Symposium on ‘Early nutrition and later disease: current concepts, research and implications’

Early nutrition and long-term health: a practical approach

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Nutrition in early life, a critical period for human development, can have long-term effects on health in adulthood. Supporting evidence comes from epidemiological studies, animal models and experimental interventions in human subjects. The mechanism is proposed to operate through nutritional influences on growth. Substantial evidence now supports the hypothesis that ‘accelerated’ or too fast infant growth increases the propensity to the major components of the metabolic syndrome (glucose intolerance, obesity, raised blood pressure and dyslipidaemia), the clustering of risk factors that predispose to cardiovascular morbidity and mortality. The association between infant growth and these risk factors is strong, consistent, shows a dose-response effect and is biologically plausible. Moreover, experimental data from prospective randomised controlled trials strongly support a causal link between infant growth and later risk factors for atherosclerosis. Evidence that infant growth affects the development of atherosclerosis therefore suggests that the primary prevention of CVD should begin from as early as the first few months of life. The present review considers this evidence, the underlying mechanisms involved and its implications for public health.

Infant feeding: Nutrition: Growth

The importance of nutrition for health was first recognised through the association between suboptimal diet and deficiency diseases such as scurvy, beriberi and rickets and stunting in children. Early priorities in healthcare therefore focused on defining and providing nutritionally-adequate diets that could support growth and development. Historically, the greatest challenge has been to provide enough food to feed the world’s ever-increasing population. However, whilst undernutrition remains a problem, the nutritional transition occurring in many developing countries has increased the prevalence of obesity. Whilst many developing countries struggle against hunger, the prevalence of chronic diseases related to overnutrition continues to rise. In low- and middle-income countries the so-called ‘double burden’ of disease, or simultaneous undernutrition and overnutrition, threatens not only short-term health but also an increase in obesity, diabetes, vascular disease and cancer(1). This problem is not confined to developing countries; currently, 400 million adults worldwide are estimated to be obese.

In recent years, the focus of nutrition research has shifted from meeting nutritional needs and preventing deficiencies to understanding the effects of nutrition on long-term health. As a result, there is now strong evidence to suggest that nutrition and growth in early life affect adult chronic disease. The current review considers this evidence, focusing on practical aspects of early nutrition and its effects on long-term health.

Nutritional programming

The idea that nutrition in early life influences long-term health first emerged in animal models(2). Subsequently, this phenomenon was termed programming and defined as the effect of a stimulus or insult that acts at a critical time

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during development to permanently change the structure and function of an organism or system\textsuperscript{(3)}. Since this early work animal models, epidemiological observations and experimental studies in human subjects have provided strong support for the concept that early nutrition has a major impact on adult chronic disease.

**Animal models**

Evidence that nutrition in early life may influence long-term health emerged as early as the 1930s with work showing that energy restriction during early life substantially increases lifespan in rats\textsuperscript{(4)}. The effect of energy restriction during various phases of development on longevity has since been demonstrated in a range of organisms as distinct as yeast and mice and operates through conserved mechanisms that regulate the glucose insulin and insulin-like growth factor 1 pathways\textsuperscript{(5)}.

In contrast to the beneficial effects of relative under-nutrition, overfeeding in early life, leading to rapid postnatal growth, has been demonstrated to have adverse effects on long-term health. For instance, it has been shown that rats overfed during a critical window in early postnatal life are larger throughout life\textsuperscript{(2)}, while nutritional manipulation after weaning shows no such effect\textsuperscript{(6)}. Similarly, infant baboons \textit{(Papio cynocephalus)} given a nutrient-enriched formula before weaning that provides 33\% more energy have greater internal fat depots later in life\textsuperscript{(6)}. More recently, it has been demonstrated in mice that catch-up growth before weaning (particularly in those growth restricted \textit{in utero}) increases later adiposity and reduces lifespan\textsuperscript{(7)}. Obesity is most pronounced in animals fed a highly-palatable ‘cafeteria’ diet rather than normal chow after weaning, an observation that suggests an interaction between early growth and the dietary environment later in life. Rapid growth in early life has also been shown to increase the long-term risk of dyslipidaemia, insulin resistance and the metabolic syndrome\textsuperscript{(8)}. The sensitive window for these programming effects is not known, but animal models suggest that the most vulnerable period is before weaning\textsuperscript{(6)}. Whether such effects are evident in human subjects is uncertain and a critical question for public health policy and future nutrition research.

