wide DNA methylation profiling. The gut microbiome will be analysed in faeces samples using next-generation sequencing.

Conclusions: The long-term goal is to translate the findings from the proposed animal study to the human situation by performing randomized-controlled trials in pregnant and non-pregnant women. This will ultimately contribute to the design of effective intervention strategies for women of reproductive age in an effort to ensure optimal brain development and function in their children.

PO3.08.04
Infant milk feeding and incidence of food allergies in the first eight years of life in the EDEN mother-child cohort
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Background: There is no clear evidence for protective effect of breastfeeding against allergic disorders, except in at risk infants, i.e. with a familial history of allergy. As primary preventive strategy for these at risk infants, the European Agency of Allergy and Clinical Immunology recommends the use of partially hydrolyzed formula for non-breastfed infant or at breastfeeding cessation. However, the evidence of the protective effect of hydrolyzed formula on allergy is low. In this context, our study aim was to investigate the link between the type of milk consumed in the first year of life and food allergy. Firstly, we examined the role of breast milk duration/exclusivity and, secondly, the role of the type of formula (regular infant formula vs hydrolyzed) provided at breastfeeding cessation, or to non-breastfed infants.

Methods: Our analysis included 1375 children from the EDEN mother-child cohort. Infant feeding mode was reported by self- questionnaires at the age of 4, 8 and 12 months. In each questionnaire, when concerned, mothers could list up to 5 infant formulas used during the 4 previous months and their duration of use. An exposure variable summarizing the type of milk consumed during the 4 previous months was constructed: mostly hydrolyzed infant formula, mostly other formula, no type documented and breastmilk exclusively. Medical diagnosis of food allergy reported at 8 and 12 months and then every year up to 8 years, amounted to 160 cases. Associations between infant feeding and food allergy were tested by Cox regression models adjusted for recruitment center, maternal education level, maternal age, maternal smoking status, family income, sex, gestational age, caesarean birth and familial history of allergy (parents or siblings). For the analysis on type of milk consumed, we excluded food allergy cases reported at 8 months (n = 54) to limit reverse causality issues.

Results: In our birth cohort, exclusive breastfeeding duration was not related to the risk of food allergy from birth to 8 years (HR per additional month: 1.02 [0.96–1.08]). In this model, the only significant association between selected variables and incidence of food allergy was the familial history of allergy (HR = 1.45 [1.06–2.00]). The use of hydrolyzed formula as the main formula from birth to 4 months (n = 161) was not related to the incidence of food allergy (HR = 0.85 [0.44–1.62]). No interaction between infant feeding and familial history of allergy was found (all p for interaction > 0.10).

Conclusions: Our results showed an association between familial history of allergy and incidence of food allergy cases from birth to 8 years. The association persisted when adjusted on breastfeeding duration. However it disappeared when cases from birth to 8 months were excluded. We were not able to highlight any protective effect of breastfeeding or hydrolyzed infant formula on incidence of food allergy in our study. These results need to be replicated in other cohorts.

PO3.08.05
Effects of pre- and postnatal iron and n-3 fatty acid depletion, alone and in combination, on bone development in rats
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Background: Adequate iron (Fe) and omega-3 (n-3) polyunsaturated fatty acid (PUFA) status during early development may play an important role in the development of bones. The aim of this study is to investigate the effects of pre- and
postnatal Fe and n-3 PUFA depletion, alone and in combination, on bone development in rats, and to determine whether effects are reversible and sex-specific.

Methods: Using a 2 × 2-factorial design, fifty-six female Wistar rats were randomly allocated to one of 4 diet groups: Control, iron deficiency (ID), n-3 fatty acid deficiency (n-3 FAD), or ID + n-3 FAD. Rats were maintained on allocated diets throughout mating, pregnancy and lactation. At weaning (postnatal day (PND) 21), offspring either continued on their respective experimental diet (n = 24 per diet group; male: female = 1:1) or received a control diet until adolescence (PND 42 − 45). Bone mineral density (BMD) was measured in the lumbar spine and right femur using dual X-ray absorptiometry, while three-point bending tests were used in the left femurs to determine biomechanical bone strength.

Results: Preliminary results show a significant effect of n-3 FAD for lower BMD in the lumbar spine at PND 42 − 45; Offspring in the n-3 FAD and ID + n-3 FAD groups had significantly lower BMD in the lumbar spine than rats the control group. The effect of n-3 FAD for lower BMD in the lumbar spine was maintained in the rats that were switched to a control diet at weaning. There were no differences in the spinal BMD at PND 42 − 45 when comparing offspring that were placed on the control diet at weaning to those that continued on the n-3 FAD diet. We found no effect of ID on BMD.

Conclusion: These results indicate that n-3 FAD during early development might affect BMD of rats. It further seems as if this effect is irreversible, even if rats are switched to a n-3 FA sufficient diet post-weaning.

By the time of the DOHaD 2017 Congress all results will be available, including biomechanical testing of the left femurs to determine biomechanical bone strength.

PO3.08.06

Multiple prenatal exposures and airway inflammation in early adolescence


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Background: Exposures encountered in utero may be critical for shaping immune system development, with potential consequences for allergic disease susceptibility in childhood.

Methods: We aimed to examine multiple prenatal exposures (nutrient intakes and air pollutants), to determine their associations with airway inflammation in adolescence, as measured by Fractional Exhaled Nitric Oxide (FENO). We used data from 856 mother-child pairs in Project Viva, a Massachusetts-based longitudinal pre-birth cohort study. Exposures of interest were air pollutants (residence-specific 3rd trimester black carbon estimated by kriging models with land use covariates or PM2.5, from models using remote sensing satellite data and land use terms) and prenatal nutrients (1st and 2nd trimester averaged energy-adjusted dietary intakes of vitamins D, C, and E, β-carotene, folate, choline, and omega-3 and omega-6 polyunsaturated fatty acids derived from food frequency questionnaires); we conducted sensitivity analyses with intakes derived from supplements and diet combined. We applied Bayesian Kernel Machine Regression (BKMR) to test for non-linear dose responses, to detect exposure interactions, and to rank the significance of hierarchical exposure groups in association with FENO at a median age of 12.9 years (range 11.9-16.6). We modelled all nutrients within the same hierarchical group except vitamin E and β-Carotene, which demonstrated associations with FENO in the direction opposite to that observed for other nutrients. We used posterior inclusion probabilities to rank hierarchical exposure groups. Models were adjusted for maternal education, hayfever, pre-pregnancy BMI, and smoking in pregnancy and child sex, season of birth, and race/ethnicity. Exposures were expressed as z-scores of log-transformed data and we report effects in % change in FENO z-score per SD increase in log exposure.

Results: FENO levels (ppb) were 18.9 ± 2.07 (geometric mean, standard deviation), 50% of participants were male, and racial/ethnic distribution was 66% white, 14% black, 4% Hispanic, 4% Asian and 12% other race/ethnicity. Prenatal dietary intakes of vitamin D and folate were each associated with lower FENO in adolescence (-5.5% (95% CI: -11.2% to 0.5%) for vitamin D, (-6.0%, 95% CI: -15.8% to 0.2%) for folate). Conversely, higher vitamin E intake (diet + supplementation) was associated with higher FENO (5.5%, 95% CI: -1.6% to 13.0%). Prenatal air pollutant exposures were also associated with increased FENO: 6.7% (95% CI -0.4% to 19.8%) for black carbon and 7.2% (95% CI -1.1 to 16.3%) for PM2.5. We identified a potential interaction between vitamin E (diet + supplementation) and PM2.5, demonstrating an even greater increase in FENO with increasing prenatal vitamin E intake when PM2.5 was elevated (figure). This interaction was reproduced in a linear regression (p < 0.05). The main hierarchical nutrient group was ranked highest for posterior inclusion probability, followed by air pollutants, and lastly the group including vitamin E and β-carotene.

Conclusions: Our findings suggest that prenatal exposure to some nutrients (vitamin D, folate) may diminish airway inflammation in adolescence, while other nutrients (vitamin E), and air pollutants may increase it. Interactions between prenatal exposures may play an important role in airway inflammation, as evidenced by the potential synergy between vitamin E and PM2.5. Funding: R01AI102960
Prenatal Vitamin E may interact with prenatal PM 2.5 exposure to further increase FENO levels in adolescence

PO3.08.07

Folic acid supplementation during different periods of the life course induces distinct effects on the mammary gland transcriptome

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Introduction: Folate and folic acid (FA), have been implicated in cancer development and progression, however, the role of this water soluble B vitamin and its synthetic form (FA) in the etiology of cancer is highly controversial, with a number of studies although not all, suggesting a U shaped relationship between dietary folate intake and breast cancer risk. As Folic acid (FA) intake has increased over the last decade, here we have used an animal model to test whether FA intake during specific periods of the life-course leads to persistent effects on the transcriptome and morphology of the mammary gland.

Methods: Female C57BL/6 mice were fed a modified AIN93M semi-purified diet containing either 1 mg/kg FA (Reference diet containing 1x basal daily recommendation (BDR) of FA) or a folic acid supplemented diet containing 5 mg/kg FA (5 x BDR) for 4 weeks during either the juvenile-pubertal (JP) period (PND 28-56) or adulthood (PND 74-102). After this period, mice were fed the reference diet for a pubertal (JP) period (PND 28-56) or adulthood (PND 74-56 mg/kg FA (5 x BDR) for 4 weeks during either the juvenile-pubertal (JP) period (PND 28-56) or adulthood (PND 74-102). During this period, mice were fed the reference diet for a further 4 weeks and the 2nd and 3rd thoracic mammary glands isolated. Mammary gland epithelial morphology was assessed using carmine red staining and mammary epithelial cell differentiation by immunohistochemistry (α-smooth muscle actin (α-SMA), basal/myoepithelial differentiation marker: GATA3, luminal cell marker and Ki67, a marker of cell proliferation). Total RNA-seq (20 million reads, 75PE) was carried out on RNA extracted from the mammary glands of control and FA supplemented mice. DESEQ2 was used to identify differentially expressed (false discovery rate < 0.05) genes and Gene Set Enrichment Analysis (GSEA v2.2.2 software) to identify the pathways enriched by FA supplementation.

Results: There was no change in mammary gland epithelial morphology in the JP mice supplemented with FA. However FA supplementation during adulthood led to an increase in epithelial density, and increased expression of the cell proliferation marker Ki67 and the luminal cell marker GATA3.

RNA_seq analysis also showed that FA supplementation induced differential changes compared to the reference diet in the mammary gland transcriptome contingent on the time of supplementation. There were 1819 genes differentially expressed in the mammary gland of JP mice supplemented with FA compared to controls, while in the adult mice supplemented with FA only 222 genes were differentially expressed. Only 9 transcripts were commonly changed in response to FA supplementation during the two time periods. In JP mice, high FA induced differential expression in genes associated with mitochondrial function and adipogenesis, while in adult mice supplemented with FA, genes associated with epithelial mesenchymal transition (EMT) and cancer were changed.

Conclusion: These findings show that increasing dietary FA can induce changes in the mammary gland transcriptome and morphology, contingent upon the time of supplementation. The finding that pathways associated cancer development are up-regulated in adult mice supplemented with folic acid suggests that adult mammary glands may be more susceptible to increased dietary FA than developing mammary tissue. An understanding of which will be critical in determining the persistent effect of FA on mammary gland development and for current dietary recommendations for FA intake in women.

PO3.08.08

Prevalence of B12 deficiency is common in early pregnancy in a multi-ethnic UK population

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Research question: Vitamin B12 (B12), along with folic acid is essential for DNA synthesis and repair as well as vital for several metabolic processes for the developing foetus in pregnancy. B12 deficiency during pregnancy is associated with obesity, insulin resistance and gestational diabetes in Indian women. Studies in India have shown that vitamin B12 deficiency is very common and is thought to be due to vegetarianism. B12 deficiency in mid and late pregnancy is associated with gestational diabetes and offspring metabolic risk. Our recent systematic review showed that B12 deficiency is widely prevalent among pregnant women across many populations. However, there are no prospective studies which measured B12 and folate levels in early pregnancy in a UK multi-ethnic cohort in early pregnancy. Purpose of the study is to assess the prevalence of B12 deficiency and identify the maternal predictors of B12 deficiency.

Methods: Micronutrients in Pregnancy as a Risk factor for gestational Diabetes and Effects on mother and baby (PRiDE) study is an ongoing longitudinal cohort study of multi-ethnic women in early pregnancy who are at high risk of developing gestational diabetes (GDM) in the UK. Maternal characteristics, anthropometric measurements and plasma B12 and folate levels were collected during first trimester and
multivariate regression models applied. The first 2901 participants B12 and folate levels were analysed.

**Results:** Mean gestational age at the time of recruitment was 13 weeks. Mean±sd of B12 was 347±161 pg/ml. 508 (17.5%) had B12 deficiency, defined as levels <202pg/ml (<150pmol/L). 16.3% were South Asians, 70.2% White Caucasians and 13.5% other ethnic origin. Multivariate linear regression analysis showed that BMI (β = -1.7, p < 0.001), age (β = 1.5, p = 0.02) and annual household income (β = 18, p = 0.03) independently predicted B12 levels after adjusting for ethnicity, marital, employment status and smoking. All 2901 participants had folate levels within normal range, with a mean value of 18.2 ± 11.8. 19.3% had folate levels above the normal range. Age (β = 0.27, p < 0.001) was the only predictor for folate levels after adjusting for the above factors.

