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Associations between newborn thyroid-stimulating hormone concentration and neurodevelopment and growth of children at 18 months

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Abstract

The study aimed to assess the associations between newborn thyroid-stimulating hormone (TSH) concentration, a marker of iodine nutrition in early life, and childhood neurodevelopment and growth using data collected from two pregnancy studies, one in a borderline iodine-deficient setting (DHA to Optimize Mother Infant Outcome (DOMInO) Study) and one in an iodine-sufficient setting (Pregnancy Iodine and Neurodevelopment in Kids (PINK) Study). TSH data were obtained from routine newborn screening. Neurodevelopment was assessed at 18 months using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Weight, height and head circumference were measured at 18 months. In total, 1467 children were included in the analysis. Comparing the highest with the lowest TSH quartile, the mean differences (MD) in the Bayley-III scores ranged from −2·0 (95 % CI −4·7, 0·7) to −2·2 (95 % CI −5·8, 1·3) points in DOMInO and 1·0 (95 % CI −1·6, 3·6) to 2·0 (95 % CI −0·4, 4·4) points in PINK in the cognitive, language and motor scales; the MD in the anthropometric *z* scores ranged from −0·01 (95 % CI −0·5, 0·5) to −0·5 (95 % CI −0·9, −0·1) in both studies. A 1 mIU/l increase in TSH was associated with −0·3 (95 % CI −0·9, 0·2) point and 0·2 (95 % CI −0·3, 0·7) point changes in the mean cognitive score in the DOMInO and PINK, respectively. A null association between TSH and growth was also observed in both studies. Longitudinal studies that utilise newborn TSH data and examine neurodevelopmental outcomes at later ages are warranted, as neurodevelopmental assessments in older children are more predictive of later achievement.

Key words: Thyroid-stimulating hormone: Iodine: Growth: Development: Bayley Scales of Infant and Toddler Development, third edition

Iodine is an integral part of thyroid hormone, which in turn is required for normal brain development and physical growth during the early critical periods of life[1]. Insufficient maternal iodine intake in pregnancy has been linked to poor growth[2,3] and impaired neurodevelopment in children[3–5] and can result in cretinism if iodine deficiency in pregnancy is severe[3]. Because of the concern of potential adverse effects on offspring, iodine supplementation in pregnancy has been recommended in many countries, including countries with sustained programmes to combat iodine deficiency like Australia with mandatory iodine fortification of bread[6]. However, the WHO technical consultation does not recommend iodine supplementation during pregnancy in iodine-sufficient populations with sustained programmes to combat iodine deficiency[7]. Evidence from randomised controlled trials suggested that iodine supplementation during pregnancy improved child neurodevelopment and growth in severe iodine deficiency settings[2,8], but there is lack of benefit in mild iodine deficiency to iodine sufficiency settings based on limited data[2,9,10]. There is a concern of excess iodine intake in pregnant women from iodine-sufficient settings[11]. Excessive iodine intake in pregnancy has been linked with subclinical hypothyroidism and isolated hypothyroxinaemia[11,12].

Both iodine deficiency[13–15] and excess[16–18] in pregnancy were associated with elevated newborn thyroid-stimulating hormone (TSH) concentration. Newborn TSH has been suggested as a marker of iodine nutrition in pregnancy[19], and it may be

Abbreviations: Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; DOMInO, DHA to Optimize Mother Infant Outcome; HSQ, Home Screening Questionnaire; PINK, Pregnancy Iodine and Neurodevelopment in Kids; TSH, thyroid-stimulating hormone.

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useful to identify children at risk of neurodevelopmental or growth delay in countries where newborn screening is routinely practiced.

There are several studies that assessed the association between newborn TSH concentration and childhood neurodevelopment. Studies in iodine-deficient populations showed that newborns with higher TSH concentrations of ≥5 mIU/l[20–22] had an increased risk of developmental delay, but the association between newborn TSH and neurodevelopmental scores was inconsistent in iodine-sufficient populations[23–26]. Most published studies had methodological limitations like inadequate adjustment for potential confounders[20,22], small sample sizes of <30 participants[27] or subjective assessment of the outcome[23,24]. Only a few studies have examined the association between newborn TSH concentration and childhood growth[23,28,29].

The quality of the studies examining the relationship between newborn TSH concentration and neurodevelopment or growth of children was limited, and the findings were inconsistent. The objective of the current study was to investigate the associations between newborn TSH concentration and neurodevelopment and growth of children at 18 months of age utilising data collected from two large pregnancy studies in Australia, one in a borderline iodine-deficient setting before the implementation of the mandatory iodine fortification of bread and the other in an iodine-sufficient setting after fortification, with adjustment for key confounding variables.

Methods

Study design, setting and participants

Participants were children from two pregnancy studies conducted in the same area of Australia: the DHA to Optimize Mother Infant Outcome (DOMInO) trial[30] and the Pregnancy Iodine and Neurodevelopment in Kids (PINK) study[4]. Children in the DOMInO study were born before the implementation of the mandatory iodine fortification of bread (born between 2005 and 2008), when the general population was defined as borderline iodine deficient (defined by the median urinary iodine concentration < 100 μg/l), and children in the PINK study were conceived and born after the implementation of the mandatory fortification (born between 2011 and 2013), when the population was defined as iodine sufficient (median urinary iodine concentration ≥ 100 μg/l). Detailed descriptions of DOMInO and PINK are reported elsewhere[4,30]. Briefly, DOMInO was a multicentre randomised controlled trial that investigated the effect of DHA supplementation during pregnancy on postnatal depression and childhood cognitive and language development. Neurodevelopment and growth were assessed in a subset of children at 18 months of age (n 724), consisting of a random sample of children born at term (n 628) and all children born preterm (n 96) from Adelaide, South Australia. The overall results of the trial showed DHA supplementation during pregnancy had no effect on the neurodevelopmental scores of children at 18 months, though the DHA treatment group had a lower risk of cognitive delay[30]. PINK was a prospective cohort study investigating the relationship between maternal iodine intake during pregnancy and the neurodevelopment of children at 18 months of age. The results of the PINK study showed that maternal iodine intake during pregnancy in the lowest (<220 μg/d) or highest (≥391μg/d) quartiles was associated with poorer Bayley Scales of Infant and Toddler Development third edition (Bayley-III) scores when compared with maternal iodine intake in the middle quartiles[4]. The inclusion criteria were similar for both the DOMInO and PINK studies: healthy pregnant women <21 weeks of gestation attending antenatal clinics were eligible to take part in the studies. Women with known fetal abnormalities or the following attributes were excluded in both studies: drug or alcohol abuse, English not spoken at home or unable to give informed consent. Mothers with known thyroid disease were also excluded in the PINK study, while the DOMInO study excluded multiple pregnancies. For compatibility, children from multiple pregnancies in the PINK study were excluded in the analysis in the current study. The study protocols were approved by the institutional review boards at each participating centre in both DOMInO (REC1657/12/2007) and PINK (REC2230/12/15 and 076.10), and each participant provided informed consent.

Assessment of outcomes

Neurodevelopment of children. Neurodevelopment of children was assessed at 18 months of age using the Bayley-III in both studies[4,30]. The Bayley-III Scale consists of cognitive, language, motor, adaptive behaviour and social emotional scales. The cognitive scale assesses sensorimotor development, exploration, manipulation, object relatedness, concept formation, memory and other aspects of cognitive processing. The language scale assesses both receptive and expressive communications. Both fine and gross motor skills were assessed using the motor scale. The adaptive behaviour and social emotional scales assess parent reported child behaviours[31].

