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Neonatal Thyroxine, Maternal Thyroid Function, and Cognition in Mid-childhood in a US Cohort

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Abstract

Objective Examine the associations of maternal thyroid hormones, maternal dietary information, and newborn T_4 levels with cognitive outcomes in mid-childhood.

Methods We studied 921 children born 1999–2003 at gestational age ≥ 34 weeks, who were participants in Project Viva, a prospective pre-birth cohort study in Massachusetts. We examined maternal dietary information, maternal thyroid hormone levels, and neonatal levels of T_4. Research staff performed cognitive testing in mid-childhood (median age 7.7 years).

Results We included 514 women with measured first trimester thyroid hormone concentrations (mean 10.2 weeks); 15% of women had a thyroid stimulating hormone (TSH) level ≥ 2.5 mU/L, and 71% were college graduates. Newborn T_4 was collected from 375 infants (mean 17.6 µg/dl; SD 4.0), on day 2 (mean 1.9 days; SD 0.7) as part of the newborn screening program. Mean (SD) verbal and nonverbal IQ, memory, and motor scores of children were 113.2 (14.3), 107.1 (16.7), 17.1 (4.4), and 92.5 (16.6) points, respectively. In multivariable analysis, first trimester maternal thyroid function (total T_3, total T_4, free T_4, thyroid stimulating hormone (TSH) or total thyroid peroxidase (TPO) antibody levels) or newborn T_4 were not associated with any of the cognitive outcomes in mid-childhood after adjustment for sociodemographic and perinatal variables.

Conclusions for Practice Maternal or neonatal thyroid hormone levels were not associated with cognitive outcomes in mid-childhood in this population with generally normal thyroid function. As we studied a highly educated cohort residing in an iodine-sufficient area, findings may not be generalizable.

Keywords Thyroxine · Childhood cognition · Neonatal · Maternal · Newborn screening

Significance

What is already known on this subject: It has been well established that severe maternal and neonatal thyroid hormone deficiency are associated with poor childhood cognitive outcomes. Studies examining the impact of mild thyroid deficiency in the perinatal period on early childhood cognition show conflicting results.*What this study adds*: To our knowledge this is the first study to examine the associations of both maternal and neonatal thyroid hormone levels with long-term cognitive outcomes in mid-childhood. In this cohort, maternal or neonatal thyroid hormone levels and childhood cognition were not associated.

Background

The relationships among maternal iodine consumption, maternal thyroid function, neonatal thyroid function, and offspring neurodevelopment are complex. Thyroid hormone is essential for metabolism and brain development, and iodine is essential for the production of thyroid hormone. (de Escobar et al. 2004) The development of the fetal brain is completely dependent upon maternal thyroid hormone until the fetus begins producing its own thyroid hormone at about

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16 to 20 weeks gestation. However, fetal thyroid function depends on replete maternal iodine levels throughout the whole pregnancy. (de Escobar et al. 2004).

Maternal thyroid hormone deficiency, due to hypothyroidism or severe hypothyroxinemia, has been shown to be associated with poor childhood cognitive outcomes.(Haddow et al. 1999; Henrichs et al. 2010) Additionally, after excluding women with overt hypothyroidism or hyperthyroidism during pregnancy, a large cohort study showed that both low and high free thyroxine during pregnancy were associated with lower IQ in offspring aged 8 years. (Korevaar et al. 2016b) However, two adequately-powered trials that randomised pregnant women to antenatal thyroid screening versus no routine screening (Lazarus et al. 2012), or randomised to levothyroxine treatment or placebo following screening for thyroid deficiency (Casey et al. 2017), found no effect on cognitive function in early childhood. These negative findings may be explained by the late initiation of treatment in both trials and the high dose of levothyroxine employed by Lazarus et al.

Severe neonatal thyroid deficiency is associated with poor childhood cognitive outcomes, with congenital hypothyroidism (CH) the most common cause of preventable intellectual disability in children (Rastogi and LaFranchi 2010). Transient CH, thyroid deficiency at birth that typically recovers to normal levels in the first months of life, is commonly caused by maternal iodine deficiency. Children born in areas of severe iodine deficiency and without iodine supplementation have an average IQ that is 13.5 points lower than children living in iodine replete areas. (Qian et al. 2005) Prompt newborn screening and treatment for CH using levothyroxine to normalise neonatal thyroid levels has been shown to result in normal child neurodevelopmental outcomes (Albert et al. 2013) and is recommended for infants with transient or permanent CH.(American Academy of Pediatrics, 2006) However, clinical uncertainty remains regarding whether mild neonatal thyroid deficiency is also associated with poor neurodevelopment (Lain et al. 2017) and if so, whether mild neonatal thyroid deficiency is a mediator between maternal thyroid deficiency and infant cognitive development (Korevaar and Peeters 2016).

