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ORIGINAL ARTICLE

Gestational thyroid hormone concentrations and risk of attention-deficit hyperactivity disorder in the Norwegian Mother, Father and Child Cohort Study

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Abstract

Background: Maternal thyroid function plays an important role in foetal brain development; however, little consensus exists regarding the relationship between normal variability in thyroid hormones and common neurodevelopmental disorders, such as attention-deficit hyperactivity disorder (ADHD).

Objective: We sought to examine the association between mid-pregnancy maternal thyroid function and risk of clinically diagnosed ADHD in offspring.

Methods: We conducted a nested case–control study in the Norwegian Mother, Father and Child Cohort Study. Among children born 2003 or later, we randomly sampled singleton ADHD cases obtained through linkage with the Norwegian Patient Registry ($n = 298$) and 554 controls. Concentrations of maternal triiodothyronine (T3), thyroxine (T4), T3-Uptake, thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (TPO-Ab) were measured in maternal plasma, collected at approximately 17 weeks' gestation. Indices of free T4 (FT4i) and free T3 (FT3i) were calculated. We used multivariable adjusted logistic regression to calculate odds ratios and accounted for missing covariate data using multiple imputation. We used restricted cubic splines to assess non-linear trends and provide flexible representations. We examined effect measure modification by dietary iodine and selenium intake. In sensitivity analyses, we excluded women with clinically significant thyroid disorders ($n = 73$).

Results: High maternal T3 was associated with increased risk of ADHD (5th vs 1st quintile odds ratio 2.27, 95% confidence interval 1.21, 4.26). For FT4i, both the lowest and highest quintiles were associated with an approximate 1.6-fold increase in risk of ADHD, with similar trends found for T4. The FT4i association was modified by dietary iodine intake such that the highest risk strata were confined to the low intake group.

Conclusions: Both high and low concentrations of maternal thyroid hormones, although within population reference ranges, increase the risk of ADHD in offspring. Increased susceptibility may be found among women with low dietary intake of iodine and selenium.

KEYWORDS
attention-deficit hyperactivity disorder, hypothyroidism, hyperthyroidism, hypothyroxinemia, maternal, MoBa, The Norwegian Mother, Father and Child Cohort Study, thyroid

1 | BACKGROUND

Attention-deficit hyperactivity disorder (ADHD) is among the most commonly diagnosed mental health disorders in children, with a worldwide prevalence of approximately 5%.[1] Although heritability is high (estimated between 70% and 90%[2,3]), a considerable amount of the variance in ADHD has been attributed to non-genetic causes. These include maternal prenatal smoking, prematurity and paracetamol use during pregnancy, as well as exposure to certain environmental toxicants[4,5]; however, there is as yet insufficient evidence to call any of these risk factors causal.[4]

Maternal thyroid function plays a crucial role in foetal brain development.[6] In the first half of pregnancy, the foetus is entirely dependent on the active transport of maternal thyroid hormones across the placenta.[6] The consequences of severe maternal and foetal/neonatal hypothyroidism have been well described.[7,8] Recently, the potential importance of clinical and subclinical maternal thyroid hormone dysregulation during pregnancy in ADHD aetiology has received substantial attention.[9,10] However, previous studies have focused on a relatively limited assessment of thyroid function with little overlapping methodology.