**Conclusion:** Maternal B12 deficiency was common in early pregnancy in the UK. On the contrary, folate deficiency was rare and worrying that 560 had supraphysiological levels of folate. Maternal BMI, age and annual household income independently predicted B12 levels in a multi-ethnic group. The role of early pregnancy B12 deficiency and the imbalance of low B12 and high folate on the metabolic risk of the mother and offspring is important to explore. PRiDE study’s recruitment is just completed (n = 4500) and will answer some of these questions.

**PO3.08.09**

The associations between maternal nutrition and lifestyle knowledge and a healthy eating index in pregnancy

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**Introduction:** Maternal nutrition impacts the health of both the woman and her offspring. Pregnancy is a unique opportunity for health intervention and to potentially improve health outcomes post-partum and long-term for the woman and the neonate. The aim of this study is to determine contemporary maternal, nutritional and lifestyle knowledge levels in early pregnancy and the association with maternal nutritional intakes in a developed country.

**Methods:** Women were recruited at their convenience after sonographic confirmation of a singleton pregnancy. Women’s demographic details were recorded. Weight and height were measured and body mass index was calculated. Women completed a nutritional knowledge and lifestyle questionnaire adapted for pregnancy from a validated nutritional knowledge questionnaire. Nutrition knowledge scores were calculated and categorised as low level (< mean - 1 standard deviation), medium level (mean ± 1 standard deviation) or high level (> mean + 1 standard deviation) for descriptive statistics. Maternal diet was assessed using a supervised four-day retrospective food diary. Dietary analysis was carried out using the nutritional software package Nutritics version 4.3 Academic Edition. Black’s equation was used to exclude dietary misreporters. A healthy eating index in pregnancy was devised based on meeting recommended intakes for important nutrients in pregnancy.

**Results:** A total of 225 women returned the knowledge and lifestyle questionnaire. The mean age was 32.1 ± 5.0 years, mean body mass index was 26.0 ± 6.1 kg/m², and 44.4% were nulliparous. Of the women, 74.7% (n = 160) had a third level educational qualification and 9.6% were in relative deprivation (n = 20). A total of 188 women completed a food diary and corresponding individual physical activity level, of these 22.2% (n = 50) were energy under-reporters and removed from analysis. A total sample of 138 women who completed the knowledge questionnaire had a corresponding dietary data, excluding women who were dietary mis-reporters. Of those with a low level of nutrition knowledge, 22.6% of women were less than 30 years (14/62) compared to 7.4% of those greater than 30 years (12/163) (p = 0.001). Additionally, of those with a low nutrition knowledge, 22.6% (12/53) did not have a third level education qualification compared to 6.9% (11/160) of those with a third level qualification (p = 0.001). There were no differences in the proportion of women with low levels of nutrition knowledge in terms of obesity, parity, planned pregnancy, or relative deprivation (p > 0.05). There was a positive correlation between women’s nutrition and lifestyle knowledge scores and their Healthy Eating Index in Pregnancy scores (r = 0.26, p = 0.002).

**Conclusion:** The findings of this study suggest that improving dietary knowledge scores in early pregnancy may improve the number of women meeting recommended nutrient intakes. It also suggests that pregnancy dietary and lifestyle educational interventions may benefit from prioritising women who do not have a third level education and who are less than 30 years of age as these women are more likely to fall in the category of a low level of nutrition and lifestyle knowledge in early pregnancy.

**PO3.08.10**

Influences on where women learn about what to eat during pregnancy: Preliminary evidence from the Mothers to Babies (M2B) study

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**Research Question:** The Developmental Origins of Health and Disease (DOHaD) hypothesis holds that early life environmental cues influence a child’s development and her disease risks throughout life. Maternal adiposity and diet during
pregnancy are crucial among these cues, strongly predicting a baby’s risks of developing obesity-related diseases later in life. While a mother’s adiposity is largely outside of her control, mothers (with appropriate supports) may be able to change their diets during critical windows in pregnancy so as to attenuate risks to children. Knowledge about which dietary changes to make and when may affect women’s ability to make these changes. Currently, however, little is known about: 1) where pregnant women acquire such knowledge, 2) whether sources of this knowledge vary among sub-populations of women, and 3) whether knowledge sources influence women’s familiarity with concepts underpinning the DOHaD hypothesis (e.g. knowledge of long-term effects of pregnancy diet).

Methods: To begin to address these three questions, we conducted a pilot survey of pregnant women living in Hamilton, Canada. Complete data were obtained for 73 women through a questionnaire on sources of information about what to eat during pregnancy, basic socio-demographic factors, and DOHaD knowledge (DOHaDK). We used participants’ responses to investigate whether women received pregnancy diet information from any of twelve sources and tabulated the number and type of sources from which women received information. We then plotted sources of pregnancy diet information by socio-demographic factors known to influence health. We also plotted DOHaDK by number/type of pregnancy diet informational sources. Lastly, we used general mixed modeling to assess whether number of informational sources was associated with socio-demographic factors and whether DOHaDK was independently associated with number/type of informational sources.

Results: Most participants identified pregnancy health care provider(s) (midwives, doctors) and print media as important sources of pregnancy diet information. Whether other source types were also reported as important varied systematically among sub-populations. In particular, 100% of both indigenous participants (n = 5) and refugee and temporary resident participants (n = 7) identified family members and friends as key informational sources, but this was the case for only 59% of other participants (n = 61). Women with pre-pregnancy Body Mass Indexes (BMIs; weight/height²) greater than 30, nulliparous women, younger women and temporary residents reported receiving information from more sources than other women. While inspection of uncorrected plots suggested that DOHaDK varies with number and type of informational sources, multivariate analyses show that these effects are not independent of socio-demographic factors.

Conclusions: Our findings suggest that where women report obtaining pregnancy diet information varies socio-demographically, with personal social support networks emphasized by indigenous and new Canadians. Additionally, women from some sub-populations report receiving information from more sources than women from others. Notably, though, information from more sources is not associated with more DOHaDK, suggesting that having more information sources does not directly increase knowledge bases.

Efforts to improve pregnancy diet and thus reduce children’s later-life disease risks should account for variation among sub-populations in number/type of information sources and should aim to facilitate navigation of complicated information landscapes.

PO3.08.11
Governance of WASH in sub-Saharan Africa and associations with nutritional status in children under five years: A systematic review.

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Background: In 2011 global estimates put the number of children in the developing world that were stunted at 165 million. African prevalences have stagnated since 1990 at about 40%, with little improvement expected. Stunting emanates from a variety of determinants, including antenatal, intrauterine, and postnatal malnutrition and is a major public health concern because of associations with adult health and disease risk later in life. Focus on the first 1000 days of life and early-life programming is important in this regard. Observational studies have found associations between the frequency of open defecation and prevalence of stunting, thus linkages between different forms of malnutrition and environmental conditions, including WASH, may contribute towards persistently poor child health outcomes. The realisation that physical growth cannot completely be improved by optimized diet and reduced diarrhoea has led to the hypothesis that another underlying cause of stunting is early exposure to poor WASH and recurrent infectious episodes leading to immune impairment across the lifecourse.

Methods: A systematic review is underway to examine the governance of WASH in sub-Saharan settings and associations with nutritional status in children under five years of age. All combinations of the following keywords are being used to select publications from PubMed Central, Science Direct, and ProQuest Social Science databases published between 1990 and 2017: Governance, Policy, Management; Water, Sanitation, Hygiene, WASH; Undernutrition, Malnutrition, Stunt-ed/ing, Underweight, Wast-ed-ing; Children, Infant, Under Five Years of Age, Preschool; Africa. The PRISMA Statement, evidence-based guidelines that provide a set of items to report in systematic reviews and meta-analyses, is being utilised while this systematic review will also be registered with PROSPERO.

Results: Initial searches and preliminary results have yielded <50 items per search-string indicating a limited body of knowledge on the nexus between governance, water, sanitation, hygiene, and nutritional status in children in the African context. Of importance are gaps in financing, with SSA countries on average committing a mere 0.52% GDP to WASH.
expenditure. Furthermore, aid commitments for WASH to SSA have declined from US$ 3.8 billion to US$ 1.7 billion from 2012 to 2015. While actors and stakeholders at various levels in the policy and governance arena advocate for multi- and inter-sectoral approaches most indicators show disappointing results. Promotion of breastfeeding, food fortification, as well as micronutrient supplementation during pregnancy and infancy, has not been sufficient to shift the prevalence of stunting. Further analysis of the literature is being undertaken.

**Conclusion:** Undernutrition has a complex set of political, social, and economic causes, none of which are amenable to easy solutions. Important knowledge gaps still remain concerning critical aspects of child malnutrition, including environmental risks in the neonatal and infant periods, in the SSA context. Reflecting on the governance of WASH by disentangling the various actors, role players and stakeholders at various levels, while unravelling the policy environment in comparison to particular health related outcomes in terms of nutritional status and growth in children is imperative to the understanding, design and implementation of WASH initiatives targeted at addressing the burden of maternal and child malnutrition.

**PO3.08.12**

Early life biomarkers in the context of a nutrition transition: a cohort study from the Bolivian Amazon

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**Background:** Nutrition transitions are characterized by shifts to a cash economy, a “Western” diet, and eventually, an increase in the prevalence of overweight/obesity and chronic diseases. This trend can be observed worldwide, particularly within low and middle income populations. We sought to evaluate multilevel factors that influence two biomarkers of early life exposures, stunted growth and dental enamel hypoplasia (EH), in the context of a population in transition from a subsistence to market economy. These biomarkers are often relied upon in low-resource settings to predict subsequent health status, when childhood exposures are not known.

**Methods:** This cohort study of 349 Amerindian adolescents (10-17 years of age) in rural Bolivia was derived from the young children included in the 9-year Tsimane’ Amazonian Panel Study. We considered the influence of community characteristics (including distance from the nearest town), household wealth (a locally-developed sum of 23 traditional and modern capital measured by value in the local currency, bolivianos (Bs)) and weekly food consumption, such as that of sugar (measured in kg,) during early childhood on growth stunting and EH. The outcomes of interest included: stunted growth (height-for-age z-score < -2.0) and EH extent (none, < 1/3, 1/3-2/3, >2/3 of the tooth surface affected). Log-binomial regression with robust standard errors will be used to estimate the prevalence ratio and 95% confidence intervals of stunted growth and EH extent associated with dietary consumption, household wealth and community characteristics, adjusted for potential confounders. Mediation and hierarchical analyses will be used to better understand the inter-connected relationship of EH and growth stunting with dietary consumption and social factors, including household wealth and community characteristics (Figure 1).

**Results:** The study sample has a high prevalence of biomarkers that reflect a physiologically stressful childhood environment: growth stunting (75%) and dental enamel defects (92%). The study sample had wide variation in community distance from the nearest market town (mean: 4.5 hours walking ± 4.7), household wealth (mean: 3,424 Bs ± 2,344) and sugar consumption (mean: 1.46 kg ± 0.97). Greater community distance from the nearest market town was associated with greater household wealth (p < 0.01) but less sugar consumption (p < 0.01). Yet, greater household wealth during childhood was associated with greater childhood sugar consumption (p < 0.001). Greater childhood sugar consumption was associated with greater EH extent (p < 0.01) but not stunted growth.

**Conclusions:** This study will describe the inter-connected relationships of two childhood stressor biomarkers with dietary consumption and social factors within the context of an Amerindian population during a nutrition transition in the Bolivian Amazon. We will describe the extent to which dietary consumption mediates the effect of social factors on EH and growth stunting. We will also investigate whether community level characteristics modify dietary consumption patterns. These findings will be important for understanding what two childhood biomarkers reflect when relying on them to indicate health risk later in life.

**PO3.08.13**

Iodine status of complementary-fed infants receiving lipid-based nutrient supplements in South Africa: a randomized controlled trial

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**Background:** The transition to complementary feeding from exclusive breastfeeding poses serious risk for deteriorating iodine status. This can be managed through iodine fortification of complementary foods. The objectives of this study were to...
assess iodine status of peri-urban complementary-fed South African infants and to test the efficacy of small-quantity lipid-based nutrient supplements (SQ-LNS) in maintaining adequate iodine status.

**Methods:** In a randomized controlled trial, infants aged six months (n = 750) were assigned to one of two SQ-LNS per day, both fortified with 45μg iodine, or a control group not receiving SQ-LNS. Urinary iodine concentrations (UIC) were measured at baseline (n = 386) and at 12 months (n = 262).

**Results:** The geometric mean (95%CI) urinary iodine concentration (UIC) at baseline was 333.8 (310.5,358.9) μg/L and decreased to 214.9 (189.2,242.6) μg/L at 12 months. Infants who no longer breastfed had lower UIC (159.6 [65.9,397.5] μg/L) and greater odds (OR = 4.9 [2.5, 9.3]) for being deficient (UIC <100 μg/L), than infants who continued to be breastfed (373.2 [202.6,522.9] μg/L) at 12 months. Infants receiving SQ-LNS (combined group) had higher UIC (P = 0.025) and lower odds (OR = 0.289 [0.11, 0.75]) for deficiency at 12 months than controls; adjusting for maternal baseline UIC, age, sex and continued breastfeeding. In sub-group analysis, the effect of SQ-LNS for higher UIC at 12 months was only apparent in non-breastfed infants (P = 0.039). These effects were no longer significant after adjusting for infant baseline UIC, reducing the sample size to n = 124.