Oken et al. previously reported associations of maternal thyroid hormone levels and neonatal thyroxine (T_4) levels with early childhood neurodevelopment, using data from the Project Viva cohort (Oken et al. 2009). This study found no significant associations of maternal or neonatal thyroid function with cognitive outcomes at 3 years of age, but there has been no study of cognitive outcomes in later childhood in this population. Although the cognitive tests used at 3 years have been shown to be correlated with subsequent intelligence in childhood and early adolescence, they did not specifically measure visual and verbal memory. These cognitive domains are important to assess as they have been shown to be associated with both maternal and neonatal thyroid deficiency (Haddow et al. 1999; Henrichs et al. 2010; Williams et al. 2013). In the present study, we aim to examine associations of newborn T_4 levels, first trimester maternal thyroid hormone levels, and maternal dietary information with cognitive outcomes in mid-childhood.

Materials and Methods

Study Population

The study population included women and children recruited into the Project Viva cohort. (Oken et al. 2015) In brief, research assistants recruited women less than 22 weeks pregnant from 1999 through 2002 during their first prenatal visit at Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts. After obtaining written informed consent, in-person study visits with participating mothers were performed during pregnancy, and with mothers and children after delivery, in infancy, early childhood (median 3.3 years), and mid-childhood (median 7.7 years). A previous study in Project Viva examined the associations of maternal and neonatal thyroid function with cognitive outcomes at 6 months (N = 500) and 3 years (N = 433) (Oken et al. 2009).

Of 2128 women who delivered a live infant, we excluded 45 whose gestational age at delivery was < 34 weeks (Fig. 1). Of the remaining 2083 women and infants, 1747 had maternal or neonatal exposure data and 973 had mid-childhood outcome data. We excluded 52 missing covariate data, thus our analysis sample included 921 mother-infant pairs (Fig. 1). Compared with the 1,207 excluded children, the 921 included children had higher birth weight for gestational age z-score using a U.S. national reference (Oken et al. 2003) (0.21 vs. 0.14), longer gestation length (39.7 vs. 39.2 weeks), and were more likely to be female (51 vs. 46%). Their mothers were more likely to be white (72 vs. 62%) and to have a college degree (71 vs. 60%), but did not differ on history of thyroid disease, prevalence of elevated TSH, or mean dietary intake of foods high in iodine.

The University of Sydney Human Research Ethics Committee and the Harvard Pilgrim Health Care Institutional Review Board approved this study. All women provided written informed consent at recruitment and at each postpartum follow-up visit.

Maternal Dietary Information and Thyroid Function

We collected maternal blood samples at the time of the routine first trimester clinical blood draw (mean 10.2 weeks gestation), and stored plasma within 24 h at − 70 °C. Maternal TSH, total T_4, total T_3 and total thyroid