Despite scientific and clinical interest in this topic, very few studies have included both a comprehensive assessment of thyroid function and a clinical diagnosis of ADHD, though two systematic reviews conclude that evidence is suggestive of an association between thyroid dysfunction and ADHD.[9,10] A recent meta-analysis of the INMA, Generation R and ALSPAC cohorts found no clear evidence that FT4 or TSH was associated with ADHD, although ADHD was assessed by parent- or teacher-rated inventories and included a range of years from the preschool to early childhood periods.[11] To date, most studies have assessed early gestational TSH and/or FT4, or TPO-Ab. The concentrations have typically been categorised to address clinical classifications of maternal thyroid function on ADHD symptoms, as rated by parents or teachers. To our knowledge, only one study, based on 27 children, has measured FT3 and T3.[12] Clinical thyroid conditions have received somewhat more attention. Maternal hypothyroidism and hyperthyroidism have both been associated with a higher odds of ADHD or worse ADHD symptoms.[13–17] Maternal hypothyroxinemia has also been associated with ADHD symptoms[18] and a higher than expected frequency of ADHD diagnosis in the child.[12] However, not all of the evidence has been supportive.[16,19] Additionally, both iodine and selenium are required for the biosynthesis and metabolism of thyroid hormone,[20] and low maternal prenatal iodine intake has been found to increase ADHD symptoms.[21] However, no studies to date have examined how nutrient intake levels modify the relationship between thyroid function and ADHD.

Synopsis

Study Question

We sought to examine the association between mid-pregnancy maternal thyroid function and risk of clinically diagnosed attention-deficit hyperactivity disorder (ADHD) in offspring.

What's already known

Maternal thyroid function plays an important role in foetal brain development; however, little consensus exists regarding the relationship between normal variability in thyroid hormones and common neurodevelopmental disorders, such as ADHD.

What this study adds

Our study is unique in that we obtained clinical ADHD diagnoses from a patient registry and obtained comprehensive measures of multiple maternal thyroid hormones, including triiodothyronine (T3), thyroxine (T4), T3-Uptake, thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (TPO-Ab) at 17 weeks' gestation. We found that both high and low concentrations of maternal thyroid hormones, although within population reference ranges, increase risk of ADHD in offspring.

Our objective was to conduct a comprehensive assessment of maternal thyroid function in mid-pregnancy and to estimate relationships of thyroid hormone concentrations with the occurrence of clinician-diagnosed ADHD in childhood.

2 | METHODS

2.1 | Study population

The Norwegian Mother, Father and Child Cohort Study (MoBa) enrolled 114,479 pregnancies between 1999 and 2008.[22,23] Pregnant women were recruited at their first ultrasound appointment at approximately 17 weeks' gestation. Questionnaires were completed by the mother and returned three times during pregnancy: a general health and behaviour questionnaire at 17 and 30 weeks' gestation and a food frequency questionnaire at 22 weeks' gestation. The analytic sampling frame is shown in Figure 1.

2.2 | Selection of ADHD cases

The Norwegian Patient Registry (NPR) is a national database containing all persons with diagnoses recorded from 2008 onward, from government-funded facilities, which captures an estimated 90%–95% of ADHD diagnoses.[24] In our study, children were considered cases if they had at least two registrations of "*Hyperkinetic disorder*" (ICD-10 codes F90, F90.0, F90.1, F90.8 or F90.9). Two registrations were required in order to exclude erroneous registrations or false diagnoses. The ICD-10 criteria for ADHD are "early onset; a combination of overactive, poorly modulated behaviour with marked inattention and lack of persistent task involvement; and pervasiveness over situations and persistence over time of these behavioural characteristics".[25] ADHD cases born 2003 or later were identified via linkage of MoBa with the NPR. Cases were required to reside in the same catchment areas as the Preschool ADHD substudy, described below, to have returned the 36-month questionnaire, were singleton births without Down Syndrome or Cerebral Palsy, and had maternal biospecimens available for analysis. We selected all cases that met these eligibility criteria.

2.3 | Selection of controls

Index children born at one of the larger hospitals in Norway between April 2004 and January 2008, and who completed the 36-month MoBa questionnaire, were eligible to participate in the MoBa Preschool ADHD substudy[26] (Figure 1). From this eligible population, we randomly selected a control population of 554 mother–child pairs. We nested our control group within the population eligible to participate in the Preschool ADHD substudy so that future studies could utilise the same control population for preschool ADHD cases, which were diagnosed via a systematic neuropsychological evaluation of the child at age 3.5 years.[27] Apart from eligibility criteria, no other information from the Preschool ADHD substudy entered into this analysis.