**Evidence in human subjects**

The first evidence for nutritional programming in human subjects was based on epidemiological studies linking low birth weight with adverse long-term health effects\textsuperscript{(9)}. Impaired fetal growth, evidenced by low birth weight, was shown to be associated with development of the metabolic syndrome, a cluster of CVD risk factors including glucose intolerance, insulin resistance, hypertension, central obesity and dyslipidaemia. This evidence led to the fetal origins of adult disease hypothesis, which proposes that environmental factors, such as suboptimal nutrition, \textit{in utero} trigger metabolic adaptations and programme an increased risk of later chronic disease\textsuperscript{(9)}. Factors affecting fetal growth such as hormonal and growth factors, placental function and maternal nutrition and body composition could therefore influence long-term CVD. For instance, epidemiological evidence from infants born to mothers exposed to famine suggest that exposure to maternal malnutrition in early, but not late, gestation is associated with an increased risk of childhood obesity (OR 1·9 (95\% CI 1·5–2·4))\textsuperscript{(10)}.

More recently, it has become apparent that the relationship between size at birth and later CVD risk becomes stronger after adjustment for current weight, suggesting both fetal factors and postnatal growth may be influential\textsuperscript{(11)}. As infants born of low birth weight show faster postnatal growth, it has been suggested that rapid postnatal growth (upward centile crossing) could partly account for adverse later health outcomes in these infants\textsuperscript{(12)}. Growth acceleration in early life might therefore be seen, in its own right, as the primary mechanism by which nutrition programmes later risk of disease.

**Long-term benefits of breast-feeding**

In addition to the effects of maternal–fetal nutrition, the second main focus in programming research has been the impact of infant feeding on long-term human health. Breast-feeding compared with formula feeding has been shown to have long-term beneficial effects on CVD risk factors such as blood pressure\textsuperscript{(13,14)}, insulin resistance\textsuperscript{(15)}, dyslipidaemia\textsuperscript{(16,17)} and obesity\textsuperscript{(18)}. For instance, two systematic reviews (of twenty-six studies) have shown that both systolic and diastolic blood pressure are lower (effect size 0·5–1·5 mmHg) in breast-fed infants compared with formula-fed infants\textsuperscript{(13,14)}. Breast-feeding is protective against insulin resistance (mean percentage difference 3), glucose intolerance (mean difference 0·17 mmol/l) and, in a meta-analysis of seven studies, risk of diabetes (OR 0·61)\textsuperscript{(15)}. Cholesterol concentrations in infants given breast milk compared with formula are also lower, as summarised in four systematic reviews\textsuperscript{(16,17,19,20)}. Effect sizes are larger and more consistent for infants exclusively breast-fed (mean −0·15 mmol/l) compared with those given both formula and breast milk (mean −0·01 mmol/l).

The strongest evidence for a protective effect of breast-feeding for later health is for a lower risk of obesity. Four systematic reviews have shown that breast-feeding is associated with a lower risk of obesity, by ≥20\% in some studies\textsuperscript{(18,21–23)}. Furthermore, in all reviews a longer duration of breast-feeding is associated with a lower risk of obesity, suggesting a dose–response effect\textsuperscript{(23)}.

Whilst results are consistent across studies, the effects of breast-feeding on later health outcomes are based on observational studies and so should be interpreted with caution\textsuperscript{(19,20)}. For example, publication bias is likely and important predictors of health, such as socio-economic status and maternal demographic factors, are not accounted for in all studies. Exposures and outcomes are not always defined unambiguously and methodological quality is judged to be poor in some studies. Overall, however, associations between breast-feeding and CVD risk factors are significant even after adjustments for potential confounding factors\textsuperscript{(19,20)}.