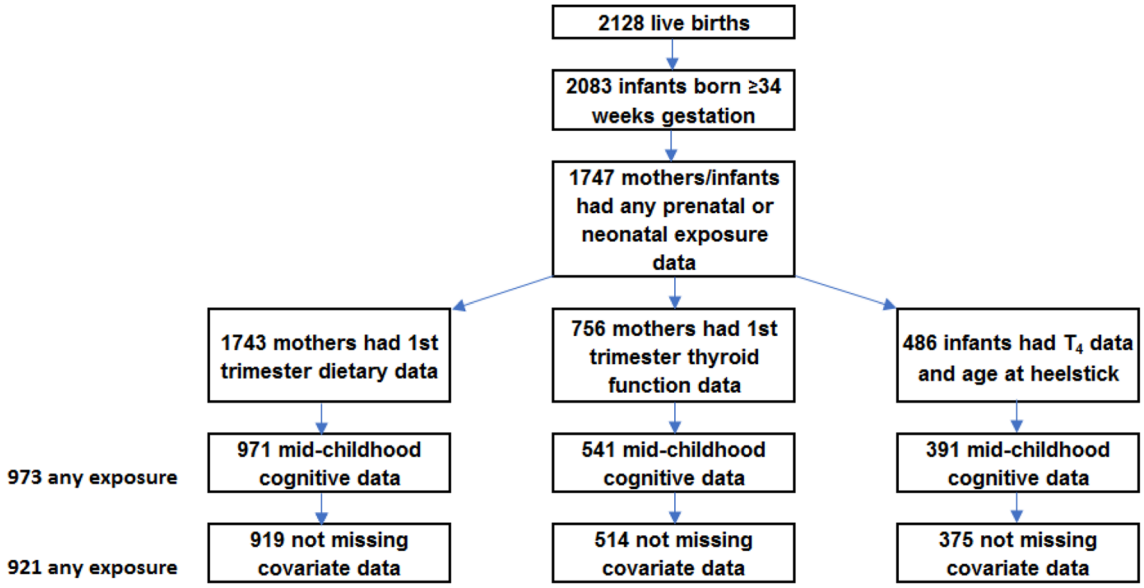

Fig. 1 Flowchart of study population. Note: The majority of mothers and infants with thyroid hormone results are a true subset of mothers with dietary information. Of 919 mothers with first trimester dietary and covariate data, 512 mothers had thyroid hormone information and 373 infants had T_4 results and heelprick information

peroxidase (TPO) antibody levels were assayed on the stored plasma. (Oken et al. 2009) We categorized maternal TSH levels as $<$ or $\geq$ 2.5 mU/L and maternal TPO antibody levels as TPO antibody levels $\leq$ or $>$ 2.0 mU/L.

At the initial study visit women completed a self-administered validated food frequency questionnaire including questions regarding the frequency of eating certain foods that are high in iodine (eggs, fish and dairy) 'during this pregnancy.' Women also reported information regarding their intake of vitamins and supplements, and history of thyroid disease via separate questionnaires.

Neonatal Thyroid Function

Nurses collected newborn whole blood sample by heelstick onto filter paper on approximately day 2 after birth, before discharge from the hospital. The samples were sent to the New England Newborn Screening Program, where T_4 was measured using a solid-phase time-resolved fluoroimmunoassay performed on an AutoDELFIA analyser (PerkinElmer Life and Analytical Sciences, Turku, Finland). As reported in the previous study using these data, the mean newborn T_4 was 17.6 mU/L (range 8.4–35.7 mU/L) and neonatal T_4 was not significantly associated with maternal thyroid function, maternal antibody status or maternal dietary intake (Oken et al. 2009).

Child Cognition at Mid-childhood

At an in-person visit (median age 7.7 years, range 6.6–10.9) trained research assistants conducted a number of cognitive development assessments with children. The Kaufman Brief Intelligence Test, Second edition (KBIT-2), includes assessments of verbal (KBIT verbal) and nonverbal (KBIT nonverbal) cognitive ability to generate an IQ composite, presented as two scores. The KBIT correlates with full-scale IQ assessments such as Wechsler Intelligence Scale for Children. (Chin et al. 2001) The Wide Range Assessment of Memory and Learning, Second Edition (WRAML) assesses memory function using design and picture memory tests; these two scores are summed to produce one score. The drawing subtest of the Wide Range Assessment of Visual Motor Abilities (WRAVD) assesses visual motor abilities.

Covariates

During the first study visit, women provided information regarding parental demographics and health history by questionnaire and interview. Infant sex, birth weight and date of delivery were abstracted from hospital medical records. The length of gestation was calculated by subtracting the date of the last menstrual period (LMP) from the date of delivery. If gestational age according to the 2nd-trimester ultrasound differed from that according to the LMP by $>$ 10 days, we

used the ultrasound result to determine gestational duration. We determined birth weight-for-gestational age and sex (fetal growth) *z*-score from a US national reference (Oken et al. 2003). At the mid-childhood visit, women completed the Home Observation Measurement of the Environment-Short Form (HOME-SF) questionnaire, a measure of the quality of a child's home environment. Women also themselves completed the KBIT-2.

Statistical Analysis

We used linear regression models to first examine the crude associations of maternal first trimester thyroid function (TSH, T_4 and TPO levels, and self-reported history of thyroid disease), maternal dietary factors known to impact iodine status (consumption of fish, dairy, eggs and dietary supplement) and neonatal T_4 levels with mid-childhood cognition. We included all cognitive scores as continuous outcomes and examined models to confirm that they met standard modelling assumptions. We then included additional covariates into multivariable linear regression models if they were confounders based on our conceptual model. We conducted all analyses using SAS (SAS Institute, Cary NC) v9.4.