**Conclusions:** Iodine status of infants decreased from six to 12 months; however, this was only evident in infants that were no longer breastfed. In these infants, the provision of 45 μg iodine per day as SQ-LNS resulted in higher or improved UIC at 12 months, but was not efficacious in counteracting an overall decline in iodine status. This trial is registered at clinicaltrials.gov as NCT01845610.

**PO3.08.15**

**Materno-fetal transfer of stable isotopes labelled fatty acids in obese pregnant women**

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**Background:** Prepregnancy obesity is considered a major predictor of offspring obesity. The pathophysiological mechanisms involved in the early programming of obesity are not fully understood. We aimed to investigating the role of materno-fetal transfer of fatty acids (FA) in pregnant women with and without maternal obesity.

**Methods:** Ten normal weight and ten pregnant women with obesity since prepregnancy (pre-pregnancy Body Mass Index (BMI) >30 kg/m2) received orally 13C-labelled FA 12h before elective caesarean section: oleic acid (OA) 0.5mg/kg, linoleic acid (LA) 0.3mg/kg and docosahexaenoic acid (DHA) 0.1mg/kg. Maternal plasma was sampled before tracer administration and every 4h until delivery, when cord blood and placenta samples were taken as well. 13C enrichment and FA concentrations were determined by gas chromatography combustion isotope ratio mass spectrometry (GC-C-IRMS). Values are statistically different at P < 0.05. Data are expressed as means ± SEM.

**Results:** The BMI of obese women was higher than the control at delivery (35.6 ± 1.1 kg/m2 vs. 28.2 ± 0.6 kg/m2, P < 0.001). Placental weight and plasma insulin tended to be higher in obese women. Serum triglycerides and cholesterol levels were similar in both groups. Incorporation of labelled FA into maternal plasma lipids was similar in control and obese group, but, higher concentrations of 13C-LA and 13C-DHA were found in non-esterified FA fraction of obese mothers. Placental tracer FA composition was similar in obese and normal weight women (OA: 0.69 ± 0.3 nmoL/g vs. 0.74 ± 0.04 nmoL/g, P = 0.322, LA: 1.69 ± 0.09 nmoL/g vs. 1.66 ± 0.16 nmoL/g, P = 0.854, DHA: 0.35 ± 0.04 nmoL/g vs. 0.38 ± 0.04 nmoL/g, P = 0.545). However, when considering placenta weight, obese subjects tended to accumulate more labelled FA in placenta than controls (OA: 502.52 ± 40.34

**PO3.08.14**

**The Effect of Periconceptional Multi Micronutrient Supplementation in Preventing Maternal DNA Damage**

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The current study was aimed to evaluate the effect of periconceptional multi micronutrient supplementation in preventing maternal DNA damage. The research was conducted in four subdistricts in the city of Makassar, South Sulawesi, Indonesia with double blind randomized controlled trial design. Of 240 preconception women recruited, 43 of them were pregnant and they were divided into intervention group (n = 23), and control group (n = 20). The intervention group received multi micronutrient (MMN) capsules until they were declared pregnant by urine pregnancy test. DNA damage was examined using Enzyme Linked Immunosorbent Essay (ELISA) to measure the level of 8 hydroxy deoxyguanosine (8OHdG). The Statistical analysis was conducted using Wilcoxon and Mann-Whitney test. The results showed that the average level of 8OHdG decreased not significantly in the intervention group (-70.6 ± 249.3 pg/ml; p = 0.47) and control group (-86.2 ± 234.6 pg/ml; p = 0.10). The difference between the two groups was not significant (p = 0.57). Periconceptional MMN supplementation can prevent maternal DNA damage even though it was not significant compared to the iron folic acid.
Conclusion: Materno-fetal transfer of polyunsaturated FA is reduced in obese pregnant women.

Funding: This study was supported by the European Union’s 7th Framework Programme Early Nutrition project (grant agreement No. 289346), the European Research Council Advanced Grant META-GROWTH (ERC-2012-AdG 322605), and the Excellence Network for Maternal and Child Health and Development (RED SAMID III, RD 16/0022/0009).

PO3.08.16

Gene expression profile changes in mice fatty liver induced by undernourishment in utero with or without endoplasmic reticulum stress alleviation

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Background: Increasing evidence suggests that prevalence of NAFLD (Non Alcoholic Fatty Liver Disease) is rising not only in western developed countries but also in developing countries implying maternal malnutrition might be responsible. Emerging concept of the DOHaD (Developmental Origins of Health and Disease) asserts that adverse early-life exposures - most notably unbalanced nutrition - lead to an increased risk for a range of NCDs (Non-Communicable disease). In our prior studies we reported that the undernourishment in utero prime hepatic steatosis under obesogenic diet and alleviation of ER (Endoplasmic Reticulum) stress by a chemical chaperon TUDCA improved the adversity in mouse model (Sci Reports; 16867,2015) however the underlying cellular mechanism is unclear. We speculate that maternal diet programs fatty liver disease in offspring by genetic regulation. Therefore for further evaluation we performed Microarray to determine changes in gene expression profile.

Method: The study included sampling of blood and liver of CN57Bl mice (n = 16) aged 22 weeks, pups (group A; n = 8) obtained from dams with free access to food with normal nutrition (NN) and pups (group B; n = 8) from dams with 40% caloric restriction with undernutrition (UN). After weaning (upto 8 weeks) pups were fed high fat diet (HFD) through 22weeks and from 17weeks onward we have subdivided both group to vehicle (Veh) and Tauroursodeoxycholic acid (TUDCA, a chemical chaperon of ER stress) administrated group. Then we randomly selected 4 pups per each group and extracted RNA from their liver tissues by QIAGEN RNeasy Lipid Tissue Mini Kit (50) and performed Microarray Analysis using Affymetrix Gene Chip® WT PLUS Reagent Kit and Transcriptome analysis software for statistical analysis.

Result: Among 30 thousand genes investigated, undernourishment in utero significantly up-regulated 38 genes while significantly down-regulated 15 genes (group A [NN] vs group B [UN]; Fold change ≥2 or ≤-2, Anova p<0.05, respectively). Administration of chemical chaperon TUDCA down-regulated 22 genes and up-regulated 18 genes (group A [NN] vs group B [UN]; Fold change ≥2 or ≤-2, Anova p<0.05, respectively).

Conclusion: These results suggest that undernourishment in utero causes some significant changes in genetic profile yet identification of genes are required. Future analysis of these genes might shed a light upon molecular and physiologic mechanism leading to fatty liver in not only the current generation, but also in the next generations, especially concerning the regulation of local ER stress integration in the liver.

Volcano plot of genetic expression profile in undernourishment in utero before (A) and after (B) ER stress alleviation

PO3.08.17

Dandropanax morbifera Extracts reduced the inflammation of digestive-related disease in animal models

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Background: Dandropanax morbifera Lev. is belongs to araliaceous and can be found only along the southern coast of South Korea and islands around. It has been reported its liaceous and can be found only along the southern coast of South Korea and islands around. It has been reported its functional food. But, its efficacy does not evaluated and confirmed on scientific methods such as in vivo approach with animal models. In the present study we have investigated its...
function on anti-inflammation in digestive-related disease model in animals. **Methods:** We divided the animals group as following: (1) vehicle control, (2) disease control (3) 1.7ml/kg Dandropanax morbifera extracts, (4) 8.3ml/kg Dandropanax morbifera extracts, (5) positive drug control (gastritis model only). To make gastritis model, indomethacin was given at 30 minutes after Dandropanax morbifera extracts administration. 25 mg/kg indomethacin was given to all rats (n = 10) by oral gavage in 3% sodium bicarbonate. Seven hours after, the entire rats were sacrificed and confirmed gastrointestinal erosions and ulcers, and then verified further using histological analysis. To make colitis model, 6-8 weeks mice (n = 10) was given 2% DSS in distilled water ad-libitum during 7days following replaced regular drinking water for 1day. Mice were daily checked the body weight, bleeding and diarrhea for DAI index. At the autopsy, the rectum was photographed, measured the length and then further progressed the Swiss roll for histological analysis. **Results:** Dandropanax morbifera extracts decreased the score of gastric damage in gastritis disease model (P < 0.05) as well as reduced the colon length shortening in colitis animal model (P < 0.05) as a dose dependent manner. It is confirmed on histological index data with H&E staining with gut and colon mucosal damage as well as DAI index in colitis model. And also, the entire tissue section of each group treated the extracts showed decreasing the expression of inflammation markers such as COX2, TNF-a, iNOS. **Conclusions:** Our data suggests that Dandropanax morbifera extracts functions the decreasing effect on the inflammation of digestive-related disease such as gastritis and colitis. It may useful to applicate as a medicine or functional food with further progressed.

PO3.09 - Interventions

PO3.09.01

How can we improve recruitment to clinical trials during pregnancy? A mixed methods investigation.

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**Background:** Nutrition in pregnancy has far reaching health implications for both mothers and babies, and clinical trials provide the best evidence for ways to improve their health. Clinical trials involving pregnant women face specific enrolment challenges; they often require large sample sizes to detect significant differences in clinical outcomes for the mother or baby. Recruitment rates for pregnancy trials are consistently low, with only 30% of eligible women agreeing to participate. This risks unrepresentative samples, jeopardising external validity of the trials. Such trials are also unusual in that they involve paired participants, the mother and the unborn baby, which may complicate the decision to participate. Little is known about why some women decline to participate. This study aimed to examine the reasons underlying women’s agreement or refusal to participate in a pregnancy trial and thus identify ways of increasing recruitment.

**Methods:** The study recruited women who had participated or declined to participate in one of two clinical trials of vitamin D supplementation. A questionnaire asking them to indicate the main reasons for their decision was completed by 296 women who declined to participate in one of the two trials. Qualitative interview data were collected from two samples of women: 1) 30 pregnant women who declined to participate but completed the questionnaire; and 2) 44 women who participated in one of the two clinical trials. Thematic analysis was conducted to explore what influences women’s decisions to take part in clinical trials during pregnancy and identify ways of improving recruitment. This was done by contrasting the experiences of women who took part with those of women who declined.

**Results:** The most common reasons reported in questionnaires by women who declined to participate in a trial were being too busy or concerned about study requirements, such as not wanting to take the study medication, have a bone scan or extra blood tests. Thematic analysis identified that women who declined and women who participated had similar practical barriers to participation, but women who participated were willing and able to find ways of overcoming these barriers, whereas for those who declined, these barriers appeared insurmountable. What seemed fundamental in determining whether or not women took part in the trials was their level of trust in medical research. Participants believed that the research would cause no harm, while those who declined felt they would be taking a risk.

**Conclusions and Recommendations:** Recruitment methods for pregnancy trials should focus on building women’s trust in the trial and research team, perhaps through improving visibility and credibility of the research team pre-recruitment by providing testimonials from previous participants and advertising study safety and ethical conduct. Women’s confidence to meet the trial requirements could also be enhanced. One approach would be to train staff in an empowering style of communication enabling women to feel heard; addressing their concerns and supporting them to overcome practical barriers associated with participation. These strategies could be implemented relatively easily into pregnancy trial protocols, and effectiveness tested through their impact on recruitment rates.

PO3.09.02

Why do some pregnant women engage more than others with interventions to improve diet and increase physical activity?

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Background: Women who are overweight or obese in pregnancy are at increased risk of developing non-communicable diseases and of having children with increased risk of these in later life. Interventions that support pregnant women to adopt and maintain a healthy diet and be sufficiently physically active are needed. In response, myriad interventions have been trialled, most with only small or moderate short-term changes. Interventions are usually designed for a general population of pregnant women, and trial outcomes represent an average impact that does not capture the impact on individuals who may respond differently to the same intervention. Interventions should be more personalised to maximise improvement in population health and the health of the next generation. To inform the development of future interventions, this study explored how women responded to a pregnancy intervention and the factors that influenced their diet and physical activity, and aimed to identify their needs with regards to further support for maintaining healthy behaviours.

Methods: Women who completed the SPRING (Southampton PRegnancy Intervention for the Next Generation) trial of vitamin D supplementation and nurse support in pregnancy were invited to be interviewed by a member of the research team. Seventeen women were interviewed about their lifestyles during pregnancy, the support they had in the study for eating well and exercising, and the additional support they would have liked. Transcripts were analysed thematically to capture how women prioritised their diets and physical activity in pregnancy, how they engaged with the support offered by the research nurses, and what further support they wanted.

Results: Women identified barriers to eating well or being physically active, with pregnancy-specific issues like nausea and pain common amongst most participants. Other issues varied between participants and appeared to place them on a continuum of motivation that affected their engagement with diet and physical activity support. At one end, women struggled to identify significant barriers as they self-identified as being generally healthy. Women at the other end of this spectrum struggled to identify barriers or facilitators to improving their health behaviours because they were not interested in making changes; they believed that their diets and levels of physical activity were not very important. Women who were between these extremes often stated that it was important to exercise or eat well, but identified many barriers such as lack of time or access to services.

Conclusions: Lifestyle support interventions in pregnancy should be adaptable to meet the needs of individuals. Some women do not require much support, some believe that their lifestyle in pregnancy is important, but struggle to change. Other women’s health behaviours will be harder to improve because they are not motivated to change. It is important to support these women to engage with and reflect on messages that highlight the potential impact of their health behaviours on the lifelong health of their offspring. Adaptive multi-component interventions are therefore needed to address specific barriers and more effectively support women at all points on the continuum to adopt and/or maintain healthier behaviours during pregnancy.