2.4 | Maternal thyroid hormone measurement

We obtained a variety of measures to provide a comprehensive assessment of thyroid function. Total thyroxine (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) are well-established measures of thyroid function.[28–31] Although free T4 is an important clinical measure of thyroid hormone action, pregnancy is a time when analogue measures of free hormones are compromised because of changes in serum thyroid hormone-binding proteins.[32,33] Therefore, we measured thyroid hormone binding via T3-Uptake to obtain estimates of free T4 and T3, described in more detail below.

Maternal bloods collected in EDTA tubes at 17 weeks' gestation were shipped overnight, unrefrigerated, to a central biospecimen processing lab.[34] Plasma was separated and stored in 1 ml cryovials at −80°C. Before shipment to the analysis laboratory, one, 0.93 mL plasma aliquot was thawed and transferred to a Sarstedt 5mL tube for analysis. Plasmas were shipped frozen on dry ice to ARUP Laboratories (Salt Lake City, Utah, USA) for analysis of thyroid hormone concentrations. TSH was measured using a quantitative chemiluminescent immunoassay on the Roche Cobas e602. T3, T4 and T3-Uptake were measured using a quantitative

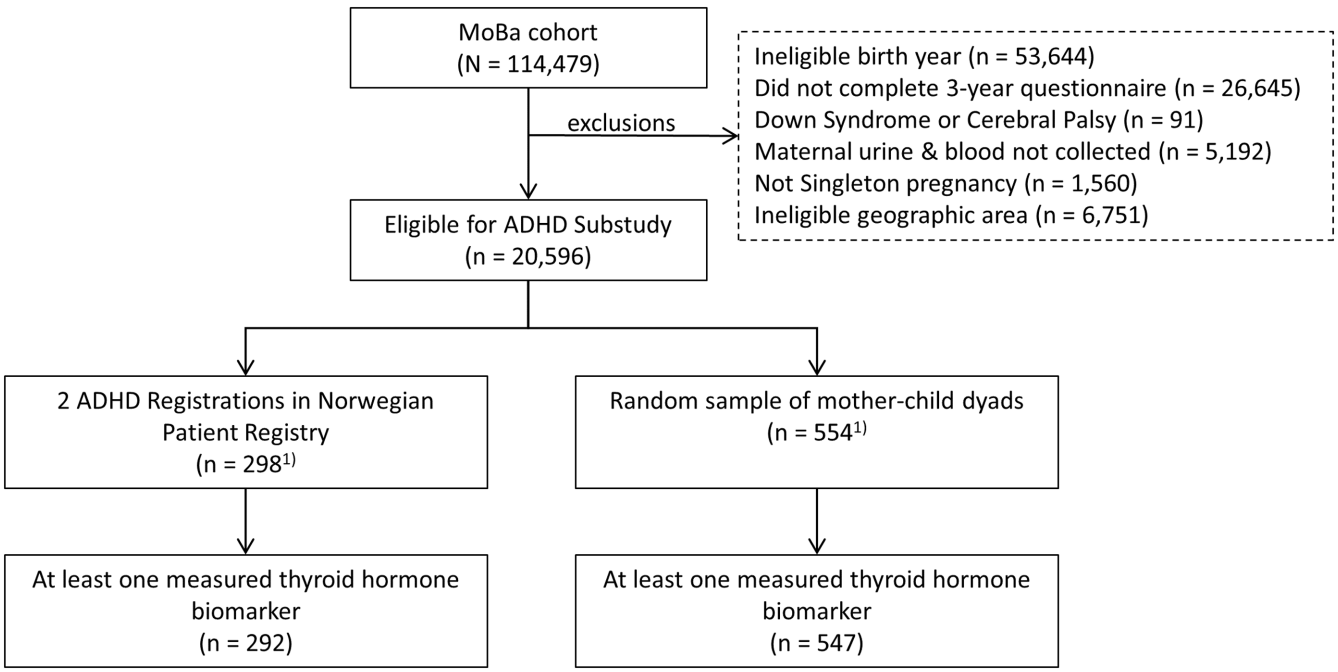

FIGURE 1 Selection into nested case–control study. Relevant exclusions to arrive at eligible populations are detailed. [1]Two ADHD cases were also randomly selected into the control population. These individuals were treated as cases in the analysis.