We also examined the associations of maternal TSH ≥ 4.0 mU/L with childhood cognitive outcomes to reflect a recent change to the upper limit of normal TSH levels in the first trimester advised by the American Thyroid Association (Alexander et al. 2017). For neonatal T_4, we also used a 3-category exposure to reflect different newborn screening cut-offs (< 10 µg/dl, 10 to < 15 µg/dl, ≥ 15 µg/dl) (Daliva et al. 2000).

Results

Table 1 outlines the characteristics of the study population. We had information on at least one cognitive outcome in mid-childhood and confounding variables for 921 children whose mothers provided first trimester dietary information or thyroid data. Of these 921 women and children, 514 women had maternal thyroid hormone information, and 375 children had newborn thyroid hormone levels.

None of the examined exposures reflecting maternal thyroid function were associated with any of the mid-childhood cognitive outcomes (Table 2), including first trimester TSH ≥ 4.0 mU/L (5.9% of women—data not shown). Maternal dairy intake (servings per day) was associated with childhood KBIT verbal results (β 1.05, 95% CI 0.43, 1.68) and WRAML (β 0.28, 95% CI 0.09, 0.47) in the unadjusted models. The association between dairy intake and WRAML remained statistically significant after adjustment for confounding variables (β 0.22, 95% CI 0.03, 0.42) (Table2), but the magnitude of the point estimate was small.

Associations of neonatal T_4 with cognitive outcomes were not statistically significant in the univariate models (not shown) or after adjustment for demographic and birth variables (Table 2). Associations of neonatal T_4 as a 3-category exposure with cognitive outcome were also not statistically significant in unadjusted and multivariable adjusted models (not shown).

Discussion

In this study we did not find an association between maternal or neonatal thyroid function and cognitive outcomes in mid-childhood (median 7.7 years). This result is consistent with the findings of Oken et al. (2009) when examining cognitive outcomes in early childhood (median 3.3 years) in the same cohort. The Project Viva cohort is one of the few studies that have data available on both maternal and newborn thyroid function and childhood cognition, and has comprehensively assessed potential confounders. The association between maternal dairy intake and memory and learning, although statistically significant, was most probably attributable to chance given the number of exposures and outcomes tested, and was small in magnitude.

In this population with generally normal thyroid function, we did not find an association between maternal thyroid hormone levels in early pregnancy and childhood neurodevelopment. The association between maternal thyroid deficiency and infant and early childhood cognitive outcomes has been thoroughly examined in prior studies. Three systematic reviews and meta-analyses on the topic have been published since 2016 (Fan and Wu 2016; Thompson et al. 2018; Wang et al. 2016) with one review finding 39 eligible studies. All three meta-analyses found a significant association between thyroid hormone deficiency in pregnancy and cognitive outcomes in children, however publication bias and heterogeneity of studies were identified as limitations. Further, the majority of studies included in the meta-analyses reported cognitive outcomes in infancy and early childhood (< 3 years). Evidence of ongoing impact of maternal thyroid hormone levels on childhood neurodevelopment is limited. A recent large observational study, not included in any of the meta-analyses, examining cognitive outcomes at school age found no association between maternal thyroid hormone levels and scholastic performance (Nelson et al. 2018). Furthermore the recent publication of longer-term outcomes from the trial that randomised pregnant women to treatment following antenatal screening for hypothyroidism (Lazarus et al. 2012) found no difference in cognition at age 9.5 years (Hales et al. 2018).