PO3.09.03
Effects of a lifestyle intervention during pregnancy and first postpartum year - 1-year follow-up of the RADIEL study
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Background: The incidence of type 2 diabetes is increasing worldwide causing an extensive burden on the health care system as well as on those suffering from the disease. Women with a history of GDM form an important risk group because they have a seven-fold risk of developing type 2 diabetes and they also are at a higher risk for other metabolic disturbances later in life. There is strong evidence showing that type 2 diabetes can be prevented by lifestyle intervention. However, only limited data exist on how a lifestyle intervention during pregnancy will affect the future risk of type 2 diabetes and cardiovascular risk among women at high GDM risk. In the present study our aim was to evaluate the effects of a lifestyle intervention initiated in early pregnancy and continued up to one year postpartum on glucose regulation during the first postpartum year, as well as on weight retention, and other metabolic characteristics.

Methods: This is a 1-year follow-up of the women recruited in early pregnancy, with normal glucose tolerance at recruitment, in the Finnish Gestational Diabetes (GDM) Prevention study (RADIEL). In total 269 women with a previous history of GDM and/or a pre-pregnancy BMI $\geq$ 30 kg/m$^2$ were enrolled before 20 weeks of gestation and allocated to either a control or an intervention group. Lifestyle counseling provided by study nurses and dietitians was carried out in each trimester of pregnancy and 6 weeks, 6 months, and 12 months postpartum. This study includes the 200 participants who attended study visits 6 weeks and/or 12 months after delivery. The main outcome was incidence of impaired glucose regulation (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes).

Results: At six weeks postpartum impaired glucose regulation was diagnosed in 7.2% of the study participants in the control group and in 1.0% in the intervention group [OR 0.18 (95% CI 0.05, 0.69), $p = 0.064$]. Over time postpartum impaired glucose regulation was present in 13.3% of the participants in the control group and in 2.7% in the intervention group [crude OR 0.18 (95% CI 0.05, 0.69),...
Methods: The Smarter Pregnancy platform consists of group subscribers with inadequate vegetable intake at baseline.

Interaction tests were performed for ethnicity, pregnancy status and participation as a couple.

Results: At baseline, significant differences were observed between women from deprived (n = 467; 18.3%) and non-deprived neighbourhoods (n = 2,087; 81.7%) for inadequate vegetable intake [71.9% vs. 79.0% respectively; OR 0.72; 95% CI 0.56–0.92] and folate acid supplement use [13.3% vs. 12.2% respectively; OR 1.55; 95%CI 1.09–2.23]. These associations only persisted in Western and pregnant women. Although residents from deprived neighbourhoods are in general difficult to reach, they showed a significantly higher compliance to the platform than residents from non-deprived neighbourhoods (74.1% versus 66.8% respectively; p < 0.01). Women from deprived neighbourhoods were less likely to improve inadequate behaviours, especially vegetable intake (Figure 1).

Conclusions: More women from deprived compared to non-deprived neighbourhoods had less inadequate vegetable intake, although their improvement of inadequate lifestyle behaviours in general was less. These findings suggest that personalisation of the platform according to the needs and health literacy of residents of deprived neighbourhoods has to be addressed in the further implementation of mHealth coaching on lifestyle behaviours of (pre)pregnant women.
interventions during pregnancy for overweight/obese women. Despite an increasing number of randomized controlled trials (RCTs) and systematic reviews, which traditionally provide the highest level of evidence for informing practice, practical challenges persist in stipulating the “ideal” lifestyle intervention(s). This is attributable to the multifaceted nature of interventions within complex social structures, where success depends heavily on an individual’s response within a specific social environment. Assessment of such complex interventions has been purported to be more amenable to a realist review, generating a conceptual framework, which can then be tested in different contexts.

**Methods:** Best quality evidence was deemed to be well-designed RCTs. Inclusion criteria were (1) a RCT with intervention during pregnancy; (2) inclusion of overweight/obese participants (BMI ≥ 25 kg/m² or BMI ≥ 23 kg/m² if high-risk ethnicity); and (3) efficacy in achieving improvement(s) in at least one primary or secondary outcome. Exclusion criteria were: (1) observational studies; (2) interventions using medication and designed to treat gestational diabetes. Pre-agreed data were extracted on 5 domains by independent assessment of at least two trained reviewers: 1) general characteristics (drop-outs, adherence); 2) outcomes (primary and secondary); 3) behavior change techniques (Michie taxonomy); 4) targeted aspects of diet (adherence to general nutritional guidelines, macronutrient proportions, glycemic index, energy restriction, specific food item recommendations, personalization); and 5) physical activity (mode, intensity, personalization etc) intervention. Standardized effect-sizes and weighting by study size were calculated for each outcome that was reported as significant.

**Results:** Sixteen trials were included. Sample sizes varied greatly (n = 60 to >2000). Drop-out ranged from 0.5%–26% (median ± IQR 5 ± 12%). On average (when reported), 84% of participants adhered to the intervention. Behavior change techniques used in successful interventions in order of decreasing frequency were social support (93%), self-monitoring (75%), goal-setting (62.5%) and instruction on performance (56%) of behaviors, problem-solving (38%) and action planning (38%). Studies offering personalized (compared to generic) nutritional advice had a greater standardized effect-size (0.38 versus 0.06 SD, p = 0.007). Greater effect-size was also associated with interventions focused on diet alone compared with a combined diet/physical activity intervention (0.66 versus 0.13 SD, p < 0.001).

**Conclusions:** Common components in most effective trials included high adherence, low withdrawal rates and use of behavioral change techniques (social support, paired with self-monitoring of behavior). We propose a framework with a hierarchy of essential components, namely mandatory achievement of intervention fidelity and high engagement, through the use of behaviorchange techniques focused on behaviors (not outcomes) and a dietary component. Supplementary components which may aid effectiveness are additional behavioral change techniques which promote self-efficacy (such as goal-setting and instruction on performance of the behavior) and personalization of nutritional advice. This framework developed through a realist review requires iterations and reevaluation as future trials provide additional data. Concepts within it should be tested for real-life applicability using context-specific methods of delivery.

**PO3.09.06**

**Improving periconception nutrition using the mHealth program Smarter Pregnancy: a randomized controlled trial.**


**Erasmus MC, ROTTERDAM, The Netherlands**

**Background:** The evidence is overwhelming that healthy maternal nutrition and lifestyle improve fertility as well as pregnancy course and outcome. Therefore, we developed the successful mHealth coaching program Smarter Pregnancy (http://www.slimmerzwanger.nl; English version: www.smarterpregnancy.co.uk) to empower couples to increase intakes of folic acid, fruits and vegetables and to quit smoking and alcohol consumption before and during pregnancy. The primary objective of this study was to investigate the compliance and effectiveness of ‘Smarter Pregnancy’ in adopting healthy nutrition in women after 24 weeks of coaching.

**Methods:** Women between 18 and 45 years of age, trying to conceive or pregnant (<13 weeks of gestational age) were eligible for inclusion in a randomized controlled trial. The intervention group received personal online coaching based on the identified nutrition and lifestyle risk factors at baseline. Coaching comprises recipes, incentives, additional questions including feedback and text and e-mail messages, with a maximum of three per week and aimed on vegetable intake, fruit intake, folic acid supplement use, smoking and alcohol consumption. The control group did not receive coaching or feedback, but did receive one recipe per week to maintain adherence to the program. Screening questionnaires were sent in both groups at 6, 12, 18, and 24 weeks of the program to monitor the change in the identified risk factors. These risk factors were translated into a dietary risk score (DRS), which was calculated as the sum of vegetable intake (0 ≥ 200 gram per day, 1 = 150-200 gram per day, 2 ≤ 150gram per day), fruit intake (0 ≥ 2 pieces per day, 1 = 1,5-2,0 pieces per day, 2 ≤ 1,5 piece per day and folic acid supplement use (0 = adequat, 2 = inadequate), ranging from 0 to 6 in which a higher DRS depicts unhealthy behavior. We used a linear regression model, based on the intention-to-treat principle, including the baseline value of the DRS and randomization, to measure the primary outcome: improvement of the DRS after 24 weeks compared to baseline.

**Results:** A total of 218 women was analyzed of which 177 (intervention: n = 91, control: n = 86) completed the program, resulting in a compliance of 83% in the intervention group and 79% in the control group. After 24 weeks, we observed a

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significantly larger improvement of the DRS in the intervention group compared to the control group ($\beta = 0.42\ 95\%\ CI: 0.08; 0.76$). This improvement was mainly due to increased vegetable intake ($\beta = 0.30\ 95\%\ CI: 0.98; 0.51$) and not due to folic acid supplement use and fruit intake ($\beta = 0.05\ 95\%\ CI: -0.07; 0.18$ and $\beta = 0.06\ 95\%\ CI: -0.15; 0.27$, respectively).

**Conclusions:** The high compliance of more than 80% and effectiveness of improving nutrition, especially of vegetable intake, in women contemplating pregnancy or already pregnant, emphasizes the potential of the mHealth program Smarter Pregnancy to contribute to normal pregnancy course, pregnancy outcome, health in later life and the health of future generations.

**PO3.09.07**

A systematic review of school-based educational interventions to improve diet, physical activity, BMI and body composition in adolescents (aged 10-19)

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**Background:** Adolescence is a transitionary period, marked by critical changes in body composition, insulin sensitivity, physical activity (PA), sedentary and dietary behaviours, and psychological issues that place adolescents at an increased risk of becoming overweight and maintaining obesity in adulthood. Health education in school may improve health literacy by encouraging adolescents to think critically about these issues. To develop effective interventions, it is necessary to understand which elements are effective. We conducted a systematic review of school-based educational interventions to increase PA, improve diet and achieve a healthy body mass index (BMI) in adolescents (aged 10 to 19).

**Methods:** In October 2016 a search of MEDLINE, PsycINFO, CINAHL, and ERIC was conducted using a combination of MeSH and free text terms. The searches and screening for diet and PA outcomes were conducted separately. Titles and abstracts were assessed by two independent researchers. Review inclusion criteria were: a) intervention studies conducted in schools in high income countries with a control or comparison group, b) participants aged 10-19 years, c) interventions that included a health education component, d) studies that measured a diet, PA or BMI/body composition related outcome at baseline and follow-up. We defined health education as: ‘any combination of learning experiences designed to facilitate voluntary adaptations of behaviour conducive to health’ (Green, 1982). Studies focusing on overweight/obese populations, LMICs and without a health education component were excluded. Data were extracted from included studies and were assessed, using a form developed for capturing key information to address the research question.

**Results:** Searches identified 20,213 publications for PA and 8961 for diet interventions, of which 312 full texts were selected as potentially meeting the inclusion criteria. 226 of these studies were excluded based on the following: a) studies did not include a control or comparison group, b) sampling was limited to a specific ethnic group, and c) studies did not investigate the effectiveness of health education within the specified age group. Finally, 86 studies met inclusion criteria for this review, 10 of which include a digital component. Preliminary findings suggest that school-based interventions are effective in producing significant health behaviour change in adolescents, and that the use of emerging technology such as mobile applications shows promise along with multi-component interventions, including parents and/or family members and incorporating goal setting strategies and improving self-efficacy to enable behaviour change.

**Conclusions:** This systematic review of school-based educational interventions demonstrates the features associated with effectiveness in improving diet, PA, and BMI outcomes. It also supports the use of emerging technologies as a means of delivering interventions to adolescents. Our findings are in line with previous reviews, but we have included recent publications that have extended the evidence base. Our review reinforces the evidence base that shows the need for school-based interventions to link with other components targeting individual adolescents and their families.


**PO3.09.08**

Postpartum support: an existing gap in prenatal and postpartum care

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**Background:** The postpartum period is emerging as an important target for promoting optimal preconception health for subsequent pregnancies. Studies suggest the need for more mother-centered support in the postpartum period. However, there is little information on the types of support mothers’ feel are needed in this time. The purpose of this analysis was to further understand mothers’ perceptions of gaps in postpartum care.

**Methods:** Seventy medically low-risk pregnant women, ≤20 weeks gestation were recruited for a prenatal study in Edmonton, Alberta, Canada. Recruitment occurred through traditional recruitment approaches in addition to Facebook advertisements. Upon study entry, women were randomized into one of two study groups in which they received differing amounts of additional lifestyle support from a Registered
Dietitian. During pregnancy, women completed 4 questionnaires. One to three months after delivery, women completed a postpartum questionnaire and could optionally participate in a focus group. A third study group consisted of women ≤1 year postpartum who were recruited through similar approaches. This postpartum study group only completed a postpartum questionnaire. Data for this analysis were generated from 104 postpartum questionnaires and two focus groups (n = 6). The postpartum questionnaire had two open-ended questions from which data was withdrawn from. The questions asked women to reflect on what additional supports they would have liked from their healthcare provider to have a healthy pregnancy. Comments regarding postpartum (n = 19) were combined from 18 mothers. Subsequently, themes were identified. Focus groups were audio recorded, and data were transcribed verbatim and double coded by two researchers. Following which themes and sub-themes were identified.