As expected, there are few experimental studies that compare long-term health outcomes in breast-fed \textit{v.} formula-fed infants. However, prospective controlled trials initiated in the 1980s randomly assigned preterm infants to...
formula or banked breast milk, either as the only diets or in addition to mothers’ own milk. Follow-up at age 16 years shows that infants randomly assigned to human milk have greater propensity to obesity, raised blood pressure, dyslipidaemia and insulin resistance. There is a dose–response association so that a higher proportion of human milk intake has greater beneficial effects, supporting a causal link between breast-feeding and later CVD risk.

To the authors’ knowledge only one experimental study has investigated the long-term benefits of breast-feeding in term infants. In the Promotion of Breastfeeding Intervention Trial maternity units were randomly assigned either to an intervention to increase the duration and exclusivity of breast-feeding or to receive usual infant feeding advice\(^{24}\). The study shows no effects of breast-feeding on later risk of obesity; however, because most mothers initiated breast-feeding from birth the study could not address the possible benefits of breast-feeding early in infancy.

The potential mechanisms by which breast-feeding protects against later CVD risk, although unknown, can be broadly categorised as those that influence behaviour and those related to the unique nutritional composition of human milk. Behavioural explanations may include the possibility that breast-feeding is more common in families that adopt healthier lifestyle habits. Breast-fed babies may also control the amount of milk they consume and so learn to self-regulate their energy intake better than those given formula, although whether this difference persists into adult life is unknown\(^{21,25}\).

Nutritional explanations for the benefits of breast-feeding on CVD risk may include the presence of bioactive nutrients in human milk that are absent from some formulae (e.g. long-chain PUFA). Differences in early protein intake (≥70% greater in formula-fed than breast-fed infants) could also affect later adiposity, possibly by mechanisms that involve an earlier age of adiposity rebound\(^{26}\). Finally, and most recently, it has been suggested that the benefits of breast-feeding for long-term obesity may be a result of a slower pattern of growth in breast-fed infants compared with formula-fed infants, the growth acceleration hypothesis\(^{12}\).

**Growth acceleration**

The effect of faster weight gain throughout childhood on health outcomes, and particularly the risk of obesity, later in life have been reported in at least twenty-one studies, in different populations and at different ages. The effect has been seen for faster linear growth and for growth from as early as the first month of life. Importantly, this effect has been seen in both high-income and low-income countries and in populations predominantly breast-fed\(^{27}\), suggesting that the underlying mechanism is related to early growth even in breast-fed infants.

Faster early growth is also associated with biochemical CVD risk factors such as insulin resistance in term infants with both normal\(^{28}\) and low birth weight\(^{29}\). In the latter study faster infant weight gain was found to be related to insulin sensitivity at 1 year of age, raising the possibility that insulin resistance could be the first CVD risk factor to emerge and may be implicated in the development of other CVD risk factors. In another example faster weight gain in the first 6 months has been shown to be independently associated with a clustered metabolic risk score (comprising fasting TAG, HDL-cholesterol, glucose and insulin concentrations, together with waist circumference and blood pressure) in adolescents, supporting the hypothesis that early growth acceleration increases later CVD risk\(^{30}\).

Rapid early growth may also directly increase the risk of atherosclerotic disease rather than its risk factors. Endothelial dysfunction, an early stage in the atherosclerotic process, is highest in adolescents in the highest quartile of growth during the first 2 weeks of life\(^{31}\). Effect sizes are large and on a population basis would be expected to reduce the incidence of myocardial and cerebrovascular events substantially. For example, the influence of early growth acceleration on endothelial function is similar to the effect of smoking or insulin-dependent diabetes in adults\(^{31}\).

Experimental studies suggest that the effect of early growth on later cardiovascular health is likely to be causal. Infants born small for gestational age and randomised from birth to a higher-protein diet have approximately 3 mmHg greater diastolic blood pressure than those randomised to a lower-nutrient diet\(^{27}\). More recently, a large multicentre randomised trial of >1000 term infants has provided support for an association between early nutrition and risk of later obesity. Infants randomised to a higher-protein diet during the first year of life have greater BMI at 2 years of age\(^{32}\).