Table 1 Characteristics of the study population

	Population with maternal dietary (N = 919) or thyroid data (N = 514) (N = 921)		Population with neonatal thyroid data (N = 375)	
	N	N (%) or mean (SD)	N	N (%) or mean (SD)
Maternal/delivery factors				
Age (year)	921	32.5 (5.1)	375	33.0 (4.5)
KBIT composite	921	107.6 (15.1)	375	110.9 (13.2)
Race/ethnicity	921		375	
Black		110 (11.9)		22 (5.9)
Hispanic		55 (6.0)		21 (5.6)
Asian		49 (5.3)		19 (5.1)
White		667 (72.4)		301 (80.3)
Other		40 (4.3)		12 (3.2)
Education	921		375	
Not a college graduate		266 (28.9)		74 (19.7)
College graduate		655 (71.1)		301 (80.3)
Smoking status	921		375	
Never		642 (69.7)		275 (73.3)
Former		193 (21.0)		69 (18.4)
During pregnancy		86 (9.3)		31 (8.3)
Cesarean delivery	921		375	
No		717 (77.9)		293 (78.1)
Yes		204 (22.1)		82 (21.9)
Maternal thyroid/dietary factors				
First trimester diet				
Total dairy (serving/day)	919	2.7 (1.5)	373	2.8 (1.5)
Fish (serving/week)	919	1.7 (1.4)	373	1.7 (1.4)
Whole eggs (serving/week)	919	2.0 (2.0)	373	1.9 (1.7)
T_4 (μg/dl)	514	10.1 (2.0)	372	10.0 (2.0)
T_3 (μg/dl)	514	21.2 (3.8)	372	21.5 (4.0)
Free T_4 index	514	2.1 (0.4)	372	2.1 (0.4)
History of thyroid problem	918		372	
No		874 (95.2)		357 (96.0)
Yes		44 (4.8)		15 (4.0)
TPO antibody (U/ml)	514		372	
≤ 2.0 (U/ml)		419 (81.5)		303 (81.5)
> 2.0		95 (18.5)		69 (18.5)
TSH (mU/l)	507		365	
< 2.5		431 (85.0)		306 (83.8)
≥ 2.5		76 (15.0)		59 (16.2)
Iodine-containing vitamins	917		372	
No		873 (95.2)		343 (92.2)
Yes		44 (4.8)		29 (7.8)
Child factors				
Sex	921		375	
Boy		448 (48.6)		187 (49.9)
Girl		473 (51.4)		188 (50.1)
Fetal growth (z value)	921	0.21 (0.96)	375	0.30 (0.95)
Birth weight (kg)	921	3.52 (0.51)	375	3.57 (0.51)
Gestational length (week)	921	39.7 (1.4)	375	39.8 (1.4)
Age at heel stick (day)		n/a	375	1.9 (0.7)

Table 1 (continued)

	Population with maternal dietary (N = 919) or thyroid data (N = 514)		Population with neonatal thyroid data	
	(N = 921)		(N = 375)	
	N	N (%) or mean (SD)	N	N (%) or mean (SD)
Neonatal T_4 (µg/dl)		n/a	375	
< 10		n/a		7 (1.9)
10 to < 15		n/a		89 (23.7)
≥ 15		n/a		279 (74.4)
English as a second language	921		375	
No		909 (98.7)		371 (98.9)
Yes		12 (1.3)		4 (1.1)
Composite HOME score	921	18.5 (2.1)	375	18.7 (2.0)
Age at cognitive test	921	7.9 (0.8)	375	7.7 (0.7)
Cognitive outcomes				
KBIT verbal	912	113.2 (14.3)	371	115.2 (13.4)
KBIT nonverbal	921	107.1 (16.7)	375	108.2 (16.5)
WRAVD	915	92.5 (16.6)	372	92.8 (16.4)
WRAML	916	17.1 (4.4)	375	17.3 (4.5)

Neonatal T_4 reported in µg/dl (1 µg/dl = 12.87 nmol/l)

HOME home observation measurement of the environment, *KBIT* Kaufman Brief Intelligence Test, *WRAVD* wide range assessment of visual motor abilities, *WRAML* wide range assessment of memory and learning

Table 2 Adjusted associations of maternal dietary and thyroid function and neonatal T_4 with child cognitive outcomes in mid-childhood from multivariable linear regression models