electrochemiluminescent immunoassay, also on the Roche Cobas e602. Thyroid peroxidase antibody (TPO-Ab) level was measured using a quantitative chemiluminescent immunoassay on the Beckman Access Dxl 800. For T3, T4, TSH and T3-Uptake, inter- and intra-assay coefficients of variation (CV) were <5% and <3% respectively. For TPO-Ab, inter- and intra-assay CVs were ≤7%. Limits of detection (LODs) are presented in Table S1.

T3-Uptake is an indirect measure of thyroxine-binding globulin (TBG) binding capacity and represents the percent of unoccupied binding sites on TBG.[35] It was used to calculate the indices of free T4 (FT4i) and free T3 (FT3i)[36] using the following equation: FT4 (or 3)i = T4 (or 3) * T3-Uptake percent/28, where 28 was the median percent unoccupied binding sites among our random controls. We also calculated the ratio of FT3i to FT4i as an indication of peripheral deiodinase activity.[37] We previously established the suitability of the calculated free thyroid hormone indices, as well as the reliability of MoBa maternal plasma for measurement of thyroid hormone concentrations, considering delays in processing and storage, and freeze–thaw cycles.[38]

In total, 292 NPR cases (98.0%) and 547 MoBa controls (98.7%) had at least one measured concentration. We created internal reference ranges for T4, T3, FT4i and FT3i using the 2.5–97.5th percentiles in our control population, excluding women who reported previously diagnosed thyroid disorders or taking thyroid medications in accordance with the practice of other studies.[33,39–43] The analytic laboratory provided second trimester reference ranges for TSH and TPO-Ab. All reference ranges are listed in Supplemental Material T1.

2.5 | Statistical analysis

2.5.1 | Covariate selection

The current analysis is based on version 9 of the MoBa quality assured data files. Confounders were selected by directed acyclic graph (Figure S1), and were included as adjustment variables if they were antecedents of thyroid hormone concentrations and/or were associated with ADHD in the child. These were maternal age at delivery, sex of the child, maternal education, marital status, year of birth and prenatal maternal smoking in the second trimester of pregnancy. We did not adjust for factors that were possible consequences of maternal thyroid hormone concentrations and/or intermediates between maternal hormone concentrations and childhood ADHD, such as maternal body mass index (BMI), child birthweight and gestational age at delivery. We did not adjust for maternal intake of iodine from diet because iodine is not hypothesised to have a direct effect on neurodevelopment, apart from its role in thyroid hormone synthesis.

2.5.2 | Model selection

The association between each thyroid hormone concentration and ADHD was evaluated in logistic regression models using quintiles. Either the first or third quantile was selected as the reference strata depending on the overall shape of dose–response trend. We also used restricted cubic splines with knots at the 20th, 40th, 60th and 80th thyroid hormone quintiles to determine whether significant non-linear trends were present and to provide a flexible representation of such trends. In the case of TPO-Ab, given the highly skewed nature of the concentrations, with only approximately 25% of the observations above 1 mIU/L, we dichotomised at the upper reference limit (9 mIU/L). Adjustments were made in each of the models for all covariates mentioned above. We performed sensitivity analyses excluding subjects who reported taking thyroid medications, who having had a pre-existing thyroid condition or who met criteria for thyroid conditions based on their measured thyroid hormone concentrations. Analyses were conducted in R Version 3.3.2.[45]

2.5.3 | Missing data

In order to account for missing covariate data, we performed multiple imputation using the R package *mice* with 50 imputed datasets.[44] All analyses are based on imputed data.