The most critical period during which programming stimuli operate is controversial. For example, faster weight gain during the first week after birth has been associated with a 30% increased risk of overweight in adulthood\(^{8}\). However, the effect of rapid growth amplifies with a greater duration of exposure and the risk of obesity is increased by 60% if the duration of exposure is increased from 1 year to 2 years\(^{33}\). Overall, therefore, modifying the pattern of early growth could have major implications for long-term cardiovascular health. The key question now is whether the mechanisms involved can be unravelled to benefit human health.

**Mechanisms**

Probably the most intriguing aspect of the developmental origins of disease concept is the delay between exposure (in the first few months or even weeks after birth) and outcome several decades later. Understanding how the memory of the exposure becomes ‘hard wired’ at the physiological, cellular or molecular level is therefore critical to understanding this concept. Two main generic hypotheses have been proposed to explain the ‘coupling mechanisms’ linking early exposures such as growth with later biological effects such as CVD risk. The first hypothesis, the role of epigenetic changes that persist throughout life, is supported by recent evidence in human subjects. Individuals who were exposed prenatally to famine during the Dutch Hunger Winter in 1944–5 have been shown to have less DNA methylation of the imprinted
insulin-like growth factor 2 gene six decades later compared with their unexposed same-sex siblings. These observations are consistent with the hypothesis that very early mammalian development is a crucial period for establishing and maintaining epigenetic signals.

The second hypothesis suggests that early growth acceleration permanently affects hormonal axes that regulate body weight, food intake and metabolism and hence fat deposition. Studies in animals suggest that set points or ranges for endocrine feedback mechanisms may be influenced by the concentrations of the hormones themselves early in life. Similar mechanisms may occur in human subjects. For instance, a higher plane of nutrition in early postnatal life may programme high leptin and particularly high insulin concentrations, which by predisposing to higher hormone concentrations later in life increase the threshold to satiety signals. Hormonal changes leading to a reduction in satiety will help drive early postnatal catch-up growth, possibly via changes to the hypothalamic circuitry involving leptin pathways. While beneficial in the short term, this higher set point for satiety may predispose to later obesity. Finally, early growth and nutrition could affect endocrine systems that control developmental processes. Consistent with this notion, faster weight gain in infancy is associated with more rapid maturation and earlier onset of puberty.

Clearly, therefore, while growth has short-term benefits for health, long-term effects may not be evident until much later in life and not always advantageous. However, given the large effect size of early nutrition and growth on later CVD risk, practical interventions to optimise nutrition in infancy could have major benefits for population health.

Practical implications

Periconceptual and maternal nutrition

Attainment and maintenance of an appropriate BMI before conception is important for fertility, maternal health and optimal pregnancy outcome. Low BMI periconceptually may be reflective of chronic nutritional deficiency and could increase the risk of intrauterine growth retardation, preterm birth and Fe-deficiency anaemia. However, maternal obesity is more often a major concern in affluent countries. In England up to one-quarter of women were obese in 2004, which is predicted to rise to one-third by 2012. Maternal obesity leads to an increased risk of infertility, spontaneous miscarriage, gestational hypertension, diabetes and pre-eclampsia. Infants of obese mothers are at risk of congenital malformations, being born large for gestational age, and obesity in later life, therefore, extremes at either end of the BMI spectrum should be avoided when planning a pregnancy.

Nutrition during pregnancy is also critical for optimal fetal growth. Prevention of both under- and overnutrition can reduce the risk of low birth weight. Consequently, current advice encourages a balanced diet, a variety of nutrients, avoidance of potentially-harmful chemicals, foods and beverages and supplementation with folic acid and vitamin D. Ideally, weight-management advice should be included when counselling pregnant women in order to protect both maternal and child health. This approach should include detailed assessment of dietary intake and patterns, evaluation of physical activity levels and monitoring of weight gain.