	KBIT verbal	KBIT nonverbal	WRAVD	WRAML
	Effect estimate (95% CI)			
Exposures maternal diet: (n = 919)				
Total dairy (servings/day)	0.25 (− 0.30, 0.81)	− 0.36 (− 1.09, 0.36)	0.21 (− 0.53, 0.95)	0.22 (0.03, 0.42)
Total fish (servings/week)	0.02 (− 0.55, 0.59)	0.21 (− 0.54, 0.96)	− 0.20 (− 0.96, 0.57)	− 0.02 (− 0.22, 0.18)
Total eggs (servings/week)	− 0.21 (− 0.62, 0.21)	0.17 (− 0.37, 0.72)	0.44 (− 0.11, 1.00)	0.06 (− 0.09, 0.21)
Iodine containing vitamins (yes vs. no)	0.95 (− 2.78, 4.68)	0.87 (− 4.06, 5.79)	3.83 (− 1.22, 8.88)	− 0.18 (− 1.52, 1.16)
Maternal thyroid function: (n = 514)				
TPO antibody (> 2 vs. ≤ 2 U/ml)	− 0.88 (− 3.71, 1.94)	− 1.96 (− 5.68, 1.77)	− 0.63 (− 4.32, 3.05)	0.53 (− 0.45, 1.51)
TSH (≥ 2.5 vs. < 2.5 mU/liter)	− 0.43 (− 3.51, 2.64)	1.67 (− 2.39, 5.73)	1.03 (− 2.94, 5.00)	0.71 (− 0.35, 1.78)
T_4 (µg/dl)	0.20 (− 0.37, 0.76)	− 0.30 (− 1.04, 0.44)	0.15 (− 0.58, 0.87)	0.09 (− 0.11, 0.28)
T_3 (µg/dl)	0.02 (− 0.27, 0.31)	0.05 (− 0.33, 0.44)	− 0.05 (− 0.43, 0.33)	0.02 (− 0.08, 0.12)
Free T_4 Index	1.32 (− 1.39, 4.02)	− 1.54 (− 5.09, 2.01)	− 0.14 (− 3.64, 3.36)	0.50 (− 0.43, 1.44)
History of thyroid disease (yes vs. no)	1.87 (− 1.89, 5.63)	− 2.52 (− 7.43, 2.40)	3.16 (− 1.83, 8.15)	0.72 (− 0.60, 2.04)
Neonatal thyroid function (n = 375)				
T_4 (µg/dl)	0.13 (− 0.20, 0.46)	0.33 (− 0.12, 0.78)	0.08 (− 0.36, 0.51)	0.07 (− 0.05, 0.19)

Maternal dietary and thyroid models adjusted for maternal race/ethnicity, education, pregnancy smoking status and KBIT; composite HOME score; and child sex and English as a second language. Neonatal thyroid model adjusted for maternal race/ethnicity, education, pregnancy smoking status and KBIT; composite HOME score; and child sex, gestational age, fetal growth z-score, age at heelstick, and English as a second language

Studies examining the relationship between neonatal thyroid hormone levels and infant and childhood cognition in healthy children also have had varied results (Choudhury and Gorman 2003; Freire et al. 2010; Lain et al. 2016; Oken et al. 2009; Riano Galan et al. 2005; Soldin et al. 2003; Trumpff et al. 2015; Williams et al. 2013). A number of differences in study design and population may explain the different results, including population iodine status,

Table 3 Literature examining neonatal thyroid hormones and childhood cognitive outcomes in term infants