Growth of children. Weight, length and head circumference were measured at the time of Bayley assessment using the standard procedures of the WHO in both studies[32]. Length was measured in a laying/supine position using a measuring board and was recorded to the nearest 0·1 cm. Weight was measured by placing the child on a calibrated weighing scale and was recorded to the nearest 10 g. Head circumference was measured using a non-stretching tape positioned above the eyebrows anteriorly and olecranon fossa posteriorly and was recorded to the nearest 0·1 cm[30]. Weight-for-age z score, weight-for-length z score, length-for-age z score and head circumference-for-age z score were calculated using the WHO's Child Growth Standard[33].

Assessment of exposure

Newborn TSH concentration data were extracted from the routine newborn screening database in the South Australian Neonatal Screening Centre[34]. The TSH concentration was measured from newborn whole blood samples taken between 3 and 4 d of infant's age by heel prick using the dissociation-enhanced fluoroimmunoassay method. The method used to measure newborn TSH was consistent between the two studies.

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Assessment of confounders

The potential confounders of child neurodevelopment and growth were identified based on the literature and are presented in Supplementary Figs S1 and S2. Socio-economic status data, including parental education and occupation, were collected using a structured self-report questionnaire. The Home Screening Questionnaire (HSQ) was completed when the parent attended the 18-month Bayley-III appointment to assess the level of cognitive, social and emotional support available to the child in the home environment[35]. The HSQ score was also used as a proxy for overall maternal care and support during pregnancy[36]. Pregnancy-related background data on smoking, alcohol consumption, multivitamin intake and history of depression were collected during pregnancy by self-report. Mother's BMI was calculated using maternal weight and height measured at enrolment. Information on caesarean-section delivery, gestational age at birth, 5-min Apgar score (a proxy for perinatal stress) and birth weight were retrieved from a case note audit at birth. Birth weight-for-gestational age z score was calculated using the Australian national birth weight percentiles by gestational age data[37].

Statistical analysis

The data were analysed using Stata 15 (Statacorp LP). Multiple imputation using chained equations was performed to handle missing information. The proportion of missing data in the variables included in the analysis ranged from 0·2 to 18·5 %. The pattern of missingness was non-monotonic, and the data were assumed to be missing at random[38]. A total of twenty imputed data sets were generated. The multiple imputation model included the exposure variable, outcome variables, auxiliary variables that affect missingness of the imputed variables or correlate with the imputed variables (age at TSH assessment, hospital of enrolment, maternal height and weight) and potential confounders (parity, ethnicity, occupation, education, smoking, alcohol consumption, supplement intake, depression, mode of delivery, mother's age, gestational age, sex of the child, Apgar score, HSQ score and birth weight-for-gestational age z score). The newborn TSH in quartiles and the binary variables (developmental delay, growth delay and dichotomised TSH as ≤5 mIU/l *v.* >5 mIU/l) were created before the imputation. We compared these variables descriptively between the observed data set and imputed data set in the DOMInO and PINK studies, and they were similar in both studies (see online Supplementary material, Supplementary Table S1). We analysed trend across categorical variables using a non-parametric test that is an extension of the Wilcoxon rank-sum test. All analyses were performed on the imputed data sets.

The primary analyses were performed on the DOMInO and PINK data separately for several reasons. First, the two studies were conducted over different time periods where the iodine status of the population differed. DOMInO was conducted in the borderline iodine-deficient setting before the implementation of mandatory iodine fortification of bread and recommendation of routine iodine supplementation for pregnant women, while PINK was conducted in the iodine-sufficient setting after those national iodine interventions. Second, the two studies may not be directly compatible due to possible changes in the demographic and economic characteristics of the general population or the type of antenatal care over time. Third, while the participants were from the same geographic area in Australia, the design of the studies differed (DOMInO was a randomised controlled trial, while PINK was a cohort study). Finally, the direction of the association between TSH and neurodevelopment differed in the two studies. Meta-analysis was performed to examine the overall effect combining both studies.

To assess the association between newborn TSH and Bayley-III and growth outcomes, the exposure variable newborn TSH was treated as a continuous variable and categorised into quartiles in separate analyses. The newborn TSH distribution differed between DOMInO and PINK studies, and hence different TSH quartile cut-offs were applied in each study. Sensitivity analyses were conducted to examine the robustness of the main findings by examining newborn TSH in tertiles, or quintiles, or applying the DOMInO TSH quartile cut points to PINK and vice versa, and using the TSH corrected for infant's age at blood sampling (TSH~age) because infants in the highest TSH quartile were sampled earlier on average than infants in the lowest TSH quartile. It is well recognised that the age at sampling affects newborn TSH concentration due to the physiological surge in newborn TSH concentration for early infant blood sampling[39]. The TSH~age variable was generated by adding the mean TSH to the residuals from the regression model of TSH on age at blood sampling. TSH and age at blood sampling were log-transformed for the analysis and back-transformed to the original scales[40,41]. TSH was also dichotomised based on the commonly reported categories in literature (>5 mIU/l *v.* ≤5 mIU/l) to facilitate comparison with previous studies[42].

There are no well-designed studies on which to base power calculations for the assessment of childhood neurodevelopment and growth outcomes between children in the lowest and highest TSH quartiles. However, a five-point difference on average in the cognitive and psychomotor development between children with adequate *v.* deficient iodine or iron intake was considered clinically significant[4,43]. With the sample sizes available in DOMInO (n 724) and PINK (n 743), a mean Bayley-III score of 100 and a SD of 15, the studies have 88 % and 90 % power to detect a difference of five points in the Bayley-III scale between children in the highest and lowest TSH quartiles.

The neurodevelopment and growth outcomes of children were analysed as both continuous and categorical outcomes. For the categorical outcomes, developmental delay was defined as Bayley-III scores below 85 and growth delay was defined as anthropometric z scores below −1 (i.e. more than 1 SD below the mean).

A linear regression model was used to analyse continuous outcomes, and a log Poisson regression model with robust variance estimation was used to analyse binary outcomes[44]. Both unadjusted and adjusted analyses were performed, with adjusted analyses considered to be the primary analysis. In DOMInO, we adjusted for DHA treatment group to investigate potential confounding as DHA may influence child development[45], though there is no known biological mechanism for an effect of DHA supplementation on iodine metabolism and newborn TSH concentration. We also stratified the analysis by the treatment group in the DOMInO study. The following confounders were controlled in the adjusted analyses for neurodevelopmental and growth

outcomes in both DOMInO and PINK: parity, ethnicity, parents' occupation, parents' education, maternal smoking and alcohol consumption during and before pregnancy (yes or no), maternal multivitamin intake (yes or no) during pregnancy, maternal depression during and before pregnancy (yes or no), mother's BMI, HSQ score, delivery by caesarean section (yes or no), mother's age, gestational age at birth, 5-min Apgar score, sex and birth weight-for-gestational age *z* score. The mean differences in Bayley-III scores with the 95 % CI estimated from the linear regression model and the relative risks (RR) and 95 % CI estimated from the log Poisson regression model were reported to indicate the magnitude and direction of the associations. In line with current best practice[46–49], we have not used *P*-values to interpret the associations. The STATA 'metan' command was used to perform the meta-analysis[50]. I^2 was used to evaluate heterogeneity between the two studies. Heterogeneity between the results was classified as low (I^2: <25 %), moderate (I^2: 25–75 %) and high (I^2: >75 %)[51,52]. A random effects model was applied due to the heterogeneity between the two studies. The pooled effect sizes were calculated to see the magnitude and direction of the associations between newborn TSH and neurodevelopment and growth. The pooled effect sizes were reported using forest plots.