**Results:** There was overlap in the emerging themes from the questionnaires and focus groups regarding postpartum. Four gaps in postpartum care were identified and included: (1) a need for preparation, (2) a need for support, (3) a need for more information, and (4) a need for more maternal support. Mothers described a desire for healthcare providers to better prepare women for the postpartum period through discussions during pregnancy. The mothers specifically requested more support and information for breastfeeding and mental health (postpartum depression and anxiety). Lactation consultants, registered dietitians, and registered nurses were all mentioned as healthcare providers that could provide support. Mothers voiced a lack of support for their own health as “the focus is all on the baby”. Interactions with healthcare providers at the pediatric check-ups were mentioned as a good opportunity for discussions to occur about their own health and nutrition.

**Conclusion:** Overall, mothers in our study mentioned gaps in their postpartum care that could be improved upon. An opportunity exists to improve the preparation, information, and support women receive in relation to the postpartum period. The development and evaluation of interventions that improve postpartum care are warranted. Future findings may inform policy or practice change to further support improvements in maternal health. Supporting maternal health in preparation for, and during the postpartum period, could be an important priority to improve women’s health, in addition to improving the health of possible future pregnancies.

PO3.09.09

How do government policies from England and Wales meet the international standard for preventing non-communicable diseases through nutrition/physical activity initiatives?

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**Background:** Non-communicable diseases (NCDs) are the primary cause of death globally. Although mortality and morbidity from NCDs occur in later life, exposure to risk factors begins in early life. Investing in initiatives that support young women and children to improve their dietary and physical activity behaviours are important for improved health across generations. The WHO Global Action Plan for the Prevention and Control of NCDs highlights the primary role of governments in responding to the NCD challenge and sets out a range of policy options at an international standard. The policy options work across the ecological model of health and target individual behaviour change, organisational environments, and macro environmental fiscal and infrastructure initiatives. This study identified the extent that national government policies in England and Wales meet the international standards of the WHO Action Plan for maternal and infant/child health.

**Methods:** The policy appraisal process involved three steps: i) identifying national policy documents in England and Wales relevant to maternal and infant health, ii) developing a policy appraisal framework using the WHO Action Plan, and iii) analysing policies using the framework. Government department and agency websites were searched for Acts, white papers and evidence-based guidelines. To create the appraisal framework, three researchers independently reviewed the WHO Action Plan and agreed on 20 policy options that covered six priority areas (see Figure 1). Inclusion and exclusion criteria were set for each policy option to aid analysis. One researcher analysed all polices; a random selection of 50% were assessed by the second researcher and the few discrepancies agreed with the third researcher.

**Results:** 44 national policy documents relevant to maternal and infant/child health, published between December 2003 and April 2017, were identified. Evidence-based guidance documents (n = 19, 43%) represented almost half of all identified policies and the Department of Health was the most prolific author (n = 17, 39%). The most common policy options were evidence-based practice (84%) and strengthening the evidence base (61%) (Figure 1). Policy options for multistakeholder collaboration, community participation and accountability frameworks also featured in more than half of the policies. Fewer than half the policies included one of the four infant/child policy options (45%). The least common maternal policy options were economic tools to improve diet (16%) and physical activity urban planning (18%); the least common health systems policy option was workforce empowerment skills (18%). Policy options to improve the macro environment were present in just over half the policies (52%). Those supporting healthy organisational environments featured slightly more frequently (57%), while those targeting individual behaviour change were most common (73%).

**Conclusions:** Policy options supporting public health processes were more frequent in English and Welsh policies than...
action-orientated options targeting maternal health, infant/child health or health systems. Future action should focus on implementing policy options to optimise infant/child and maternal health such as complementary feeding guidance, food marketing restrictions and economic tools to improve diet.

PO3.09.10
Reducing growth and developmental problems in children, design of a postnatal risk assessment in preventive child healthcare
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Background: In the past decade global awareness of medical and non-medical risk factors influencing growth and development of children has been increasing. Considerable research has been done to improve risk assessment in obstetric and neonatal healthcare. However, a postnatal risk assessment focusing on both medical and non-medical risk factors has, to our knowledge, not yet been developed. Our aim was to develop a postnatal risk assessment to be used by the Preventive Child Healthcare (PCHC) centres to identify at an early stage, children at risk for growth and developmental problems.

Methods: To design this unique assessment, we used the Intervention Mapping process steps one until four. An extensive review of the literature was performed. In addition, focus group interviews were held amongst a wide range of healthcare professionals, such as paediatricians, gynaecologists, scientists, and PCHC physicians and nurses. When available, odds ratios from the literature review were used to calculate the scores of the postnatal risk assessment.

Results: The 43 item postnatal risk assessment (the postnatal R4U) was developed. Hence, a project for implementation was designed in Preventive Child Healthcare centres. We aim to assess the predictive value of the assessment and its effectiveness in combination with the corresponding care pathways.

Conclusions: We successfully designed a postnatal risk assessment (the postnatal R4U) using the Intervention Mapping process. We were able to implement the postnatal R4U, which is currently being piloted in four PCHC organisations.

PO3.09.11
Preliminary results from a multi component kindergarten-based intervention to promote healthy diet in toddlers. A cluster randomized trial.
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Background: Concern has arisen due to the lack of diversity in children’s diet with corresponding low intake of fruit and vegetables and high intakes of unhealthy processed food which may be a factor in the rising prevalence of obesity. One reason for the lack of diversity may be food neophobia. The primary aim of the “Food for preschoolers”-intervention was to reduce levels of food neophobia in toddlers, aged 2 years, and promote healthy feeding practices among kindergarten staff and parents. The purpose of this presentation is to present effect of the intervention on dietary intake.

Methods: Food for toddlers is a cluster randomized trial. Eighteen randomly selected kindergartens located in two counties in Norway with enrolled children born in 2012 participated. The kindergartens were randomly assigned to the intervention or control groups. A 9-week multi-component intervention was implemented, with four main elements: 1) kindergarten staff implemented a pedagogical tool (Sapere method) in daily sessions to promote willingness to try new food; 2) kindergarten staff prepared and served the toddlers a cooked lunch; 3) kindergarten staff were encouraged to follow 10 meal principles on modeling, responsive feeding, repeated exposure; and 4) parents were encouraged to apply relevant feeding practices. The control group continued their usual practices. Dietary intake was assessed with food frequency questions. A sum score of healthy food; milk, water, fruits (2 items), berries (2 items), vegetables (4 items), potatoes, fish and seafood (3 items), whole grain bread (2 items) and oat meal porridge was calculated. Frequency for each item ranged from 0-10 times per week yielding a possible sum score range from 0-170.

Results: Data was analyzed by a multilevel linear mixed model with the sum score as the dependent variable. The model was adjusted for gender and parental education. The model was adjusted for kindergarten as a random effect. There was no significant difference in the healthy food sum score after the
intervention (Intervention group: 56.5 (SD: 1.9) vs. control group: 60.4 (2.4), p = 0.219).

**Conclusion:** Our results suggest that there was no intervention effect on child dietary intake measured just after the intervention. There is an ongoing data collection at age four, two years after the intervention to measure possible long term effect. Further analyses are needed to understand why there was no effect on child diet.

**PO3.09.12**

A cluster randomized web-based intervention trial among one-year-old children in kindergarten to reduce neophobia and promote healthy diets. A description.

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**Background:** A child’s first years of life are crucial for cognitive development and future health. Studies show that a varied diet with a high intake of vegetables is positive for weight development, mental health and cognitive development. A low intake of vegetables is considered one of the greatest challenges in children’s diets in Norway. Researchers suggest that one barrier for vegetable intake among children is food neophobia. Food neophobia is defined as a reluctance to taste and eat new foods. Food neophobia increases from the age of 2 years and decreases later in childhood. Our hypothesis is that interventions that can increase children’s intake of vegetables should be introduced early in life to overcome children’s neophobia.

This study aims to develop and measure the effect of two different interventions among one-year-old children in kindergartens to reduce neophobia and promote healthy diets. This abstract gives a short description of the study design and plan.

**Methods:** The kindergartens are randomized to one of three groups: two different intervention groups and one control group. A total of 306 children will be included in the study. The first intervention group will be served a warm lunch meal with a variety of vegetables, three days a week during the intervention period that will last for three months. The second intervention group will also be served the same meals and in the intervention period that will last for three months. The second intervention group will also be served the same meals and in the intervention and control groups. Other cardio-metabolic risk factors were similar in the study groups.

**Results:** The intervention period of three months will start during autumn 2017. The primary outcomes are child level of food neophobia and child dietary habits, food variety and vegetable liking. Secondary outcomes are child cognitive development, parental and kindergarten staff feeding practices, and child weight and height.

**Conclusions:** Results of this study will provide new knowledge about whether or not a Sapere-sensory education and a healthy meal intervention targeting children, kindergarten staff and parents will reduce levels of food neophobia in toddlers, improve parental and kindergarten feeding practices, improve children’s dietary variety, improve children’s cognitive development and reduce childhood overweight.

**PO3.09.13**

Longitudinal child-oriented dietary intervention-association with parental diet and cardio-metabolic risk factors. The Special Turku Coronary Risk Factor Intervention Project

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**Background:** The child-oriented dietary intervention given in the prospective Special Turku Coronary Risk Factor Intervention Project (STRIP) has been effective in decreasing saturated fat intake and lowering serum cholesterol concentration in children from infancy until early adulthood. The aim of this study was to investigate the long-term effects of the intervention on parental diet and cardio-metabolic risk factors.

**Design:** The STRIP study is a longitudinal, randomized infancy-onset atherosclerosis prevention trial where repeated dietary counselling with the main aim to reduce intake of saturated fat in the child’s diet was given for 20 years. Parental dietary intake assessed by a one-day food record and cardio-metabolic risk factors were analysed between the child’s ages of 9-19 years.

**Results:** Saturated fat intake of parents in the intervention group was lower (mothers: 12.0 vs 13.9 E%, p < 0.0001; fathers: 12.5 vs 13.9 E%, p < 0.0001) and polyunsaturated fat intake was higher (mothers: 6.1 vs 5.4 E%, p < 0.0001; fathers: 6.3 vs 5.9 E%, p = 0.0003) compared to parents in the control group. Maternal total and low-density lipoprotein cholesterol concentrations were lower in the intervention compared to the control group (mean ± SE 5.02 ± 0.04 vs 5.14 ± 0.04 mmol/l, p = 0.04 and 3.19 ± 0.04 vs. 3.30 ± 0.03 mmol/l, p = 0.03, respectively). Paternal cholesterol values did not differ between the intervention and control groups. Other cardio-metabolic risk factors were similar in the study groups.

**Conclusion:** Child-oriented dietary intervention shifted the dietary fat intakes of parents closer to the recommendations and tended to decrease total and low-density lipoprotein.
PO3.09.14

Music therapy may increase breastfeeding rates among mothers of premature newborns: a randomized controlled trial.

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Objective: To evaluate the impact of music therapy on breastfeeding rates among mothers of premature newborns.

Method: In this open randomized controlled trial, mothers of premature neonates weighting ≤ 1,750 g were submitted to music therapy sessions three times a week for 60 minutes. The endpoints were breastfeeding rates at the moment of infant hospital discharge and at follow-up visits (7-15 days, 30 and 60 days after discharge).

Results: A total of 94 mothers (48 in the music therapy group and 46 in the comparison group) were studied. Breastfeeding was significantly more frequent in the music therapy group at the first follow-up visit [relative risk (RR) = 1.26; 95% confidence interval (95%CI) = 1.01-1.57; \( p = 0.03 \); number needed to treat (NNT) = 5.6]. Moreover, this group showed higher breastfeeding rates at the moment of infant discharge (RR = 1.22; 95%CI = 0.99-1.51; \( p = 0.06 \); NNT = 6.3) and at days 30 and 60 after discharge (RR = 1.21; 95%CI = 0.73-5.6; \( p = 0.13 \) and RR = 1.28; 95%CI = 0.95-1.71; \( p = 0.09 \), respectively), but those results were not statistically significant.

Conclusions: This study demonstrated that music therapy had a significant effect in increasing breastfeeding rates among mothers of premature newborns at the first follow-up visit, and also a positive influence (although not significant) that lasted up to 60 days after infant discharge. Music therapy may be useful for increasing breastfeeding rates among mothers of premature newborns.

PO3.09.15

Effects of enteral glutamine supplementation on neurodevelopmental outcomes in very preterm children at thirteen years of age

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Background: Children born very preterm are highly susceptible for infection and inflammation and there is clear evidence that serious neonatal infection is associated with impaired brain development and poor neurodevelopmental outcome in this population. Enteral supplementation of the amino acid glutamine has been shown to positively affect neonatal infection rates and brain development in very preterm at school age. The objective of this follow-up study was to evaluate the long-term effects of enteral glutamine supplementation on neurodevelopmental outcomes in a cohort of very preterm children at thirteen years of age.

Methods: The current cohort was enrolled in a randomized placebo-controlled trial on glutamine-enriched enteral nutrition between day 3 and 30 after birth. Sixty-one very preterm children were assessed at a mean age of 13.30 years on measures of motor, intellectual, attentional, visuospatial working memory, academic, and behavioural functioning.

Results: No differences were found between the glutamine-supplemented and control group on motor, intellectual, academic, and behavioural functioning. Forward span visuospatial working memory performance was better in controls (crude/adjusted model: \( d = 0.67/0.64, p = .02/0.02 \)), whereas no difference was found on backward span. After adjustment for confounders, a difference between groups was found on parent-rated attention (crude/adjusted model: \( d = 0.47/0.73, p = .07/ .003 \)). However, scores of both groups were within the normal range.