Author, country, publication year	Study design, study n, co-variates	Thyroid hormone collection	Outcome	Study population details	Population iodine levels	Result
Studies showing no difference in cognitive outcomes between children with different neonatal thyroid levels						
Soldin et al. Washington DC, US, 2003 (Soldin et al. 2003)	Case–control, 227 cases, 948 controls, matched age, gender, race	T_4 collected at newborn screening, mean T_4 cases: 13.95 µg/dl (range 2.6–25.3) controls: 14.47 µg/dl (range 2.5–25.1)	Cases: Behavioural, cognitive, developmental, emotional, learning or language disorder diagnosed age 5–12 years at hospital clinic	No other details	Not recorded	No significant difference in T_4 levels between cases and controls
Oken et al. Mass, US, 2009 (Oken et al. 2009)	Cohort study, 500 term infants born 1999–2003, co-variates include: sex, gestational age, breastfeeding, maternal education	T_4 collected at newborn screening (mean 1.94 days), mean T_4 17.6 µg/dl (range 6.4–35.7)	VRM at 6 months; PPVT & WRAVMAs at 3 years	80% of women had a college graduate or higher	Iodine sufficient area	No significant associationsbetween T_4 & cognitive outcomes at 3 years; low T_4 levels at 6 months had higher VRM outcome
Trumpff et al. Belgium, 2016 (Trumpff et al. 2015)	Cohort study, 311 term infants (without neurological diseases) born 2008–2010, co-variates include: gender, gestational age, breastfeeding, maternal education	TSH (0-15 mlU/L) collected between 3–5 days after birth. Sample stratified by TSH; 12.5% had TSH 8–15 mlU/L	WISC at 4–6 years	73% had university degree or higher	Iodine sufficient; median UIC = 138.8	No significant result between TSH & cognitive outcomes
Studies showing significant difference in cognitive outcomes for children with different neonatal thyroid levels						
Choudhury et al. China 2003 (Choudhury and Gorman 2003)	Cohort study of 284 term infants, co-variates include: age, gender, birthweight, urban vs rural, parental education and occupation	TSH collected in cord blood; 4 groups < 5 mlU/L, 10–19.9 mlU/L, 20–9.9 mlU/L, ≥ 30 mlU/L	FTII at 7 months, BSID-II and DDST at 13 months	50% completed middle school, 33% had completed high school	Non-endemic region	Higher TSH values had significantly poorer scores for: Mental Develop Index but no difference in -Psychomotor Develop Index
Williams et al. Scotland 2013 (Williams et al. 2013)	Cohort study 100 infants born at term between 1998–2001; co-variates include: gestational age, breastfeeding, parental verbal ability,	T_4 collected from cord blood at delivery; categorized using T_4 into hypothyroid (< 10th centile), euthyroid 10–90th; hyperthyroid > -90th	MSCA at 5.5 years (± 2 months)	No details: however-Millenium cohort (of which this study is a subset) had approx. 27% of women had degree or higher	Mildly Iodine deficient (40% had low iodine intake in area)	Children with hypothyroid (low T_4) were significantly higher scores for: Global cognitive Verbal scale Memory scale
Freire et al. Spain 2010 (Freire et al. 2010)	Cohort study of 178 boys born from 2000–2002; co variates include: gestational age, breastfeeding, maternal & paternal education	TSH measured in cord blood at time of delivery. Mean TSH as 3.55, 3 had TSH > 14; top quartile TSH 4.19–17	MSCA at 4 years	14.6% of women had University degree	Not recorded	Children with TSH top quartile were significantly poorer scores for: General cognitive Quantitative Scale Memory Scale

Table 3 (continued)

Author, country, publication year	Study design, study n, co-variates	Thyroid hormone collection	Outcome	Study population details	Population iodine levels	Result
Riano et al. Spain (Riano Galan et al. 2003)	Cohort study of 61 term children excluding those with low Apgar score, SGA, and any other pathological condition related to child development born in 2000. No adjustment for confounders	TSH via bloodspot on 3rd day of life. TSH had a max value of 10 mU/L and 21.4% had value 5-10 mU/L	MSCA at 3 years	The educational level of the pregnant women ranged from basic school to low college degree	Mildly iodine deficient area (15% of pregnant women had severe deficiency)	Children with TSH > 5 had significantlypoorer scores for: General cognitive Perceptual scale Memory scale
Lain et al. Australia 2016 (Lain et al. 2016)	Record-linkage cohort study of 354,137 children born 1994–2002; co-variates include: gestational age, parental education, socioeconomic status	TSH via newborn screening collected on day 2–4; TSH centiles < 75th and above	National School Assessment at age 7–15 years	17% of womenhad a diploma or bachelor degree	Mildly iodine deficient (6.5% of infants had TSH > 5)	Children with TSH > 90th centile had significantly-poorer scores for: Numeracy Reading
Lain et al. Australia 2016 (Lain et al. 2016)	Record linkage cohort study of 149,569 children born 2002–2008; co-variates include: gestational age, socioeconomic status	TSH via newborn screening collected on day 2–4; TSH centiles < 75th and above	Early Development Instrument collected at schools at age 4–6 years	Not available	Mildly iodine deficient (6.5% of infants had TSH > 5)	Children with TSH > 98th centile were more likely to have: Special needs Developmental vulnerability

VRM visual recognition memory, *PPVT* peabody picture vocabulary test, *WRAVMA* wide range assessment of visual motor ability, *WISC* Weschsler Intelligence Scale for Children (Preschool & Primary), *MSCA* McCarthy Scale, *FTII* Fagan Test of Infant Intelligence, Bayley Scales of Infant Development-II, *DDST* Denver Development Screening Test

neonatal thyroid hormone measured, and parental education (Table 3). Studies that reported an association between neonatal thyroid deficiency and poorer cognitive outcomes were all conducted in mildly iodine deficient areas (Choudhury and Gorman 2003; Freire et al. 2010; Lain et al. 2016; Riano Galan et al. 2005; Soldin et al. 2003). That population iodine status would be an important factor makes sense, as neonatal thyroid level can be a marker of maternal iodine deficiency (Wassie et al. 2019). Both maternal iodine deficiency and iodine excess are known risk factors for transient congenital hypothyroidism. However, recently it has been hypothesised that maternal iodine deficiency may be an effect modifier of the relationship between neonatal TSH and cognitive outcomes (Lain et al. 2017). Newborn thyroid hormones may impact childhood cognitive outcomes in populations where maternal iodine is insufficient; however our study was performed in a likely iodine-replete population (Oken et al. 2009). The association between consumption of iodine-rich foods or iodine supplements and childhood cognition, not significant in this study population, may also be evident in an iodine deficient area.