Although nutritional requirements are increased in pregnancy, only a small increase in energy intake (0.8 MJ/d above prepregnancy requirements) is needed in the third trimester to meet the extra needs of fetal and maternal growth. The Institute of Medicine guidelines, which aim primarily to protect against low birth weight, suggest a pregnancy weight gain of 9.1–12.7 kg (20–28 lbs) depending on prepregnancy BMI. The guidelines have recently been re-examined to reflect changes in women of child-bearing age. In developed countries women today are heavier and a greater percentage is entering pregnancy overweight or obese, with many women gaining too much weight during pregnancy. Although weight gain above the upper limit may increase adverse neonatal outcomes, restricting energy intake is not advised in pregnancy as it risks harming fetal development and growth. Thus, overweight and obese women should be encouraged to minimise weight gain during pregnancy rather than to lose weight.

Infant and young child nutrition

Breast-feeding. Support for breast-feeding is an established priority for public health. However, in the UK only one-fifth of women who initiate breast-feeding are still exclusively breast-feeding by 6 weeks of age and a negligible percentage (<1) continue for the recommended 6 months. This situation poses an important challenge to healthcare professionals, who need to understand why mothers stop breast-feeding in order to change behaviours, e.g. by advising on adequacy of milk supply.

Expectant mothers may be most receptive to advice on infant feeding during antenatal education sessions and in the immediate postnatal period. Healthcare professionals have a valuable role in the successful initiation of breast-feeding and are well placed to discuss the importance of early nutrition and appropriate weight gain on obesity and later health. Specific advice may include, for instance, the need for on-demand breast-feeding and the avoidance of formula supplementation or early complementary feeding when the infant is perceived to be hungry despite appropriate weight gain. Importantly, the influence of upward centile crossing on later risk of obesity and CVD is not confined to formula-fed infants. For instance, an aggressive breast-feeding style is associated with greater fat mass later in life. The challenge to healthcare professionals therefore is to support and encourage optimal and exclusive breast-feeding.

Weaning. Theoretically, at some point in infancy, the volume of milk required to meet energy and other nutrient requirements exceeds the mother’s lactational capacity. The infant’s ability to consume sufficient milk to meet nutritional requirements also becomes limiting. However, there is a lack of consensus about the exact timing of this point, which varies between individuals. For some infants delaying the introduction of foods other than breast
milk may increase the risk of nutritional deficiencies (particularly Fe and Zn) and development of food allergy and inhibit development of taste preferences (51). In contrast, early introduction of solid food is associated with increased risk of later obesity. For instance, complementary feeding before 15 weeks of age is associated with higher weight and greater percentage body fat at 7 years of age (52), although it is difficult to establish causation in this observational study. Currently, exclusive breast-feeding is recommended for term infants for the first 6 months (26 weeks) after which safe nutritionally-adequate complementary (solid) foods should be gradually introduced (53). This recommendation is based on a systematic review conducted by WHO (54), but has been challenged (55) and is poorly adhered to in many developed countries.

Preschool nutrition. The preschool or ‘toddler’ period is a pivotal time during which long-term dietary habits are established with potential life-long effects on appetite, obesity and other risk factors for CVD (56, 57). An earlier age of adiposity rebound and faster weight gain in preschool children is a risk factor for later adiposity, which is often established before the age of 5 years (58) and tracks into later life (59). Nevertheless, the diet of preschool children often does not comply with recommendations, and high intakes of protein and saturated fat in this age-group could contribute to later obesity (60, 61). A higher protein intake in the preschool years is particularly associated with an increased risk of later obesity (more than doubling obesity risk in some studies (62)). Optimising the diet of preschool children could therefore be critical to the prevention of later obesity.

Nutrition in preterm infants. Nutritional requirements of preterm infants are higher than those for term infants. Consequently, meeting these requirements is a considerable challenge, with effects on morbidity and mortality in early infancy. Historically, the goal has been to replicate in utero growth, but this objective is rarely achieved (63). Initially, parenteral nutrition with minimal enteral feeding is advocated in these high-risk infants (63). Enteral feeding with human breast milk, which dramatically reduces the risk of necrotising enterocolitis, is particularly relevant to premature newborns. Once full enteral feeding is established, the challenge is to provide optimum nutrition to allow growth and cognitive development (e.g. using human breast-milk fortifiers and enriched infant formulas) and to minimise the long-term risks associated with rapid catch-up growth. Currently, the risk balance favours the promotion of rapid weight gain and high nutrient intake in these infants.