Conclusions: This is the first study on the long-term effects of enteral glutamine supplementation on neurodevelopmental outcomes. Our study provides no evidence for beneficial or adverse effects of enteral glutamine supplementation in very preterm children on motor, neurocognitive, academic, and behavioural outcomes at thirteen years of age. The positive effects of enteral glutamine supplementation on neonatal infections, time to full enteral feeding, and brain volume as shown at earlier ages are nevertheless promising. Future studies may therefore clarify under which conditions enteral glutamine supplementation is most beneficial.

PO3.09.16

Women’s engagement with an evidence-based nutrition and lifestyle website during pregnancy and the impact on neonatal outcomes: A pilot study.

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Background: Maternal nutrition intakes during pregnancy may influence the growth and development of the fetus. It may also programme the health status of the offspring later in life. Technology based dietary interventions may be a cost effective means to deliver evidenced-based nutrition information. However, to date, high attrition rates have been reported among web-based health interventions. This study aimed to...
determine women’s engagement with an evidence-based online nutrition and lifestyle website during pregnancy and the subsequent impact on neonatal outcomes.

**Methods:** Women were recruited at their convenience after sonographic confirmation of a singleton pregnancy less than 18 weeks gestation and enrolled in a randomised controlled trial. Women were allocated to either the control group, which received standard care or the intervention group, which also received access to an evidence-based nutrition and lifestyle website from their first antenatal visit. Women’s demographic details were recorded in addition to their weight and height. Body mass index was calculated. Engagement and user interaction with the intervention website between November 2015 and January 2017 was assessed.

**Results:** A total of 240 women were included. The mean age was 31.9 ± 5.1 years and 44.2% (n = 106) were nulliparous. The mean BMI was 26.0 ± 6.0 kg/m² with 21.0% obese. There were no differences between the intervention or control group for BMI (p = 0.43), nulliparity (p = 0.06), planned pregnancy (p = 0.87), or the proportion of women < 30 years (p = 0.55) or 30 years or more (p = 0.06). However, the mean age was higher in the control group (32.6 ± 5.1 years) compared to the intervention group (31.2 ± 5.0) (p = 0.03), which is unexplained. All women completed the initial website login registration. Figure 1 demonstrates women’s engagement with the website throughout the period between November 2015 and January 2017. On preliminary analysis, excluding the landing page, page views ranged from 1-35. Average length of stay ranged from 0.41–17.0 minutes. The time of day the site was most accessed was at 11:00–13:00 with the highest number of 38 visitors. This was followed by 16:00-18:00 which received the highest number of 26 visitors. On preliminary analysis, there was no difference in birthweight between the intervention (3.56 ± 0.57 kg) and control group (3.48 ± 0.62 kg) (p = 0.42).

**Conclusion:** This study found that access to an evidence-based nutrition and lifestyle website from the first antenatal visit, did not result in consistent levels engagement throughout the study period. The most common time of day in which women engaged with the site was 11:00-13:00. Further studies are needed to determine the efficacy of existing, engaging online nutrition based resources on neonatal outcomes, prior to investment of public resources in development of technology-based dietary interventions in maternity services.

**Figure 1: Total cohort trends of engagement over time**

**PO3.10 – Growth and aging**

**PO3.10.01**

**Predictors of Stunting among Children Aged 6 to 59 Months in Aksum Town, North Ethiopia: Matched Case Control Study**


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**Background:** Childhood under-nutrition continues to be a major public health problem in Ethiopia. As earlier studies are limited, this study aims to assess predictors of stunting among 6 to 59 months old children visiting health facilities in Aksum town, Tigray region, North Ethiopia.

**Methods:** Facility based sex matched case control study design was conducted on 330 (165 cases and 165 controls) who visited health facilities from October 2015 to January 2016. All 6 - 59 months old children who visited health facilities for various services during the study period were included until the required sample attained. The cases were stunted under five children and controls were normal non-stunted under five children. Data were collected by interview using pretested structured questionnaire and anthropometric measurements. Finally, conditional logistic regression model was used for analysis.

**Results:** The mean (±SD) age of cases and controls was 35.27 (±16.1) and 27.5 (±17.9) months respectively. The main predictors of stunting among 6 to 59 months old children were household monthly income of less than 1000.00 ETB [AOR = 3.1, 95% CI: 1.1-8.9], being two or more years old [AOR = 1.9, 95% CI: 1.1-3.4] and low dietary diversity [AOR = 2.6, 95% CI: 1.1-6.0]. Though the association was marginal, the findings of the present study also showed that children whose mothers always wash their hands with water only [AOR = 2, 95% CI: 1.0-4.4] and those whose mothers sometimes wash their hands with soap and water [AOR = 1.8, 95% CI: 1.0-3.4] after visiting toilet were more likely to be stunted compared to those whose mothers always wash their hands with soap and water after visiting toilet.

**Conclusion:** Lower household monthly income, being two or more than two years old and low dietary diversity were the independent predictors of stunting among 6 - 59 months old children in the study area. Policies and programmes aiming to address child stunting should focus on feeding practices, hygiene and other nutrition-sensitive interventions.

**PO3.10.02**

**Associations between antenatal glucocorticoid treatment and child growth at 3 years of age**

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Background: Previous studies have shown that exposure to antenatal synthetic glucocorticoids may be associated with small body size at birth. Small body size at birth and faster growth after birth are well known to increase the risk for obesity and cardio-metabolic diseases later in life. Yet, the association between antenatal synthetic glucocorticoid exposure and body size in early childhood remains less clear especially in those who were born at term (≥37 gestational weeks). In this study, we compared weight, height and weight-for-height ratios for age and sex of children who were or were not antenatally exposed to the synthetic glucocorticoid, betamethasone, and who were born term or preterm (<37 gestational weeks).

Methods: Participants come from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) study comprising 4777 women and their singleton children born between 2006-2010. Data on weight, height and weight-for-height ratios for age and sex according to Finnish growth charts were derived from child welfare cards in follow-ups conducted at the age of 0.7 to 6.1 years (mean = 3.1, SD = 0.8) in 2071 of these children (51.0% boys; 49 exposed to betamethasone); Weight and height at birth were derived from Finnish Medical Birth Register. We studied associations between prenatatal betamethasone exposure and body size and growth from birth to early childhood. This is true for those born at term in whom the harms of antenatal synthetic glucocorticoid may not outweigh the potential benefits.

Results: Children exposed to betamethasone had higher weight-for-height SD scores than controls (B = 0.61, 95% CI = 0.33-0.89, p < 0.001) in early childhood. This association was only significant in the group born at term (B = 0.54, 95% CI = 0.15-0.93, p = .007 for term-borns; B = 0.36, 95% CI = -0.11-0.84, p = .13 for preterm; Figure 1 panel A). This association was explained by faster growth in weight-for-height from birth to early childhood in the betamethasone exposed group in comparison to those not exposed (Figure 1 panel B). Betamethasone exposed and non-exposed did not differ in height or ponderal index at birth.

Conclusions: Our findings suggest that exposure to antenatal synthetic glucocorticoids is associated with higher weight-for-height in childhood and faster growth in weight-for-height from birth to early childhood. This is true for those born at term in whom the harms of antenatal synthetic glucocorticoid may not outweigh the potential benefits.

Weight-for-height standard deviation scores for children born term or preterm and exposed or not exposed to betamethasone.

PO3.10.03

Comparison of total nephron number in normotensive Japanese born during and after World War 2

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Background: Japan has the second highest rate of chronic kidney disease (CKD) in the world. The reason for this is not known, but we have previously shown that normotensive Japanese subjects have one of the lowest nephron counts ever reported (Kanzaki G. et al. Proc Am Soc Nephrology Kidney Week 2016) and hypertensive subjects have fewer nephrons per kidney than normotensive subjects. These subjects were born in the 1920’s-1940’s, a period of harsh conditions in Japan that included World War 2 (WW2, 1939-1945). It is possible that these subjects were born with low birth weight and low nephron number. However, following WW2, maternal prenatal nutrition in Japan was improved due to post-war economic growth which commenced in 1950. In this study we compared nephron number in subjects born in the 1920’s-1940’s with that in subjects born during or after 1950 in order to determine whether nephron number was increased in those subjects born in a period of improved nutrition and social conditions.

Methods: A total of 24 Japanese non-CKD (eGFR >62.1ml/min/1.73m2) autopsy kidneys without hypertension were collected at Nippon Medical School, Tokyo, Japan. We analyzed kidney findings in the post-WW2 group (born 1950-1981; n = 10), and compared these findings with our pre- and during WW2 group (born 1925-1948; n = 14). Total nephron number and mean glomerular volume (Vglomer) were estimated using design-based stereology. Cortical volume was estimated using the Cavalieri Principle on histological sections. Glomerulosclerosis was determined using a standardized glomerulosclerotic index.

Results: Physical characteristics and kidney data of the two groups are presented in Table 1. The 1920’s-1940’s group had significantly lower kidney weight than the post-1950 group (P < 0.05). Nephron number was 45% higher in the post-1950s group than in the 1920’s-1940’s group (P < 0.05), even though there were no significant differences in body size or eGFR between the groups (P = 0.09, P = 0.23, respectively).

Conclusions: Nephron number was significantly higher in Japanese subjects born post-1950 in the period of post-WW2 economic growth than those born in the 1920s-1940s. This difference in nephron number may be due to differences in nephron endowment at birth and/or greater nephron loss in the
Physical characteristics and kidney data in 24 Japanese subjects

PO3.10.04
New views on breast cancer through the pubertal window


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Background: Earlier age at onset of pubertal events and a longer interval between them (tempo) have been associated with increased breast cancer risk. It is unknown whether the timing and tempo of puberty are associated with adult breast density, which could mediate the increased risk.

Methods: Between 1988 and 1997, girls participating in the Dietary Intervention Study in Children were clinically assessed annually between ages 8 and 17 years for Tanner Stages of breast development (thelarche) and pubic hair (pubarche), and onset of menarche was self-reported. In 2006, 182 women aged 17.4% (12.3–22.7%) (geometric mean (95%CI) = 17.8% (15.2–20.4%)) were recruited from cataract surgery patients aged 65 and older. Studies in subjects from both periods who died at the same age will be required to determine the relative contributions of nephron endowment at birth and nephron loss with age on these final nephron counts.

Table 1. Physical characteristics and kidney data in 24 Japanese subjects (values are mean ± standard deviation)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Born 1920s–1940s (n=14)</th>
<th>Born post 1950 (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>71.4 ± 5.8</td>
<td>46.2 ± 11.6</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.3 ± 4.2</td>
<td>164.4 ± 3.9</td>
<td>0.20</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.7 ± 2.9</td>
<td>23.3 ± 4.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Kidney weight (g)</td>
<td>146.1 ± 15.7</td>
<td>185.0 ± 37.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>86.1 ± 18.0</td>
<td>99.8 ± 35.9</td>
<td>0.24</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>91.3 ± 11.0</td>
<td>96.8 ± 12.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vgtom (s/10µm³)</td>
<td>6.3 ± 1.48</td>
<td>6.3 ± 2.1</td>
<td>0.99</td>
</tr>
<tr>
<td>Vlomtotal (cm³)</td>
<td>3.2 ± 0.99</td>
<td>4.3 ± 1.64</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>%DBV (%)</td>
<td>510.718 ± 120.356</td>
<td>745.958 ± 207.449</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cortical volume (cm³)</td>
<td>74.1 ± 16.7</td>
<td>113.7 ± 26.22</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Results: Our preliminary results suggest that though ages at thelarche and menarche were not associated with %DBV, the duration between thelarche and menarche was significantly positively associated with %DBV in a multivariable model adjusted for reproductive factors (parity and oral contraceptive use), demographics (race, education) and childhood and adult body size (p-trend = 0.003). %DBV was 39% higher in women whose thelarche-to-menarche tempo was 2.9 years or longer (geometric mean (95%CI) = 22.7% (17.0–30.3%)) compared to women whose thelarche-to-menarche tempo was less than 1.6 years (geometric mean (95%CI) = 16.3% (15.2–17.4%)). Age at pubarche was not associated with %DBV.

Conclusions: Our results suggest that a longer pubertal tempo, i.e. greater number of months between thelarche and menarche, is associated with higher percent breast density in young women. Future research should examine whether breast density mediates the association between longer tempo and increased breast cancer risk.

PO3.10.05
Trajectories of life course circulating corticosterone levels in the rat are determined by developmental programming and influence length of lifespan

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Background: We recently demonstrated a fall in rat circulating corticosterone in males and females between postnatal day (PND) 450 and 650 in offspring of obese rat mothers fed a high fat diet (MO) (PMID 25953670). Corticosterone was higher than control (CTR) in offspring whose mothers ate a high fat diet and were obese. Although corticosterone levels were different in these two groups the fall in levels that occurred with aging occurred within the same age windows in MO and CTR (Fig 1 A and B). In the study reported here we examined life course changes in response to another programming challenge – maternal low protein (LP) diet.

Methods: We measured basal fasting corticosterone to determine life course profiles in male and female offspring of mothers fed a LP diet (10% casein) compared with CTR (20% casein) diet.

Results: In male and female LP offspring there was a fall in corticosterone between 220 and 650 days (Fig 1 C and D). In relation to programming of longevity, in our colony control and LP offspring survived longer than 850 days whilst MO offspring started to die around 650 days. Data presented as mean ± SEM, n = 5-14. *P < 0.05 vs control.