Prior studies have also differed in the neonatal thyroid hormones collected, thyroxine (T_4) or thyroid stimulating hormone (TSH). The only study that found a significant association between neonatal T_4 and childhood cognition found, contrary to expectation, infants with low cord T_4 measurements had improved cognitive testing results at age 5 years, compared to those infants with normal T_4 (Williams et al. 2013). However, the authors posited that this finding was by chance, due to small numbers. The earlier study using the Project Viva cohort by Oken et al. also found an association between low newborn T_4 levels and improved cognitive test at 6 months of age, a finding not replicated in this study examining outcomes in mid-childhood. The studies that found an association between thyroid hormones at birth and neurodevelopment measured neonatal TSH levels. Infants with high TSH and normal T_4 levels at birth have been shown to have significantly lower IQs than infants with normal TSH levels (Azizi et al. 2001; Calaciura et al. 1995). A theory has been suggested that not only relative levels of T_3 and T_4 but also high levels of TSH independently could impact neonatal brain development (Cuestas et al. 2015). This theory is important as both T_4 and TSH can be used for primary newborn screening tests, with optimal cut-off levels for TSH being debated internationally (Lain et al. 2017). A limitation of this study is that more information regarding newborn's thyroid function is not known, and T_4 measurement was only taken at one point in time (day 2), as such, ongoing thyroid function in infancy and childhood is not known.

The studies that have shown an association between mild neonatal thyroid deficiency and childhood cognition and those studies that have not also differed by level of maternal education (Table 3). The study populations of both Trumpff et al. (2015) and Oken et al. (2009) included highly educated women with over 70% having a university degree. The results of these studies may not be generalizable to other populations, or perhaps that maternal education and related characteristics may have a protective role against any harms of poor prenatal thyroid function for childhood neurodevelopment. Similarly, Choudery et al. found that maternal education modified the relationship between levels of TSH in cord blood and cognitive performance at 13 months (Choudhury and Gorman 2003). The impact of family factors, such as parental education and family background, on education outcomes has been well established. The period of time between birth and childhood presents a window during which factors such as supportive parenting and early childhood education can promote cognitive development.

The Project Viva cohort is one of the few datasets that include data about maternal thyroid levels, neonatal thyroid levels and childhood cognitive outcomes and provided a potential opportunity to examine whether neonatal thyroid deficiency is a mediator between maternal thyroid deficiency and neurodevelopment. However, for a variable to be a mediator between an exposure and an outcome it must have a significant correlation with the exposure (and the outcome); and within this cohort, neonatal and maternal thyroid hormone levels were not associated (Oken et al. 2009). Maternal and neonatal thyroid hormone levels are significantly correlated, although maternal thyroid levels account for only a small proportion of variability in newborn TSH or newborn free thyroxine (~1.6%) (Korevaar et al. 2016a). In the present study, the relatively small sample size and the lack of extreme thyroid hormone results in both women and infants may explain why no significant relationship was found. In the present study population, to detect a difference of 7 IQ points in children of mothers with TSH $\geq$ 4.0 mU/L (Haddow et al. 1999), a sample size of 684 would be needed, and to detect this difference in children with a $T_4 < 10$ µg/dl a sample size of 1887 would be required. One study that found an association between severe maternal hypothyroxinaemia (low Free T_4 level) and cognitive delay at 30 months examined the impact of neonatal thyroid hormone levels on a subset of their study. They found that neonatal thyroid function at birth did not act as a mediator for the relationship between maternal hypothyroxinaemia and cognitive development (Henrichs et al. 2010).

In conclusion, neonatal thyroid hormone levels, maternal thyroid hormone levels or maternal diet of food high in iodine were not associated with cognitive outcomes at 7 years of age in this well educated study population residing in an iodine-sufficient area.

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