Results

Maternal and infant characteristics

A total of 724 children in DOMInO and 743 children in PINK were included in the analysis (Fig. 1). Table 1 shows the characteristics of the DOMInO and PINK participants. The two studies differed in some sociodemographic characteristics. There were more Caucasian women, smokers and alcohol consumers in DOMInO compared with PINK. As a result of the study design that included a subset of randomly selected term infants and all preterm infants[30], there was a higher percentage of preterm infants in DOMInO. More PINK mothers completed secondary education and took multivitamin supplements during pregnancy compared with DOMInO mothers. The two studies had similar mean HSQ scores and birth weight-for-gestational age *z* scores.

As shown in Table 1, the median newborn TSH concentration was 1·7 (interquartile range 1·0, 2·9) mIU/l in DOMInO and 2·2 (interquartile range 1·4, 3·3) mIU/l in PINK. The percentage of newborns with TSH concentration >5 mIU/l was 4·6 % in the DOMInO and 5·5 % in the PINK. Newborn heel prick blood samples were collected between 48 and 96 h of age in both studies, and the median age at the TSH assessment was 57·7 h in PINK, which was 1·1 h earlier than in DOMInO. In DOMInO, the median age at sampling was 1 h earlier in preterm than term infants, but the median newborn TSH was comparable between these subgroups (1·8 mIU/l in preterm *v.* 1·7 mIU/l in term infants).

Thyroid-stimulating hormone concentration and Bayley Scales of Infant and Toddler Development third edition scores at 18 months of age

Table 2 reports the Bayley-III scores of children in the DOMInO and PINK studies. The mean cognitive score was 102 (SD 12) points in DOMInO compared with 97 (SD 13) points in PINK, and the percentage of children with cognitive delay was 4·9 % in DOMInO compared with 9·2 % in PINK. Children in the highest TSH quartile had the lowest mean Bayley-III scores in the DOMInO study but the highest mean scores in PINK study when compared with the other TSH quartiles.

There was a null association between newborn TSH and neurodevelopment. For example, when TSH was treated as a continuous exposure (Table 3 and Supplementary Fig. S3). A 1 mIU/l increase in TSH was associated with a –0·3 (95 % CI –0·9, 0·2) point change in the mean cognitive score in DOMInO, compared with a 0·2 (95 % CI –0·3, 0·7) point change in PINK, and a RR of 1·1 (95 % CI 0·9, 1·3) for cognitive delay in DOMInO compared with a RR of 0·9 (95 % CI 0·7, 1·0) in PINK. When TSH was categorised into quartiles, the mean difference for children in the highest TSH quartile compared with the lowest quartile was –2·1 points (95 % CI –4·8, 0·6) for the cognitive score in DOMInO compared with 1·0 points (95 % CI –1·6, 3·6) in PINK, and the RR was 1·7 (95 % CI 0·5, 5·6) for cognitive delay in DOMInO compared with 0·5 (95 % CI 0·2, 1·4) in PINK (Table 3).

A similar pattern of null association was observed between newborn TSH and neurodevelopment in both studies regardless of whether TSH was categorised into tertiles (see online Supplementary material, Supplementary Table S2), quintiles (see online Supplementary material, Supplementary Table S3) or dichotomised at 5 mIU/l (see online Supplementary material, Supplementary Table S4), or when the quartile cut points from the PINK study were applied to DOMInO and vice versa (see online Supplementary material, Supplementary Table S5), or when TSH was corrected for age at sampling (see online Supplementary material, Supplementary Table S6), or the analyses stratified by the treatment group in the DOMInO study (see online Supplementary material, Supplementary Table S7). Null association was also observed in the unadjusted analyses (see online Supplementary material, Supplementary Table S8).

Thyroid-stimulating hormone concentration and growth at 18 months of age

The mean weight-for-length *z* score, length-for-age *z* score, weight-for-age *z* score and head circumference-for-age *z* score scores were mostly greater than zero for both DOMInO and PINK, indicating children were larger on average than the populations used to define the WHO growth standards (see online Supplementary material, Supplementary Table S9). The percentage of children with *z* scores < –1 ranged from 3·5 % to 15·5 % in the DOMInO and 3·8 % to 15·2 % in the PINK studies (see online Supplementary material, Supplementary Table S9).

The associations between newborn TSH and growth outcomes were similar in both PINK and DOMInO. Null associations were observed between newborn TSH and growth outcomes in both studies regardless of whether TSH was treated as a continuous variable or categorised into quartiles (Table 4), tertiles or quintiles (data not shown) or when TSH was dichotomised at 5 mIU/l (see online Supplementary material, Supplementary Table S10), or when TSH was corrected for age at sampling (see online Supplementary material, Supplementary Table S11). A similar pattern of null association was also observed in

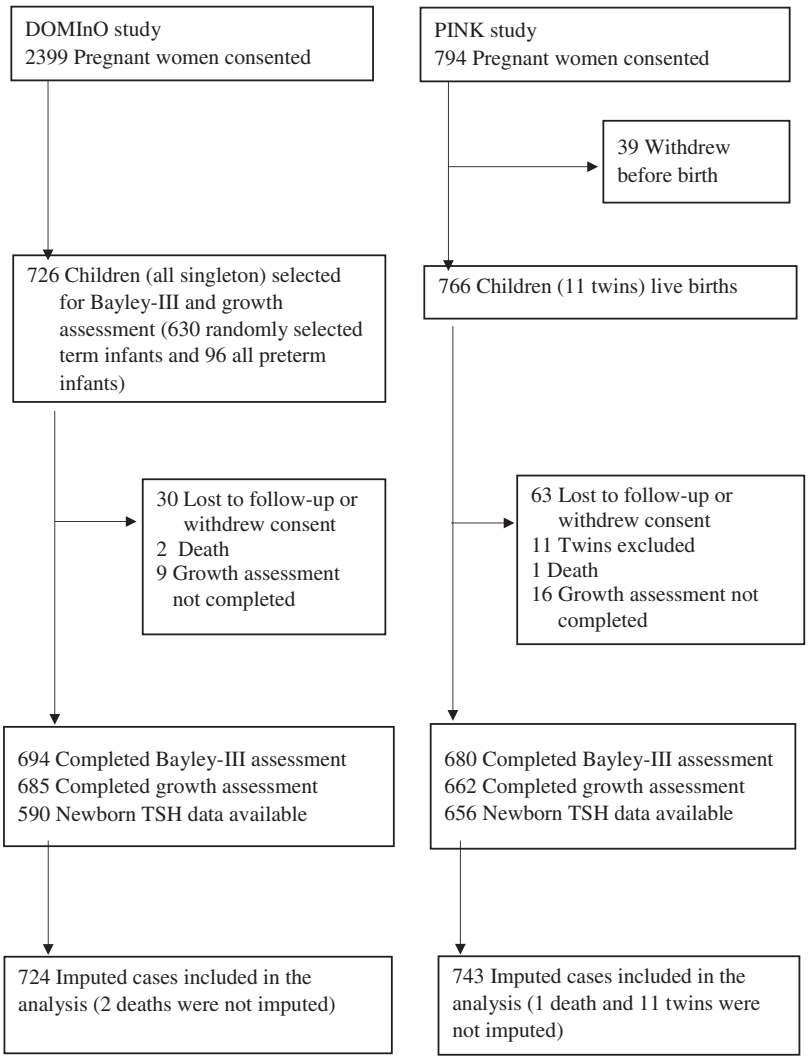

Fig. 1. Selection of participants in the DHA to Optimize Mother Infant Outcome (DOMInO) and Pregnancy Iodine and Neurodevelopment in Kids (PINK) studies. Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; TSH, thyroid-stimulating hormone.

the unadjusted analyses (see online Supplementary material, Supplementary Table S12).