2.5.4 | Effect measure modification

We assessed heterogeneity in associations across strata of iodine and selenium dietary intake estimated from the food frequency questionnaire (FFQ) completed at approximately 17–22 weeks' gestation,[46] and by child sex, on the multiplicative scale. Details regarding the assessment of iodine and selenium intake have been previously described.[46,47] Briefly, the MoBa FFQ is a semi-quantitative questionnaire that assesses dietary habits and intake from supplements during the first 4 to 5 months of pregnancy. Food and nutrient calculations were performed using FoodCalc with the Norwegian food composition table as the reference standard.[46,47] Dietary iodine calculations leveraged available data from analyses of Norwegian milk and food samples.[46] Iodine deficiency was defined as dietary iodine intake <150 μg/day, and selenium intake was dichotomised at 60 μg/day.[48] Dietary intake of iodine was previously validated against a 24-h urine iodine biomarker in a subset of MoBa.[49] While intake from 13 commonly used supplements was assessed as part of the FFQ,[46] supplement intake was not included in the dietary intake variable because previous work within MoBa established that iodine from supplements and iodine from diet had different associations with ADHD symptoms and diagnosis,[21] and supplemental iodine among women with dietary iodine insufficiency did not improve behavioural and language delay.[50] We considered effect measure modification to be significant if the Wald test for the inclusion of an interaction term was $P < 0.05$.

2.5.5 | Ethics approval

Data collection for MoBa was approved by the Norwegian Data Inspectorate and Norwegian Committee for Medical and Health

Research Ethics (REC). This current study was approved by the Norwegian REC and the Institutional Review Board at UNC Chapel Hill.

3 | RESULTS

Mothers of ADHD cases were slightly younger at delivery, less likely to be married or living with the child's father, had a slightly higher pre-pregnancy maternal BMI, lower educational attainment and their babies had a slightly earlier gestational age at delivery compared to controls (Table 1). ADHD cases were also more likely to be boys, to have been born with a low birth weight (<2500 g) and to have been exposed to maternal smoking during pregnancy.

The median maternal T3 and FT3i levels were higher among cases than controls (Table S1). The majority of correlations among thyroid hormone biomarkers were low to moderate, with the exception of T4 and FT4i ($r_s = 0.92$) and T3 and FT3i ($r_s = 0.93$), which are related by mathematical definition. Few mothers met criteria for clinical thyroid conditions based on our measured concentrations, reported thyroid-related conditions or thyroid medication usage on the MoBa prenatal questionnaires, or had thyroid-related conditions recorded on the Medical Birth Registry's birth notification form (Table 1).

In multivariable adjusted models, we found that high maternal concentrations of T3 was associated with increased risk of ADHD in the child (5th vs 1st quintile OR = 2.13, 95% CI 1.19, 3.82). We observed similar patterns across quintiles for FT3i and the FT3i/FT4i ratio. We found no association between maternal prenatal TSH or TPO-Ab positivity and ADHD (Table 2).

Maternal T4 and FT4i demonstrated U-shaped relationships with ADHD (Table 2, Figure 2). Women in the lowest and highest quintiles of FT4i had an almost a 2-fold increase in risk of ADHD relative to the referent quintile. Similar trends were found across quintiles for T4, and the T4 spline model detected a significant non-linear association with ADHD ($p = 0.01$, Table 2, Figure 2A). Overall, for both T4 and FT4i, splines and quintiles demonstrated an increase in the estimated odds of ADHD in the tails of the distribution, although we had few observations at the extreme tails and thus the confidence intervals in these regions were quite wide (Table 2, Figure 2).

In sensitivity analyses, we excluded women reporting a pre-existing thyroid condition ($n = 25$), who are taking thyroid medications ($n = 15$), or who met clinical criteria for thyroid conditions based on the 17 week' measured values ($n = 57$), and found similar associations (Table 2).