Conclusion: Although the time windows differ slightly in these studies in the MO and LP models, the importance of these data are 1) they provide further evidence that when sampled at multiple ages over a wide period of the life course, circulating
Corticosterone in control animals falls; 2) programming by both LP and MO increases the circulating levels but within the range of ages studied, the fall in corticosterone occurs at similar ages. The life course fall in corticosterone may be a) causing aging, b) protecting against aging, c) responding to aging, or d) an epiphenomenon with a fortuitously related time course to aging. The actual levels of corticosterone may be important in determining the length of the lifespan with the potential for effects of both high and low corticosterone levels.

**Funding:** RCUK-CONACyT

Corticosterone fall in £ control (open) and ¥ LP (grey) or MO (black). A) MO males; B) MO females; C) LP males; D) LP females.

**PO3.10.06**

**Associations between birth weight and adult outcomes in a large population sample: the UK Biobank**

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**Background:** Birth weight (BW) has shown to be associated with a large number of disease and well-being related outcomes in adulthood. It has been suggested that these associations reflect the long-term effects of intrauterine exposures on foetal growth, as well as organ and physiological development. However, exact mechanisms are still unclear. Using data from a large population sample, we aimed to assess the association of BW with a wide range of outcomes in middle- and old-aged adults. This may provide new insights of key mechanisms of the association of birth weight with health outcomes later in life.

**Methods:** We carried out a cross-sectional analysis of baseline (2006-2010) and posterior assessments (2012-13 and 2014 +) data of UK Biobank cohort study. Adults aged 40–69 with information on self-reported BW were included (n = 280,322). Generalized linear and fractional polynomial modelling was performed to examine the association between BW and adult outcomes related to body composition (n = 16 outcomes), cardiometabolic health (n = 10), musculoskeletal health (n = 3), cancer (n = 12), mental health (n = 6), physical activity (n = 2), cognitive performance (n = 6), and reproductive health (n = 3), adjusting for age, sex, household income, educational level, development index, and maternal smoking. We explored sex and age interactions.

**Results:** After adjusting for confounding factors, we found consistent associations of BW across a range of outcomes related to body composition. BW had an inverse association with some adiposity measures (BMI, body fat (%), trunk fat mass, arm fat), whilst showed a J-shaped distribution with other measures (fat mass, trunk fat (%), leg fat (%), leg fat mass, arm fat mass). BW was positively associated with menopause age, better cognition and some types of cancer (bone & skin, non-smoking related cancers), however some of these associations were not linear. A reverse J-shaped association was observed for Diabetes mellitus, especially type 2, whilst a J-shaped association was observed for other conditions, such as systolic and diastolic blood pressure. In general, the direction and shapes of the associations were similar among males and females, differing only in magnitude. For few cases associations with BW were present in only one sex: i.e. diabetes type 1, heel bone mineral density, reproductive cancer, lifetime bipolar disorder, and numeric memory were evident only in females, and arm fat (%) and physical activity only in males. There was no strong evidence of cohort effect.

**Conclusions:** These findings suggest that lower and higher birth weight are both related to outcomes later in life which support the evidence that intrauterine factors might have a role in adult health. Sex-differences were observed for few outcomes. Although BW distribution may vary along time, evidence of cohort effect was not found. The findings show that most associations are consistent to those observed in other studies.

**PO3.10.07**

**Do universal plagiocephaly prevention strategies influence head shape development in healthy term infants?: A Western Australian experience.**

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**Background:** Infant physical development results from a dynamic interplay between innate genetic characteristics, environmental conditions and the quality of daily interactions with others. Non-synostotic plagiocephaly (NSP) is a prevalent developmental condition. Reports linking NSP with adverse developmental outcomes accentuate parental and clinician anxiety about the risk the condition poses and a demand for preventive solutions. Intervention studies have shown that NSP can be successfully resolved or prevented using plagiocephaly
prevention behaviours (PPB) such as infant positioning, handling, and motor play. The purpose of this study was to examine if parent exposure to universal-PPB education reduced the development of NSP in infants.

Methods: A prospective longitudinal study design was used to observe 52 (26 male) healthy, term (37-41 weeks) infant-mother dyads at infant’s age one, three and ten months within their home. Infant handling behaviours were scored from video filmed during routine care activities using the Infant Handling Score, a valid and reliable tool developed specifically for the project. Head shape was measured by plagiocephalometry and motor development was assessed using the Test of Infant Motor Performance, Alberta Infant Motor Scale and the Peabody Developmental Motor Scale. Interviews were used to gather the mother’s recall of education about infant sleep, wake time and infant handling activities at one and three months. The infants were grouped into typical head shape (THS) or NSP based on the cut score for plagiocephalometry.

Results: All mothers received universal PPB brochures at delivery discharge, of these 42 (80.8%) recalled the material. Recall of direct instruction from health professionals on infant sleep positioning was moderate (61.5%), but low for wake time activity (36.5%) and infant handling (15.4%). Of the 52 infants, 33 (63.5%) had THS and 19 (36.5%) developed NSP. The distribution of males and females (THS males = 48.5%; NSP = 52.6%) and birth order (THS First born = 51.5%; NSP = 57.9%) were similar. By age 10 months, head shape became typical for 10 (66%) of NSP group. More infants in THS group had delayed motor development at 1 month (THS Delay = 48.4%; NSP = 26.3%), but were similar at 3 months (THS Delay = 18.2%; NSP = 10.5%) and 10 months (THS Delay = 15.6%; NSP = 16.7%). At 1 month more mothers (54.5%) of the THS group were competent infant handlers compared to the mothers of the NSP group (36.8%), but at 3 months scores were similar. However, mothers of THS group expressed greater confidence in handling compared to mothers of NSP at 3 months (p = .010).

Conclusions: Current universal PPB strategies used in WA do not prevent infants from acquiring NSP. Most infants who acquired NSP had typical motor abilities and head shape resolved with time. Maternal infant handling competencies improved over time but did not predict infants who developed NSP. It is possible that handling competence may be protective and assist in the alleviation of early developmental concerns. Revision of early parenting programs is recommended to develop parent confidence, enhance infant handling abilities and improve developmental outcomes for all young babies.

Background: Number of low birth weight (LBW <2,500g) has increased in Japan over past decades, despite of universal coverage of maternity check-ups and low infant mortality. However, reason of high rates of LBW and how to control of maternal body weight (BW) during gestation still remains.

Methods: Thirty three women (32.0±4.6 year-old, 19 primipara, 14 multipara) with singleton birth (6 late pre-term birth, 27 term birth) were followed by echography till delivery (18 vaginal delivery, 14 caesarian section) including echography. A total of maternal weigh gain just before delivery were subdivided into 4 major elements such as newborn birth weight (NBW), amnion fluid (AF), placenta (PL) and substantial maternal body gain (sMBG = maternal BW just after delivery minus pre-pregnant BW) by measurement and calculating. Partial correlation coefficient of factors associated with NBW were calculated after adjustment for maternal age, length of gestation (weeks), number of delivery, baby sex and others. Data of weight gain were presented as per weeks divided by number of gestational weeks (38.3±1.5 weeks).

Additionally, to attest a concept of transgenerational effect, we inspected 448 term-birth paired (2-generations) maternal handbooks that are designed to record both mother and child health condition during total length of gestation and infant phase. Based on adjustment for influential factors, partial correlation coefficient analysis was adopted to elucidate the relationship of birth weights between mother and her child across generations.

Results: NBW per weeks (75.4±8.5g) were significantly associated with pre-pregnant maternal weights (51.0±7.8kg; r = 0.42, P < 0.05), BMI (20.9±3.2; r = 0.41, P < 0.05) and sMBG per weeks (141.9±47.6g; r = 0.50, P < 0.01), but not related to total BW of mother (257.2±90.3g; r = -0.09, ns).

Conclusions: Current universal PPB strategies used in WA do not prevent infants from acquiring NSP. Most infants who acquired NSP had typical motor abilities and head shape resolved with time. Maternal infant handling competencies improved over time but did not predict infants who developed NSP. It is possible that handling competence may be protective and assist in the alleviation of early developmental concerns. Revision of early parenting programs is recommended to develop parent confidence, enhance infant handling abilities and improve developmental outcomes for all young babies.

PO3.10.08

Determinants of birth weight associated with transgenerational effect

M. Kinoshita

Hokkaido University, SAPPORO, Japan

Methods: A prospective longitudinal study design was used to observe 52 (26 male) healthy, term (37-41 weeks) infant-mother dyads at infant’s age one, three and ten months within their home. Infant handling behaviours were scored from video filmed during routine care activities using the Infant Handling Score, a valid and reliable tool developed specifically for the project. Head shape was measured by plagiocephalometry and motor development was assessed using the Test of Infant Motor Performance, Alberta Infant Motor Scale and the Peabody Developmental Motor Scale. Interviews were used to gather the mother’s recall of education about infant sleep, wake time and infant handling activities at one and three months. The infants were grouped into typical head shape (THS) or NSP based on the cut score for plagiocephalometry.

Results: All mothers received universal PPB brochures at delivery discharge, of these 42 (80.8%) recalled the material. Recall of direct instruction from health professionals on infant sleep positioning was moderate (61.5%), but low for wake time activity (36.5%) and infant handling (15.4%). Of the 52 infants, 33 (63.5%) had THS and 19 (36.5%) developed NSP. The distribution of males and females (THS males = 48.5%; NSP = 52.6%) and birth order (THS First born = 51.5%; NSP = 57.9%) were similar. By age 10 months, head shape became typical for 10 (66%) of NSP group. More infants in THS group had delayed motor development at 1 month (THS Delay = 48.4%; NSP = 26.3%), but were similar at 3 months (THS Delay = 18.2%; NSP = 10.5%) and 10 months (THS Delay = 15.6%; NSP = 16.7%). At 1 month more mothers (54.5%) of the THS group were competent infant handlers compared to the mothers of the NSP group (36.8%), but at 3 months scores were similar. However, mothers of THS group expressed greater confidence in handling compared to mothers of NSP at 3 months (p = .010).

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PO3.10.08

Determinants of birth weight associated with transgenerational effect

M. Kinoshita

Hokkaido University, SAPPORO, Japan
Does grandmaternal smoking during pregnancy have an effect on her grandchild’s birth weight?

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Background: Smoking during pregnancy (SDP) is believed to increase the risk of low birth weight and preterm birth. Recent studies have shown that the grandmother’s SDP may also have an effect on the offspring’s birth weight, suggesting that it causes epigenetic changes that are inherited by subsequent generations. However, maternal smoking during pregnancy may be an important factor on the causal pathway (mediator). Moreover, previous studies have shown different associations depending on whether the mother smoked during her pregnancy or not. Thus maternal SDP may also interact with grandmaternal SDP on her grandchild’s birth weight.

The Swedish Medical Birth Register (MBR) covers almost all births in Sweden, with some information on socio-economic factors, and since 1982 it also includes information on SDP. The Swedish personal identity number allows for unambiguous linkage to registers with information on family relationships (the Multi-Generation Register, MGR).

Our aim was to estimate the total, direct and indirect effects of grandmaternal SDP on birth weight considering the mediation and interaction effect of maternal SDP, based on Swedish registry data.

Methods: To estimate the association between grand-maternal SDP with offspring birth size and potential mediation and modification of maternal SDP we performed a study based on the Swedish registers. In this study we included all children born since 1982, who had had a child of their own by Dec 31st 2013, by linkage of MBR and MGR.

Further we used VanderWeele’s approach to mediation with interaction between exposure and mediator, which is a 4-way decomposition of the total effect.

1) Controlled direct effect, the effect of grandmothers’ SDP if the mothers didn’t smoke (CDE)
2) Reference interaction, the difference in effect if both grandmother and mother smoked, compared to the effect of only one of them did, if there (IntRef)
3) Mediated interaction, the difference in effect if both grandmother and mother smoked, compared to the effect of only one of them did (MedRef)
4) A pure indirect effect, the effect of the mothers’ smoking if the grandmothers didn’t (PIE)

Results: In total, 37% of the children were exposed to grandmaternal SDP (n=186 937 maternal and n=109 485 paternal grandmothers) and 13% were exposed to maternal SDP. Figure 1 shows that the total effect of maternal grandmothers’ smoking on their grandchildren’s birth weight was slightly positive, while it was negative for paternal grandmothers. For maternal grandmothers’ SDP the most important components were the controlled direct effect and the pure indirect effect, i.e. the main effects, while for paternal grandmothers’ SDP there was no significant CDE. In both cases there were significant, but small, negative interaction effects.

Conclusions: The effect of paternal grandmothers’ SDP seems to be mediated by maternal SDP while there seems to be a direct effect in the opposite direction for maternal grandmothers’ SDP. However, the interaction effects were very small.

References: 1Cnattingius PMID 15203816. 2Hyppönen PMID 14563745, Miller PMID 24504157, Misra PMID 5824542 Pembrey PMID 25015471, Rillamas-Sun PMID 24337862. 3VanderWeele PMID 25000145

Decomposition of effects of grandmaternal smoking during pregnancy and grandchild’s birth weight

Maternal diseases and life-style risk factors during pregnancy and newborn head circumference in a Brazilian birth cohort.

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Background: Anthropometric measures are important tools for assessing and monitoring the child’s development. Among them, head circumference is fundamental for the screening of several pathological disorders. During the peak of intrauterine brain growth, harmful exposures such as tobacco and drugs used by the mother and maternal diseases may have a high impact on the development of the central nervous system.