Meta-analysis combined the DHA to Optimize Mother Infant Outcome and Pregnancy Iodine and Neurodevelopment in Kids studies

As shown in online Supplementary Figs. S4 and S5, there was high heterogeneity between the DOMInO and PINK studies in the developmental outcomes, but low heterogeneity in the growth outcomes (see online Supplementary material, Supplementary Figs. S6 and S7) with null associations in all meta-analyses.

Discussion

Our study showed a null association between newborn TSH and both childhood neurodevelopment and growth in the DOMInO and PINK studies. However, children in the highest TSH quartile had the lowest mean Bayley-III score in the DOMInO study, whereas the opposite was observed in the PINK study where children in the highest TSH quartile had the highest mean score. We cannot rule out a different pattern of association between newborn TSH and neurodevelopmental outcomes in the two studies because of the wide CI around the effect estimates, as well as possible residual confounding. Similarly, we cannot rule out a poorer growth outcome of children in the highest TSH quartile compared with children in the lowest quartile in both studies.

Newborn TSH as an indicator of iodine nutrition during pregnancy may depend on maternal iodine intake, as either too little[13–15] or too much[16,17] iodine during pregnancy may lead to high TSH. Excess iodine intake may also lead to lower TSH in iodine-induced hyperthyroidism during pregnancy[53]. DOMInO was conducted in a borderline iodine-deficient population before the mandatory iodine fortification of bread in Australia, and newborns with TSH in the highest quartile were likely be due to suboptimal maternal iodine nutrition in pregnancy. In studies from iodine-deficient populations, like DOMInO, high newborn TSH may be due to inadequate maternal iodine intake during pregnancy. Iodine deficiency

Table 1. Characteristics of the participants
(Mean values and standard deviations; numbers and percentages; medians and interquartile ranges)

	DOMInO (*n* 724)				PINK (*n* 743)			
	Mean	SD	*n*	%	Mean	SD	*n*	%
Mother characteristics								
Caucasian ethnicity			661	91·3			631	84·9
Age (years)	28·7	5·8			29·6	5·2		
BMI (kg/m^2)	27·3	5·9			26·2	5·7		
Nulliparous			403	55·7			404	54·4
Completed secondary education			449	62·0			613	82·5
HSQ score	33·4	3·6			33·1	3·0		
Smoking during second trimester			113	15·6			43	5·8
Previous smoking			227	31·3			98	13·2
Alcohol consumption during second trimester			76	10·5			38	5·1
Previous alcohol consumption			445	61·5			494	66·5
Supplement intake during second trimester			351	48·5			661	89·0
Depression during second trimester			47	6·5			45	6·1
Previous depression			158	21·8			154	20·7
Caesarean Section			203	28·0			200	27·0
Child characteristics								
Female sex			360	49·7			362	48·7
GA (weeks)	38·7	2·2			39·0	1·8		
Birth weight-for-GA *z* score	0·2	1·0			0·0	1·0		
Preterm			91	12·6			46	6·2
5-min APGAR score	9·0	0·9			8·9	0·7		
Newborn TSH (mIU/l)								
Median	1·7				2·2			
Interquartile range	1·0, 2·9				1·4, 3·3			
Age at TSH assessment (h)	58·8	9·2			57·7	9·1		
Newborns with TSH > 5 mIU/l			33	4·6			41	5·5
Age at Bayley-III assessment (months)	18·8	1·8			19·2	7·7		

DOMInO, DHA to Optimize Mother Infant Outcome; PINK, Pregnancy Iodine and Neurodevelopment in Kids; HSQ, home screening questionnaire; GA, gestational age; TSH, thyroid-stimulating hormone; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition.

during pregnancy can lead to lower maternal-free thyroxine concentration[54] and shifts the intra-thyroidal formation of thyroxine to the more active metabolite tri-iodothyronine[16,55]. This leads to a lower transfer of thyroid hormones, primarily thyroxine, to the fetus and may cause impaired neurodevelopment in early childhood. Although a majority of studies conducted in iodine-deficient populations showed a negative association between newborn TSH and childhood neurodevelopment[20,22,56,57], all except one study[20] had a small sample size (ranged from 61 to 250 participants) and did not account for key confounders including maternal socio-economic status, gestational age at birth and home environment. Our finding of a null association in DOMInO was consistent with a large study (*n* 691) in a mildly iodine-deficient population that controlled for key confounders including maternal socio-economic status and infants age at blood sampling for TSH assessment[58]. Similar to DOMInO, Murcia *et al.*[58] used Bayley scales to assess neurodevelopment of offspring under 2 years of age. Participants in DOMInO and Murcia *et al.*[58] were healthy children from population-based cohorts unlike a study in Italy from hospitalised children[56] where the cause for a higher TSH may differ. Furthermore, outcome assessors were not blinded to the exposure variable and maternal characteristics in a prospective cohort study by Costeira *et al.*[57], which may lead to bias. All of the studies in iodine-deficient populations assessed neurodevelopment in toddlers and pre-schoolers except a large Australian study[20] that assessed educational performance at a median age of 10 years. In that Australian study[20], infants without congenital hypothyroidism whose TSH concentration was above the 99th percentile (TSH 12·4–20 mIU/l) had a higher risk of poorer school achievement than infants with TSH < 75th percentile (TSH concentration ≤ 4 mIU/l). Neurodevelopmental assessments at later ages may be more stable and a better indication of cognitive function at later ages[59].

PINK was conducted in an iodine-sufficient setting after mandatory iodine fortification in a previously iodine-deficient population[60]. In contrast to the DOMInO study, the higher TSH concentration in PINK may be due to a high maternal iodine intake as a result of concurrent mandatory iodine fortification and routine iodine supplementation. This is partially explained by the acute Wolff–Chaikoff effect that excess iodine intake in a previously iodine-deficient population temporarily inhibits synthesis of thyroid hormones and resulted in elevated TSH[16]. Our finding of a null association between newborn TSH and Bayley-III scores in PINK study is consistent with the PsychoTSH study (*n* 315)[24–26] in an iodine-sufficient population in Belgium, which is a prospective cohort study designed to assess the association between newborn TSH and neurodevelopmental outcomes in pre-schoolers. Similar to PINK, children who participated in the PsychoTSH study were born during a transitional period when Belgium introduced a voluntary programme to use iodised salt in bread making in 2009[61], and the higher TSH may be due to the transient excess in iodine intake. Although the PsychoTSH study reported no association between

Table 2. Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) outcomes at 18 months of age by newborn thyroid-stimulating hormone (TSH) concentration in quartiles
(Mean values and standard deviations; numbers and percentages)