We examined whether associations of gestational thyroid hormones with ADHD were modified by iodine or selenium intake (Table 3) or child sex. Iodine significantly modified the associations of FT4i with ADHD ($p < 0.05$). Increased risk of ADHD appeared to be limited to the low intake strata. Interaction with selenium intake was marginally significant for FT4i as well, with elevated risk in the

TABLE 1 Participant Characteristics

	MoBa controls ($N = 547$)		MoBa NPR ADHD cases ($N = 292$)	
	Mean	SD	Mean	SD
Maternal age at delivery (years)	31.0	4.2	29.3	5.1
Maternal pre-pregnancy BMI (kg/m^2)	23.5	4.0	25.7	5.9
Gestational age at delivery (weeks)	39.6	1.8	39.1	2.3
	N	%	*N*	%
Child sex (male)	271	49.7	211	72.8
Maternal education[a]				
<4-year university degree	123	22.8	157	59.5
4-year university degree	235	43.5	74	28.0
>4-year university degree	168	31.1	24	9.1
Other	14	2.6	9	3.4
Marital status				
Single/other	14	2.6	18	6.8
Cohabitating	239	44.1	139	52.4
Married	289	53.3	108	40.8
Smoking in first or second trimester	76	14.1	93	35.0
Low birthweight (<2500 g)	11	2.0	16	5.5
Self-reported or MBRN registered pre-existing maternal thyroid condition	14	2.6	11	3.8
Self-reported maternal thyroid medications	11	2.0	4	1.4
Thyroid conditions (based on measured biomarkers and reference ranges)[b]				
Overt hypothyroidism	0	0	0	0
Subclinical hypothyroidism	6	1.1	1	0.4
Hypothyroxinemia	13	2.4	8	2.8
Overt hyperthyroidism	0	0	2	0.7
Subclinical hyperthyroidism	3	0.6	1	0.4
Hyperthyroxinemia	14	2.6	9	3.1

[a]4-year university degree includes regional technical college, Bachelor's degree, nurse, teacher and engineer. Educational levels below this include secondary school, high school and junior college. More than a 4-year university degree includes graduate degrees (Master's, medical doctor, PhD). Other education was denoted by participant as not falling under any of the prior groupings.

[b]Clinical definitions based on the following criteria in accordance with Lazarus et al.[33]: overt hypothyroidism included individuals with TSH above the reference range and FT4i below the reference range; subclinical hypothyroidism included individuals with TSH above the reference range, FT4i within the reference range and TPO-Ab above 9 IU/ml; hypothyroxinemia included individuals with TSH in the reference range and FT4i below the reference range; overt hyperthyroidism included individuals with TSH below the reference range and FT4i above the reference range; subclinical hyperthyroidism included individuals with TSH below the reference range and FT4i in the reference range; and hyperthyroxinemia included individuals with TSH in the reference range, and FT4i above the reference range.

TABLE 2 Multivariable adjusted odds ratios of thyroid hormone biomarkers in relation to ADHD thyroid hormone