Objective: To assess the association between head circumference at birth and some diseases, maternal habits during pregnancy and type of delivery.

Methods: This study used data from a birth cohort evaluated in 2010 including all singleton live births in Ribeirão Preto, São Paulo State, Brazil, comprising 7402 children. Stillborn infants, twins, triplets, and those who had no information on the head circumference at birth were not included. Head circumference was measured soon after the birth with an inextensible tape by trained personnel. After the delivery, still at the hospitals, mothers were interviewed by using a pre-tested structured questionnaire about their socioeconomic profile, health and lifestyle behavior during pregnancy. Information on exposure of interest was diseases during pregnancy (gestational hypertension and diabetes), alcohol and tobacco consumption and type of delivery. Linear regression model was applied to evaluate the association of the exposures of interest with head circumference, adjusted by gestational age.

Results: The mean value of head circumference was 34.3 cm (Standard Deviation, SD, 1.95) and the median was 34.5 cm. Children from mothers who had gestational hypertension showed head circumference 0.21 cm smaller (95% Confidence Interval -0.32 to -0.08) than those from normotensive mothers; gestational diabetes was associated with a head circumference 0.28 cm higher (95%CI 0.11 to 0.45) when compared to children from non-diabetic mothers. Smoker mothers during pregnancy had children with head circumference 0.44 cm smaller (95%CI -0.57 to -0.31) than those from non-smokers. Children born by cesarean section showed a head circumference 0.72 cm higher (95%CI 0.32 to 0.36) than those born by vaginal delivery. One week increase in gestational age was associated with an increase of 0.34 cm (95%CI 0.32 to 0.36) in head circumference. Alcohol consumption during pregnancy was not associated with head circumference.

Conclusions: Gestational hypertension and tobacco consumption during pregnancy had a negative effect on newborn’s head circumference, whilst gestational diabetes, cesarean delivery and increasing gestational age were associated with higher values of this measurement.

PO3.10.12
The impact of caesarean section inflammation on infant’s length
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Background and objective: The overuse of caesarean section is a public health problem particularly in middle to high-income settings. As this is a major surgical procedure, it elicits an inflammatory response that may affect infant’s health through breastfeeding. This longitudinal study involved 64 apparently healthy mother-infant pairs to investigate the association between maternal inflammation and infant’s anthropometry at one month of age, according to type of delivery.

Methods: Exclusion criteria were adolescence, multiple pregnancies, diabetes, hypertension, hormonal disorders, infectious diseases, drug and/or alcohol consumption, preterm (<37 weeks) and post-term (≥42 weeks) delivery, low birth-weight (<2500g), Apgar score < 3, and genetic disorders of the newborn. Maternal inflammation was assessed by postpartum high-sensitivity C-Reactive Protein (hs-CRP), which was determined by a direct enzymatic method. Infant’s weight, length, head, chest and abdominal circumferences were measured 24-72 hours and one month after delivery. Gestational
age was determined by a combination of ultrasonography performed up to the 20th week of gestation, the Capurro method determined between 12 and 48 hours of birth, and the last menstrual period. Multiple regression analysis was used considering hs-CRP as the exposure variable and newborns anthropometric measurements as outcomes.

Results: hs-CRP was inversely associated with breastfed infants length (p = 0.033) at one month of age and change in length from birth to one month of age (p < 0.001), controlling for maternal pre-pregnancy body mass index, sex and age (hours) of the newborn.

Conclusion: The inverse association observed between hs-CRP and length in the first month of life is possibly due to elevated pro-inflammatory cytokines in breast milk. Pro-inflammatory cytokines may interfere with bone development, and can affect growth hormone concentrations in breast milk.

PO3.10.13

Ethnic differences in height growth trajectories in contemporary children and adolescents: findings from the UK Millennium Cohort Study

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Background: Height is an important biomarker for early life exposures that influence adult disease risk. Recent evidence suggests that height of UK children differs by ethnicity. Research to date on this subject was mostly based on cross-sectional data. The few available studies using longitudinal data focused on growth in the first few years in life, or for a short period during early childhood. We investigated whether height trajectories from early childhood into adolescence differed between ethnic groups, and the role of early life covariates.

Methods: We used the data from 15 317 (White, South Asian, Black African and Black Caribbean) singletons in the UK Millennium Cohort Study. Mixed effects fractional polynomial models were applied to height repeatedly measured between 3 and 14 years.

Results: Compared with White counterparts, South Asians (9% of study sample) were taller at 3 years by 0.5cm, had similar childhood trajectories, but became shorter in adolescence, particularly in girls, by 0.7cm (95% CI: 0.1, 1.2) at 11 years, increasing to 3.2cm (2.7, 3.7) at 14 years in girls. Boys were shorter by 0.5cm (0.2, 1.2) at 14 years. Height of South Asians relative to White children increased after adjusting for parental height and further for birthweight, but changed little with additional adjustment for prenatal and socioeconomic factors. Black African/Caribbean boys and girls (3.3% of sample) were taller at 3 years by 2.2cm (1.7, 2.7) and 3.2cm (2.6, 3.8), respectively. Differences increased to 3.8cm (3.0, 4.7) and 5.5cm (4.5, 6.4) at 11 years, but reduced to 3.1cm (2.0, 4.2) and 2.5cm (1.7, 3.4) at 14 years. Adjustment for early life covariates did not alter these differences.

Conclusions: South Asians had shorter parents and lower birthweight. When adjusting for these factors height differences (relative to White children) increased, indicating greater intergenerational height gains and early life growth in South Asians. South Asians were slightly taller in early life, but shorter by adolescence. Black African and Black Caribbean children were the tallest, with smaller differences in adolescence. Distinct child-to-adolescence height trajectories may partly be due to their different growth tempo.

PO3.10.14

Growth across life course and cardiometabolic risk markers in 18 years old adolescents: the 1993 Pelotas Birth Cohort


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Background: Growth trajectories may have effects on metabolic risk profile later in life. It has been suggested that weight gain and linear growth may have different consequences, therefore, it is important to disentangle the effect of weight gain from that of height gain. We aimed to evaluate the associations of height growth independent of weight gain, and weight gain independent of height growth (relative weight gain) throughout infancy, childhood and adolescence, with several cardiometabolic risk markers at age 18 years in a birth population based cohort.

Methods: Conditional relative weight (CWh) and conditional length/height (CH) were assessed using data from six follow-ups of the 1993 Pelotas Birth Cohort (at birth, 1, 4, 11, 15 and 18 years). The outcomes, measured at age 18 years, were: C-reactive protein (CRP), total cholesterol (TC), LDL-C, HDL-C, TGL, systolic and diastolic blood pressure (SBP and DBP), BMI and waist circumference (WC).

Results: In both sexes, greater CWh at 1 year was positively associated with BMI and WC, whereas greater CWh at most age periods in childhood and adolescence predicted increased values of CRP, TC, LDL-C, TGL, SBP, DBP, BMI and WC, and decreased HDL-C. Higher CH during infancy and childhood was positively related with SBP in boys and girls, and with BMI and WC only in boys.

Conclusion: In a population-based cohort of a middle-income country, adolescents who gain weight more rapidly than their peers after the first year of life had a worse cardiometabolic risk profile at 18 years old. The lack of anthropometric data at two years is a limitation in our study, since there is evidence suggesting that the hazards of rapid weight gain appear particularly after the two first years of life. Overall, our study support the “first 1000 days initiative” suggesting that prevention of excessive weight gain after age two years might be important in reducing subsequent cardiometabolic risk.
PO3.10.15

The effect on early life growth on the size, tempo and velocity of adolescent growth

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Background: Modelling adolescent growth could assist in studying factors that influence the timing and magnitude of the growth spurt and its potential influence on adult body size and composition. Growth in early life is associated with the timing of puberty. Using the superimposition by translation and rotation (SITAR) we assessed (i) ethnic differences in the size, tempo and velocity of adolescent growth, and (ii) the association between early life size and adolescent growth.

Methods: Data were obtained from the prospective Birth to Twenty birth cohort, which followed 3273 children born between April and June 1990 in the Greater Johannesburg Municipality. A total of 2107 black and white, females and males with serial height and weight measurements between 7 to 23 years were included in the study. Growth was modelled using sitar, a shape invariant model which allows for comparison of individual growth on size, tempo and velocity. The World Health Organization (WHO) 2006 growth standards for children between birth and 5 years were used to develop height-for-age (HAZ), weight-for-age (WAZ), BMI-for-age (BMIZ) and weight-for-height (WHZ) z-scores. Models were refitted for black children only to include stunting in infancy and at 1 year for height, and undernutrition at birth, infancy and waz change between birth and infancy for BMI.

Results: White children were taller than black children and white boys heavier than black boys. In girls, there were no differences in weight and BMI. Black boys reached peak height velocity later than white boys while the reverse was true in girls for height. Peak BMI velocity was earlier in white than black children. Stunting at both ages was associated with the size but not the tempo and velocity of height growth in boys. In girls, stunting at 1 year was associated with size. Change in weight-for-age z scores was negatively associated with the tempo of BMI accrual in boys but not in girls.

Conclusion: Ethnic differences in the tempo of height growth are sexually dimorphic. An increment is weight-for-age z scores from birth to infancy is associated with an earlier tempo in BMI for boys.

PO3.10.16

Direct comparisons of relative morbidity caused by various disorders in the populations of Chile and one of Brazil’s southern region

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Earlier we have studied age-related dynamics and gender differences of morbidity and mortality in three southern Brazilian states and in the populations of Argentina and Chile. In presented work direct comparisons of relative mortality parameters were made in the populations of Argentina and southern region of Brazil, including three states: Rio-Grande-do-Sul, Santa-Catarina and Paraná. For realization of this task we have utilized the data from official site belonging to the Ministry of Health of Argentina and from Brazilian national database called DataSus, employing methodological principles that were described in our previous publications, however with adjustment of age categories to 0-24, 25-44, 45-64 and > 65 years and in two chronological periods (2001-2003 and 2005-2007). The main reason for such direct comparisons was ethnic similarity of predominantly European origins in both geographical areas studied. Besides, we have southern region, as well as in the populations of Chile and Argentina. In the present work direct comparisons of relative morbidity indices were performed in the populations of Chile and southern brazilian state of Rio-Grande-do-Sul (RS). In order to do this, we have used the data from the official site of chilean Ministry of Health and from brazilian national database called DataSus, employing methodological approaches described earlier, but with adjustment of the age categories: 0-19, 20-24, 25-44, 45-64 and > 65 years, and in two chronological periods (2006-2008 and 2009-2011). The reasons for such direct comparisons included ethnic similarity of predominantly european origins in both geographical areas studied, as well as similar total numbers of inhabitants. The results obtained indicate, for example, the postponement of morbidity from arterial hypertension, renal insufficiency and femoral fraction to more advanced age category in chilean population, as compared to southern brazilian state of RS. On the other hand, population of Chile had higher morbidity from rheumatoid arthritis in younger age categories, in comparison to southern brazilian state of RS. No differences were observed between two chronological periods examined. On our opinion, such comparative data are quite important to be considered in the frame of DOHaD concept, and the next step would be obviously the comparisons of more distant geographical regions of similar ethnical profile (for example, some Latin-American and european countries). The gender differences must be also carefully interpreted, including the pubertal and menopausal transitions. In conclusion, such epidemiological comparisons should be continued, aiming finally at construction of detailed geographical maps for age-related dynamics of morbidity and mortality, as well as their gender differences.

PO3.10.17

Direct comparisons of relative mortality caused by various disorders in the populations of Argentina and southern region of Brazil

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Earlier we have studied age-related dynamics and gender differences of morbidity and mortality in three southern Brazilian states and in the populations of Argentina and Chile. In presented work direct comparisons of relative mortality parameters were made in the populations of Argentina and southern region of Brazil, including three states: Rio-Grande-do-Sul, Santa-Catarina and Paraná. For realization of this task we have utilized the data from official site belonging to the Ministry of Health of Argentina and from Brazilian national database called DataSus, employing methodological principles that were described in our previous publications, however with adjustment of age categories to 0-24, 25-44, 45-64 and > 65 years and in two chronological periods (2001-2003 and 2005-2007). The main reason for such direct comparisons was ethnic similarity of predominantly European origins in both geographical areas studied. Besides, we have
decided to compare the population of Argentina with the whole southern region of Brazil, rather than with any single southern Brazilian state separately, in order to employ more comparable numbers of inhabitants in two geographical areas examined. We have observed the postponement of relative mortality caused by septicemia and tuberculosis to more advanced age categories in the population of Argentina, as compared to southern region of Brazil. On the other hand, relative mortality caused by suicides was rather homogeneously distributed along the age scale in Argentina, whereas it was highly concentrated in the intermediate age categories in Brazil’s southern region. What for gender differences, our study has established that feminine fraction of mortality was lower in Argentina, as compared to southern region of Brazil, for diabetes mellitus, arterial hypertension and ischemic myocardial disease, at least for some age categories. However, feminine fraction was higher in Argentina, as compared to Brazil’s southern region, for mortality caused by tuberculosis. There were no marked differences in parameters of mortality between the two chronologic 3-year periods examined in both geographical areas studied. The results obtained in this and our parallel work allow to conclude that caution should be made in discussions related to developmental programming on the basis of epidemiological data, due to inherent differences between the countries or their regional parts, as referred to age-related dynamics and gender differences of relative morbidity and mortality.