	DOMInO*						PINK†					
		Bayley-III score			Developmental delay‡			Bayley-III score			Developmental delay‡	
	n	Mean	SD	*P*§	*n*	%	*n*	Mean	SD	*P*§	*n*	%
Cognitive scale												
All children	724	101·9	11·9		36	4·9	743	96·5	12·6		69	9·2
Quartile 1	183	103·2	12·2	0·02	8	4·3	186	97·2	12·9	0·94	15	8·3
Quartile 2	177	101·7	11·2		6	3·2	184	95·6	14·2		22	11·9
Quartile 3	187	101·8	12·1		10	5·4	185	95·0	12·5		23	12·2
Quartile 4	177	100·3	11·9		12	6·5	188	98·4	12·9		8	4·3
Language scale												
All children	724	97·4	14·7		125	17·3	743	94·3	18·8		208	28·0
Quartile 1	183	98·6	14·7	0·02	24	12·9	186	95·1	20·2	0·18	45	24·5
Quartile 2	177	98·3	14·5		29	16·5	184	92·0	18·5		53	28·9
Quartile 3	187	96·9	14·6		35	18·8	185	94·9	21·5		53	28·6
Quartile 4	177	94·9	14·6		37	21·1	188	96·5	20·4		53	28·0
Motor scale												
All children	724	102·6	11·2		37	5·1	743	99·2	12·3		31	4·1
Quartile 1	183	103·7	10·6	0·03	6	3·5	186	99·8	11·6	0·39	9	4·9
Quartile 2	177	102·7	10·4		8	4·3	184	98·7	13·9		8	4·1
Quartile 3	187	102·7	11·4		8	4·2	185	97·8	15·1		9	4·7
Quartile 4	177	100·9	12·2		15	8·3	188	101·1	10·8		5	2·3
Social emotional scale												
All children	724	106·7	17·8		36	5·0	743	103·8	15·5		40	5·4
Quartile 1	183	107·7	18·5	0·29	10	5·4	186	104·0	15·1	0·30	5	2·8
Quartile 2	177	107·5	17·8		8	4·8	184	102·8	18·0		13	6·9
Quartile 3	187	107·1	17·7		9	4·7	185	104·4	17·1		10	5·2
Quartile 4	177	104·6	16·8		9	5·1	188	104·8	15·9		10	5·2
Adaptive behaviour scale												
All children	724	100·1	14·5		87	12·0	743	102·2	15·1		82	11·0
Quartile 1	183	100·2	15·1	0·94	20	10·9	186	101·5	15·0	0·95	15	8·0
Quartile 2	177	100·5	14·5		21	11·7	184	98·2	17·0		27	14·6
Quartile 3	187	100·1	13·4		21	11·1	185	100·9	16·1		21	11·4
Quartile 4	177	99·1	14·6		25	14·2	188	101·3	14·8		16	8·7

DOMInO, DHA to Optimize Mother Infant Outcome; PINK, Pregnancy Iodine and Neurodevelopment in Kids.
* TSH was categorised into quartiles: quartile 1: <1·1 mIU/l; quartile 2: 1·1–1·7 mIU/l; quartile 3: 1·8–2·9 mIU/l; quartile 4: ≥3·0 mIU/l.
† TSH was categorised into quartiles: quartile 1: < 1·5 mIU/l; quartile 2: 1·5–2·2 mIU/l; quartile 3: 2·3–3·3 mIU/l; quartile 4: ≥3·4 mIU/l.
‡ Developmental delay was defined as Bayley-III scores below 85.
§ *P* values from the trend test using the extension of the Wilcoxon rank-sum test.

TSH level and most of the neurodevelopmental scales[24–26], it showed higher mean verbal IQ scores in children with TSH concentration in the range 5–9 mIU/l compared with children whose TSH concentration < 5 mIU/l[26]. We cannot rule out a higher neurodevelopmental score in children with TSH in the highest quartile (median TSH of 4·5 mIU/l) in the PINK study due to the wide CI around the estimates. In contrast, though not directly compatible to our study, a smaller (*n* 250) prospective cohort study by Cuestas *et al.*[23] in an iodine-sufficient population in Argentina showed a higher odds of developmental delay in school-age children with newborn TSH ≥ 10 mIU/l compared with TSH < 10 mIU/l at birth; however, the developmental outcome assessment was by parents' evaluation of developmental status, and TSH was sampled earlier at 2–3 d of age outside the WHO recommendation[42]. Prospective cohorts or population data linkage studies using exposure data from newborn screening and cognitive function at later ages may help to evaluate long-term effect of the newborn TSH concentration on cognition.

The newborn TSH level is influenced by the timing of blood sampling due to physiological surge within 48 h after birth. Higher TSH level may also be a reflection of earlier blood sampling in newborn screening[39]. Although the median age at blood sampling was earlier in PINK than DOMINO overall, children in the highest TSH quartile had an earlier blood sampling compared with the other quartiles in both the DOMInO and PINK studies. Therefore, age at the newborn TSH assessment is unlikely to explain the different patterns of associations observed between newborn TSH and neurodevelopmental outcomes in the two studies.

There is only one study (*n* 250)[23], which examined the association between newborn TSH in full-term infants and childhood growth, which was conducted in Argentina, an iodine-sufficient population. It showed no difference in the weight and height at 6 years of age between children with newborn TSH ≥ 10 mIU/l and those with newborn TSH < 10 mIU/l at birth though no adjustment was made for potential confounding variables. While the Argentina study is not directly compatible to our study,

Table 3. Adjusted associations between newborn thyroid-stimulating hormone (TSH) concentration and Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) outcomes at 18 months of age
(Mean differences (MD), relative risks (RR) and 95 % confidence intervals)