In the short-term a higher plane of nutrition in preterm infants is important for survival and improves short-term linear growth and weight gain (64). Enriched infant formulas have also been shown to improve later cognitive function (65) and bone health (66). For instance, infants given enriched formula in the first month of life have a six-point intelligence quotient advantage at age 16 years compared with those given standard formula (67). However, the effect of enriched formulas after discharge from the neonatal unit is more controversial, although the most vulnerable infants (e.g. those with respiratory disease or marked growth retardation) may benefit from a higher plane of nutrition (68).

Growth monitoring. Monitoring growth is an essential part of good paediatric care. The pattern of growth is not only a marker of the immediate physical and emotional well-being of the child but has long-term implications for health. Historically, there has been a perception that faster growth is good (a ‘bouncing’ baby desirable) and that small babies should be encouraged to ‘catch up’. Although it may be counter-intuitive, current evidence suggests that the risk benefit in healthy term babies does not favour the promotion of faster growth.

Growth is conventionally monitored by both parents and healthcare professionals using growth charts that express the growth of a child relative to that of a reference population. Parents often use these charts to compare their child’s growth with a perceived ‘normal’ growth pattern. Rapid growth is usually seen as a measure of good parenting (69) and mothers often perceive a higher centile as desirable for their baby (70). Previously, healthcare professionals have focused on identifying growth faltering. Recently, however, because centile crossing (usually defined as upward centile crossing of two centiles) has been accepted by the Scientific Advisory Committee on Nutrition and the Royal College of Paediatrics and Child Health as a risk factor for later obesity (71), the healthcare professionals have been encouraged to identify both downward and upward centile crossing in infancy. With the current obesity epidemic there is also increasing focus on identifying overweight and obese children (defined as BMI ≥ 91st and 98th centiles respectively on the UK 1990 growth reference (72)). As most obesity is established in the preschool age-group (58) with increased risk of adverse effects on long-term health, healthcare professionals have an important role in monitoring growth in this critical period (33).

In the UK growth is monitored using growth reference charts derived from predominantly formula-fed populations (72). These charts are being replaced by the WHO growth charts, which are based on a multiethnic population (Brazil, Ghana, India, Norway, Oman, USA), exclusively or predominantly breast-fed for ≥ 4 months and living in optimal conditions (73). As these charts are based on slower-growing breast-fed infants, they are expected to increase the number of infants diagnosed as growing too fast and reduce the diagnosis of growth faltering. This change is likely to reduce healthcare costs, as there will be fewer referrals for growth faltering, and also to improve long-term risk of obesity and CVD (74).

Nevertheless, the WHO growth charts, although representing a major improvement in the monitoring of infant growth, have some limitations. For instance, mean weight and length at birth in the UK is higher than that on the WHO growth charts (71). Thus, against WHO standards UK infants appear to be large at birth and to show growth faltering during very early infancy. This position could lead to inappropriate referral and supplementation in breast-fed infants to promote growth (75). Also, WHO growth standards are confined to term infants and children < 5 years of age, necessitating the use of existing population growth references to bridge these gaps.
Conclusions

The issues surrounding nutrition and health are complex and challenging and depend on the population under consideration. For instance, infants from less-developed settings are at greater risk of undernutrition, neonatal mortality and poorer long-term health and social outcomes. In Brazil, for instance, suboptimal nutrition is associated with reduced adult height, schooling and economic productivity. Clearly, the risk benefit favours the promotion of faster growth in these vulnerable infants. However, in more developed environments, whilst there are short-term benefits of a higher plane of nutrition for some individuals (e.g. infants born preterm), the effects of promoting faster weight gain in term infants born with birth weight appropriate or low for gestational age are less clear. In these populations healthcare professionals have an important role in optimising nutrition in infancy, in monitoring growth and in reducing the long-term burden of CVD.

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References


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