	DOMInO					PINK				
		Bayley-III score		Developmental delay*			Bayley-III Score		Developmental delay*	
	n	MD†§	95 % CI	RR‡§	95 % CI	*n*	MD†§	95 % CI	RR‡§	95 % CI
Cognitive scale										
1 mIU/l increase in TSH‖	724	−0·3	−0·9, 0·2	1·1	0·9, 1·3	743	0·2	−0·3, 0·7	0·9	0·7, 1·0
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−1·1	−3·8, 1·6	0·9	0·2, 4·5	184	−1·7	−4·4, 1·0	1·5	0·7, 3·1
Quartile 3	187	−1·6	−4·3, 1·2	2·2	0·6, 7·5	185	−2·1	−4·7, 0·4	1·6	0·8, 3·4
Quartile 4	177	−2·1	−4·8, 0·6	1·7	0·5, 5·6	188	1·0	−1·6, 3·6	0·5	0·2, 1·4
Language scale										
1 mIU/l increase in TSH‖	724	−0·5	−1·2, 0·3	1·1	1·0, 1·2	743	0·5	−0·3, 1·2	1·0	1·0, 1·1
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−0·1	−3·1, 3·2	1·2	0·7, 2·1	184	−3·4	−7·1, 0·3	1·2	0·8, 1·7
Quartile 3	187	−1·4	−4·8, 2·0	1·5	0·9, 2·6	185	−0·02	−4·1, 4·0	1·2	0·8, 1·8
Quartile 4	177	−2·2	−5·8, 1·3	1·4	0·8, 2·5	188	1·4	−2·3, 5·3	1·1	0·7, 1·6
Motor scale										
1 mIU/l increase in TSH‖	724	−0·3	−0·9, 0·3	1·2	1·0, 1·4	743	0·3	−0·2, 0·8	0·9	0·7, 1·2
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−0·8	−3·4, 1·8	1·4	0·4, 4·6	184	−0·8	−3·5, 1·7	0·7	0·2, 2·4
Quartile 3	187	−1·3	−3·9, 1·3	1·5	0·5, 4·8	185	−1·7	−4·3, 0·9	0·9	0·3, 2·4
Quartile 4	177	−2·0	−4·7, 0·7	2·2	0·8, 6·6	188	2·0	−0·4, 4·4	0·5	0·1, 1·8
Social emotional scale										
1 mIU/l increase in TSH‖	724	0·0	−1·0, 1·0	0·9	0·7, 1·2	743	0·5	−0·2, 1·2	1·0	0·8, 1·2
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−0·6	−4·8, 3·5	1·1	0·4, 3·5	184	−1·1	−4·5, 2·4	2·1	0·7, 6·6
Quartile 3	187	−0·2	−4·3, 3·9	0·8	0·3, 2·4	185	0·6	−2·3, 3·9	1·8	0·6, 6·1
Quartile 4	177	−2·4	−6·7, 2·0	0·9	0·3, 2·5	188	1·8	−1·6, 5·1	1·7	0·5, 6·0
Adaptive behaviour scale										
1 mIU/l increase in TSH‖	724	0·1	−0·8, 0·6	1·0	0·9, 1·1	743	0·1	−0·7, 0·8	1·0	0·8, 1·2
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	0·3	−3·1, 3·7	1·1	0·6, 2·1	184	−3·7	−6·9, −0·4	1·9	0·9, 3·6
Quartile 3	187	−0·1	−3·3, 3·2	1·0	0·5, 2·0	185	−0·1	−3·2, 3·1	1·1	0·5, 2·2
Quartile 4	177	−0·3	−3·6, 2·9	1·2	0·6, 2·2	188	0·2	−2·9, 3·2	0·9	0·4, 1·9

DOMInO, DHA to Optimize Mother Infant Outcome; PINK, Pregnancy Iodine and Neurodevelopment in Kids; Ref, reference category.
* Developmental delay was defined as Bayley-III scores below 85.
† The MD and 95 % CI were estimated with multivariable linear regression model.
‡ The RR and 95 % CI were estimated with multivariable log Poisson regression model with robust variance estimation.
§ The regression models were adjusted for sex, parity, ethnicity, occupation, education, smoking during second trimester, previous smoking, alcohol consumption during second trimester, previous alcohol consumption, supplement intake during second trimester, previous depression, depression during second trimester, mode of delivery, mother's age, gestational age at birth, 5-min Apgar score, mother's BMI, home screening questionnaire score and birth weight-for-gestational age *z* score in both DOMInO and PINK studies. In addition, treatment group in the DOMInO study was also added to the adjusted models when analysing the DOMInO data.
‖ TSH is modelled continuously.
¶ TSH was categorised into quartiles separately in DOMInO and PINK. DOMInO quartile 1: <1·1 mIU/l; quartile 2: 1·1–1·7 mIU/l; quartile 3: 1·8–2·9 mIU/l; quartile 4: ≥ 3·0 mIU/l. PINK quartile 1: <1·5 mIU/l; quartile 2: 1·5–2·2 mIU/l; quartile 3: 2·3–3·3 mIU/l; quartile 4: ≥3·4 mIU/l.

both suggested no difference in the growth of children between newborns with high or low TSH in populations of mild iodine deficiency or iodine sufficiency.

The WHO defines iodine deficiency in populations when >3 % of newborns have TSH concentration >5 mIU/l[42]. Several studies examining the association between newborn TSH and developmental outcomes dichotomised TSH into ≤5 mIU/l or >5 mIU/l[22,24], but it is important to note that TSH > 5 mIU/l alone is not a criterion in classifying iodine deficiency either in populations or individuals. Further research is warranted to establish a newborn TSH cut-off associated with impaired neurodevelopment to identify children at risk of developmental delay for monitoring and early intervention as appropriate.

Our results should be interpreted with caution because our study is a secondary analysis utilising data from the DOMInO and PINK studies that differed in the distribution of several confounders. In the DOMInO study, for instance, there was an over-representation of preterm infants due to the study design. Although preterm birth was adjusted for in all models, and Bayley-III scores were assessed based on the child's corrected age, preterm birth may increase TSH concentration and confound the association. The association did not differ when the analysis was restricted to full-term infants (data not shown). The timing of newborn screening was earlier in PINK, as there was a shift towards earlier discharge from hospitals after birth. We attempted to address this through correcting TSH for

Table 4. Adjusted associations between newborn thyroid-stimulating hormone (TSH) and growth outcomes at 18 months of age (Mean differences (MD), relative risks (RR) and 95 % confidence intervals)

	DOMInO					PINK				
		Anthropometric *z* score		Growth delay*			Anthropometric *z* score		Growth delay*	
	n	MD†§	95 % CI	RR‡§	95 % CI	*n*	MD†§	95 % CI	RR‡§	95 % CI
WLZ										
1 mIU/l increase in TSH‖	724	0·01	−0·04, 0·05	0·8	0·6, 1·1	743	−0·03	−0·08, 0·03	1·0	0·9, 1·2
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−0·2	−0·4, 0·0	1·5	0·3, 8·2	184	−0·2	−0·4, 0·0	1·4	0·4, 5·2
Quartile 3	187	−0·1	−0·3, 0·1	2·3	0·5, 10·2	185	−0·2	−0·5, 0·0	1·6	0·5, 5·3
Quartile 4	177	−0·02	−0·2, 0·2	0·5	0·1, 3·9	188	−0·2	−0·5, 0·1	1·7	0·5, 5·7
LAZ										
1 mIU/l increase in TSH‖	724	−0·01	−0·04, 0·06	1·0	0·9, 1·1	743	−0·01	−0·06, 0·05	1·0	0·9, 1·1
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−0·1	−0·3, 0·1	1·1	0·6, 2·0	184	0·1	−0·1, 0·3	1·0	0·6, 1·9
Quartile 3	187	−0·1	−0·3, 0·1	1·1	0·6, 2·0	185	0·0	−0·2, 0·3	1·5	0·8, 2·6
Quartile 4	177	−0·2	−0·4, 0·1	1·3	0·8, 2·5	188	−0·1	−0·3, 0·2	1·2	0·6, 2·2
WAZ										
1 mIU/l increase in TSH‖	724	0·01	−0·04, 0·06	1·0	0·8, 1·2	743	−0·08	−0·15, −0·01	1·1	0·9, 1·3
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−0·2	−0·4, 0·0	0·6	0·2, 2·0	184	−0·4	−0·8, 0·0	1·2	0·4, 3·8
Quartile 3	187	−0·1	−0·3, 0·1	0·8	0·3, 2·6	185	−0·5	−1·0, −0·1	1·7	0·7, 4·7
Quartile 4	177	−0·1	−0·3, 0·1	1·2	0·4, 3·0	188	−0·5	−0·9, −0·1	1·9	0·7, 5·3
HCZ										
1 mIU/l increase in TSH‖	724	−0·01	−0·06, 0·04	1·1	0·9, 1·3	743	−0·02	−0·11, 0·06	0·8	0·6, 1·1
TSH in quartiles¶										
Quartile 1	183	Ref		Ref		186	Ref		Ref	
Quartile 2	177	−0·2	−0·4, 0·0	1·4	0·3, 5·8	184	−0·2	−0·6, 0·1	1·2	0·3, 5·0
Quartile 3	187	−0·1	−0·3, 0·1	2·4	0·8, 7·5	185	−0·2	−0·5, 0·1	1·4	0·4, 5·0
Quartile 4	177	−0·2	−0·4, 0·1	2·2	0·7, 7·5	188	−0·01	−0·5, 0·5	0·6	0·1, 3·0

DOMInO, DHA to Optimize Mother Infant Outcome; PINK, Pregnancy Iodine and Neurodevelopment in Kids; WLZ, weight-for-length *z* score; LAZ, length-for-age *z* score; Ref, reference category; WAZ, weight-for-age *z* score; HCZ, head circumference-for-age *z* score.

* Growth delay was defined as *z* scores below 1 SD.

† The MD and 95 % CI were estimated with multivariable linear regression model.

‡ The RR and 95 % CI were estimated with multivariable log Poisson regression model with robust variance estimation.

§ The regression models were adjusted for sex, parity, ethnicity, occupation, education, smoking during second trimester, previous smoking, alcohol consumption during second trimester, previous alcohol consumption, supplement intake during second trimester, previous depression, depression during second trimester, mode of delivery, mother's age, gestational age at birth, 5-min Apgar score, mother's BMI, home screening questionnaire score and birth weight-for-gestational age *z* score in both DOMInO and PINK studies. In addition, treatment group in the DOMInO study was also added to the adjusted models when analysing the DOMInO data.

‖ TSH is modelled continuously.

¶ TSH was categorised into quartiles in both DOMInO and PINK. DOMInO quartile 1 (lowest): <1·1 mIU/l; quartile 2: 1·1–1·7 mIU/l; quartile 3: 1·8–2·9 mIU/l; quartile 4 (highest): ≥3·0 mIU/l. PINK quartile 1 (lowest): <1·5 mIU/l; quartile 2: 1·5–2·2 mIU/l; quartile 3: 2·3–3·3 mIU/l; quartile 4 (highest): ≥3·4 mIU/l.

infant's age at blood sampling but residual confounding may still present. Furthermore, iodine status of the DOMInO cohort was inferred from the general population as maternal UIC in pregnancy was not assessed in the DOMInO study. Despite these limitations, our study had adequate statistical power, the outcome assessments were blinded and confounders were adjusted in analyses. The possible different patterns of the association between newborn TSH and developmental outcomes in an iodine-deficient *v.* iodine-sufficient setting highlights the importance of considering iodine status of the study population when examining and interpreting the relationship.

Conclusion

Our study shows a null association between newborn TSH and both childhood neurodevelopment and growth. However, we cannot exclude the possibility of poorer neurodevelopment or growth in infants with high TSH in a borderline iodine-deficient setting, and better neurodevelopment in infants with high TSH up to 5 mIU/l in an iodine-sufficient setting, due to the wide CI around the estimated effects. Follow-up studies that utilise newborn TSH data obtained from routine newborn screening and examine neurodevelopmental outcomes at later age are warranted to evaluate whether newborn TSH predicts long-term neurodevelopmental outcome.

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M. M. W., L. G. S., L. N. Y., M. M. and S. J. Z. designed the study. M. M. W. performed the analysis and drafted the manuscript. S. J. Z. oversaw the study conduct and critically reviewed the manuscript. L. G. S. contributed to the data analysis, interpretation of the results and reviewed the manuscript. L. N. Y. and M. M. contributed to interpretation of results and reviewed the manuscript. All authors approved the final manuscript.

The authors declare that there are no conflicts of interest.

Supplementary material

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References

1. Zimmermann MB (2009) Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. *Am J Clin Nutr* **89**, 668S–672S.
2. Farebrother J, Naude CE, Nicol L, *et al.* (2018) Effects of iodized salt and iodine supplements on prenatal and postnatal growth: a systematic review. *Adv Nutr* **9**, 219–237.
3. Zimmermann MB (2011) The role of iodine in human growth and development. *Semin Cell Dev Biol* **22**, 645–652.
4. Zhou SJ, Condo D, Ryan P, *et al.* (2019) Association between maternal iodine intake in pregnancy and childhood neurodevelopment at age 18 months. *Am J Epidemiol* **188**, 332–338.
5. Abel MH, Caspersen IH, Meltzer HM, *et al.* (2017) Suboptimal maternal iodine intake is associated with impaired child neurodevelopment at 3 years of age in the Norwegian Mother and Child Cohort Study. *J Nutr* **147**, 1314–1324.
6. National Health and Medical Research Council (2010) NHMRC Public Statement: Iodine Supplementation for Pregnant and Breastfeeding Women. https://www.nhmrc.gov.au/about-us/publications/iodine-supplementation-pregnant-and-breastfeeding-women (accessed August 2020).
7. Andersson M, de Benoist B, Delange F, *et al.* (2007) Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr* **10**, 1606–1611.
8. Zhou SJ, Anderson AJ, Gibson RA, *et al.* (2013) Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials. *Am J Clin Nutr* **98**, 1241–1254.
9. Gowachirapant S, Jaiswal N, Melse-Boonstra A, *et al.* (2017) Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* **5**, 853–863.
10. Zhou SJ, Skeaff SA, Ryan P, *et al.* (2015) The effect of iodine supplementation in pregnancy on early childhood neurodevelopment and clinical outcomes: results of an aborted randomised placebo-controlled trial. *Trials* **16**, 563.
11. Shi X, Han C, Li C, *et al.* (2015) Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China. *J Clin Endocrinol Metab* **100**, 1630–1638.
12. Pearce EN, Lazarus JH, Moreno-Reyes R, *et al.* (2016) Consequences of iodine deficiency, excess in pregnant women: an overview of current knowns, unknowns. *Am J Clin Nutr* **104**, 918S–923S.
13. Sareen N, Kapil U, Nambiar V, *et al.* (2016) Iodine nutritional status in Uttarakhand State, India. *Indian J Endocrinol Metab* **20**, 171–176.
14. Kapil U, Pandey RM, Sareen N, *et al.* (2015) Iodine nutritional status in Himachal Pradesh state, India. *Indian J Endocrinol Metab* **19**, 602–607.
15. WHO, ICCIDD & UNICEF (1994) *Indicators for Assessing Iodine Deficiency Disorders and their Control through Salt Iodization*. Geneva: World Health Organization.
16. Markou K, Georgopoulos N, Kyriazopoulou V, *et al.* (2001) Iodine-induced hypothyroidism. *Thyroid* **11**, 501–510.
17. Chen W, Sang Z, Tan L, *et al.* (2015) Neonatal thyroid function born to mothers living with long-term excessive iodine intake from drinking water. *Clin Endocrinol* **83**, 399–404.
18. Sait H, Kapoor S, Jindal A, *et al.* (2019) Association between neonatal thyroid stimulating hormone status and maternal urinary iodine status. *Indian Pediatr* **56**, 472–475.
19. Rohner F, Zimmermann M, Jooste P, *et al.* (2014) Biomarkers of nutrition for development–iodine review. *J Nutr* **144**, 1322S–1342S.
20. Lain SJ, Bentley JP, Wiley V, *et al.* (2016) Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. *Lancet Diabetes Endocrinol* **4**, 756–765.
21. Freire C, Ramos R, Amaya E, *et al.* (2010) Newborn TSH concentration and its association with cognitive development in healthy boys. *Eur J Endocrinol* **163**, 901–909.
22. Riano Galan I, Sanchez Martinez P, Pilar Mosteiro Diaz M, *et al.* (2005) Psycho-intellectual development of 3 year-old children with early gestational iodine deficiency. *J Pediatr Endocrinol Metab* **18**, 1265–1272.
23. Cuestas E, Gaido MI & Capra RH (2015) Transient neonatal hyperthyrotropinemia is a risk factor for developing persistent hyperthyrotropinemia in childhood with repercussion on developmental status. *Eur J Endocrinol* **172**, 483–490.
24. Trumpff C, De Schepper J, Vanderfaeillie J, *et al.* (2016) No association between elevated thyroid-stimulating hormone at birth and parent-reported problem behavior at preschool age. *Front Endocrinol* **7**, 161.
25. Trumpff C, De Schepper J, Vanderfaeillie J, *et al.* (2016) Neonatal thyroid-stimulating hormone concentration and psychomotor development at preschool age. *Arch Dis Child* **101**, 1100–1106.
26. Trumpff C, De Schepper J, Vanderfaeillie J, *et al.* (2015) Thyroid-stimulating hormone (TSH) concentration at birth in belgian neonates and cognitive development at preschool age. *Nutrients* **7**, 9018–9032.
27. Calaciura F, Mendorla G, Distefano M, *et al.* (1995) Childhood IQ measurements in infants with transient congenital hypothyroidism. *Clin Endocrinol* **43**, 473–477.
28. Korzeniewski SJ, Soto-Rivera CL, Fichorova RN, *et al.* (2014) Are preterm newborns who have relative hyperthyrotropinemia at increased risk of brain damage? *J Pediatr Endocrinol Metab* **27**, 1077–1088.
29. Shields BM, Knight BA, Hill A, *et al.* (2011) Fetal thyroid hormone level at birth is associated with fetal growth. *J Clin Endocrinol Metab* **96**, E934–E938.
30. Makrides M, Gibson RA, McPhee AJ, *et al.* (2010) Effect of DHA supplementation during pregnancy on maternal depression

and neurodevelopment of young children: a randomized controlled trial. *JAMA* **304**, 1675–1683.
31. Bayley N (2006) *Bayley Scales of Infant and Toddler Development*, 3rd ed. San Antonio, TX: Pearson Education, Inc.
32. WHO (1995) *Physical Status: The Use and Interpretation of Anthropometry: Report of a WHO Expert Committee*. Geneva: World Health Organization.
33. WHO (2011) *Child Growth Standards. Anthro and Macro*. Geneva: World Health Organization.
34. South Australian Neonatal Screening Center (2010) *Screening Tests for Your New Baby: Helping to Ensure the Health of Your Child*. Adelaide, SA: Women's and Children's Hospital.
35. Frankenburg WK & Coons CE (1986) Home Screening Questionnaire: its validity in assessing home environment. *J Pediatr* **108**, 624–626.
36. Iltus S (2006) Paper commissioned for the EFA Global Monitoring Report 2007, Strong foundations: early childhood care and education. Significance of home environments as proxy indicators for early childhood care and education. https://unesdoc.unesco.org/ark:/48223/pf0000147785 (accessed December 2020).
37. Dobbins TA, Sullivan EA, Roberts CL, *et al.* (2012) Australian national birthweight percentiles by sex and gestational age, 1998–2007. *Med J Aust* **197**, 291–294.
38. Sterne JA, White IR, Carlin JB, *et al.* (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* **338**, b2393.
39. Li M & Eastman CJ (2010) Neonatal TSH screening: is it a sensitive and reliable tool for monitoring iodine status in populations? *Best Pract Res Clin Endocrinol Metab* **24**, 63–75.
40. Murcia M, Espada M, Julvez J, *et al.* (2018) Iodine intake from supplements and diet during pregnancy and child cognitive and motor development: the INMA Mother and Child Cohort Study. *J Epidemiol Community Health* **72**, 216–222.
41. Willett WC, Howe GR & Kushi LH (1997) Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* **65**, 1220S–1228S.
42. WHO, UNICEF & ICCIDD (2007) Assessment of iodine deficiency disorders and monitoring their elimination – a guide for programme managers. https://www.who.int/nutrition/publications/micronutrients/iodine_deficiency/9789241595827/en/ (accessed August 2020).
43. Walter T, De Andraca I, Chadud P, *et al.* (1989) Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics* **84**, 7–17.
44. Zou G (2004) A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* **159**, 702–706.
45. Makrides M (2013) DHA supplementation during the perinatal period and neurodevelopment: do some babies benefit more than others? *Prostaglandins Leukot Essent Fatty Acids* **88**, 87–90.
46. Amrhein V, Greenland S & McShane B (2019) Scientists rise up against statistical significance. *Nature* **567**, 305–307.
47. Greenland S, Senn SJ, Rothman KJ, *et al.* (2016) Statistical tests, *P* values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* **31**, 337–350.
48. Wasserstein RL & Lazar NA (2016) The ASA's statement on *P*-values: context, process, and purpose. *Am Stat* **70**, 129–131.
49. Wasserstein RL, Schirm AL & Lazar NA (2019) Moving to a World beyond "$P < 0{\cdot}05$". *Am Stat* **73**, 1–19.
50. Harris RJ, Bradburn MJ, Deeks JJ *et al.* (2008) Metan: fixed-, random-effects meta-analysis. *Stata J* **8**, 3–28.
51. Holger S, Jan B, Gordon G, *et al.* (2013) *GRADE Handbook, Handbook for Grading the Quality of Evidence, the Strength of Recommendations Using the GRADE Approach*. Hamilton: The GRADE Working Group.
52. Higgins JP, Thompson SG, Deeks JJ, *et al.* (2003) Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560.
53. Parveen S, Latif SA, Kamal MM, *et al.* (2009) Iodized salt induced thyrotoxicosis: Bangladesh perspective. *Mymensingh Med J* **18**, 165–168.
54. Glinoer D (2004) The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. *Best Pract Res Clin Endocrinol Metab* **18**, 133–152.
55. Chan SY, Vasilopoulou E & Kilby MD (2009) The role of the placenta in thyroid hormone delivery to the fetus. *Nat Clin Pract Endocrinol Metab* **5**, 45–54.
56. Belcari F, Placidi G, Guzzetta A, *et al.* (2011) Thyroid-stimulating hormone levels in the first days of life, perinatal factors associated with sub-optimal neuromotor outcome in pre-term infants. *J Endocrinol Invest* **34**, e308–e313.
57. Costeira MJ, Oliveira P, Santos NC, *et al.* (2011) Psychomotor development of children from an iodine-deficient region. *J Pediatr* **159**, 447–453.
58. Murcia M, Rebagliato M, Iniguez C, *et al.* (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. *Am J Epidemiol* **173**, 804–812.
59. Dietrich KN, Eskenazi B, Schantz S, *et al.* (2005) Principles and practices of neurodevelopmental assessment in children: lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Perspect* **113**, 1437–1446.
60. Nohr SB & Laurberg P (2000) Opposite variations in maternal and neonatal thyroid function induced by iodine supplementation during pregnancy. *J Clin Endocrinol Metab* **85**, 623–627.
61. Vandevijvere S, Mourri AB, Amsalkhir S, *et al.* (2012) Fortification of bread with iodized salt corrected iodine deficiency in school-aged children, but not in their mothers: a national cross-sectional survey in Belgium. *Thyroid* **22**, 1046–1053.

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