	Total population ($N = 839$)		Euthyroid population ($N = 754$)[a]	
	OR (95% CI)	*P* value for non-linear trend[b]	OR (95% CI)	*P* value for non-linear trend[b]
Thyroid-stimulating hormone (TSH) (mU/L)				
Q1 (0.01–1.11)	1.00 (Reference)	0.91	1.00 (Reference)	1.00
Q2 (>1.11–1.45)	0.97 (0.55, 1.72)		0.92 (0.50, 1.69)	
Q3 (>1.45–1.82)	1.54 (0.88, 2.71)		1.49 (0.82, 2.70)	
Q4 (>1.82–2.37)	0.98 (0.55, 1.74)		1.05 (0.57, 1.94)	
Q5 (>2.37–17.3)	1.20 (0.68, 2.13)		1.34 (0.73, 2.49)	
Triiodothyronine (T3) ng/dl				
Q1 (92–147)	1.00 (Reference)	0.45	1.00 (Reference)	0.53
Q2 (>147–161)	1.13 (0.63, 2.03)		1.18 (0.63, 2.20)	
Q3 (>161–177)	1.23 (0.68, 2.22)		1.25 (0.67, 2.31)	
Q4 (>177–194)	1.10 (0.61, 1.98)		1.14 (0.62, 2.11)	
Q5 (>194–284)	2.13 (1.19, 3.82)		2.15 (1.15, 4.00)	
Free triiodothyronine index (FT3i)				
Q1 (108–147)	1.00 (Reference)	0.65	1.00 (Reference)	0.68
Q2 (>147–161)	1.01 (0.56, 1.81)		0.93 (0.50, 1.72)	
Q3 (>161–173)	1.09 (0.60, 1.97)		0.99 (0.54, 1.83)	
Q4 (>173–189)	1.12 (0.62, 2.02)		1.08 (0.58, 1.99)	
Q5 (>189–286)	1.73 (0.96, 3.09)		1.55 (0.83, 2.90)	
Thyroxine (T4) ug/dl				
Q1 (6.09–9.18)	1.39 (0.79, 2.46)	0.01	1.44 (0.79, 2.63)	0.02
Q2 (>9.18–10.1)	0.80 (0.45, 1.43)		0.86 (0.48, 1.55)	
Q3 (>10.1–10.9)	1.00 (Reference)		1.00 (Reference)	
Q4 (>10.9–11.9)	1.06 (0.60, 1.87)		1.18 (0.66, 2.12)	
Q5 (>11.9–17.8)	1.68 (0.96, 2.96)		1.64 (0.89, 3.02)	
Free thyroxine index (FT4i)				
Q1 (5.79–9.12)	1.98 (1.09, 3.58)	0.25	1.80 (0.97, 3.33)	0.32
Q2 (>9.12–9.91)	1.59 (0.89, 2.84)		1.42 (0.79, 2.56)	
Q3 (>9.91–0.8)	1.00 (Reference)		1.00 (Reference)	
Q4 (>10.8–11.8)	1.88 (1.05, 3.38)		1.78 (0.98, 3.23)	
Q5 (>11.8–21.7)	1.88 (1.05, 3.36)		1.56 (0.84, 2.89)	
Thyroid peroxidase antibody (TPO-Ab) level above 9 mIU/L	0.95 (0.49, 1.85)	NA	1.09 (0.51, 2.35)	NA
FT3i/FT4i ratio				
Q1 (8.59–14)	1.00 (Reference)	0.35	1.00 (Reference)	0.12
Q2 (>14–15.5)	1.77 (0.99, 3.18)		1.72 (0.93, 3.18)	
Q3 (>15.5–16.8)	1.37 (0.75, 2.48)		1.22 (0.65, 2.28)	
Q4 (>16.8–18.4)	1.43 (0.80, 2.59)		1.22 (0.65, 2.28)	
Q5 (>18.4–32.6)	2.10 (1.17, 3.77)		2.08 (1.11, 3.90)	

Note: Models adjusted for child sex, maternal age, maternal education, maternal marital status, smoking during pregnancy and year.

[a]Excludes women who report a pre-existing thyroid condition ($n = 14$), who report taking thyroid medications ($n = 6$), or who meet clinical criteria for thyroid conditions based on the 17 week' measured values ($n = 53$).

[b]Test of non-linearity based on a restricted cubic spline model using a Wald test.

1st and 5th FT4i quintiles of the low intake strata; however, there were also elevated associations in the high intake strata, although imprecise. Dietary intake of iodine and selenium were moderately correlated ($r_s = 0.66$), likely due to some common sources,[48] and therefore, it is difficult to disentangle their impacts. We found no evidence of modification by child sex.

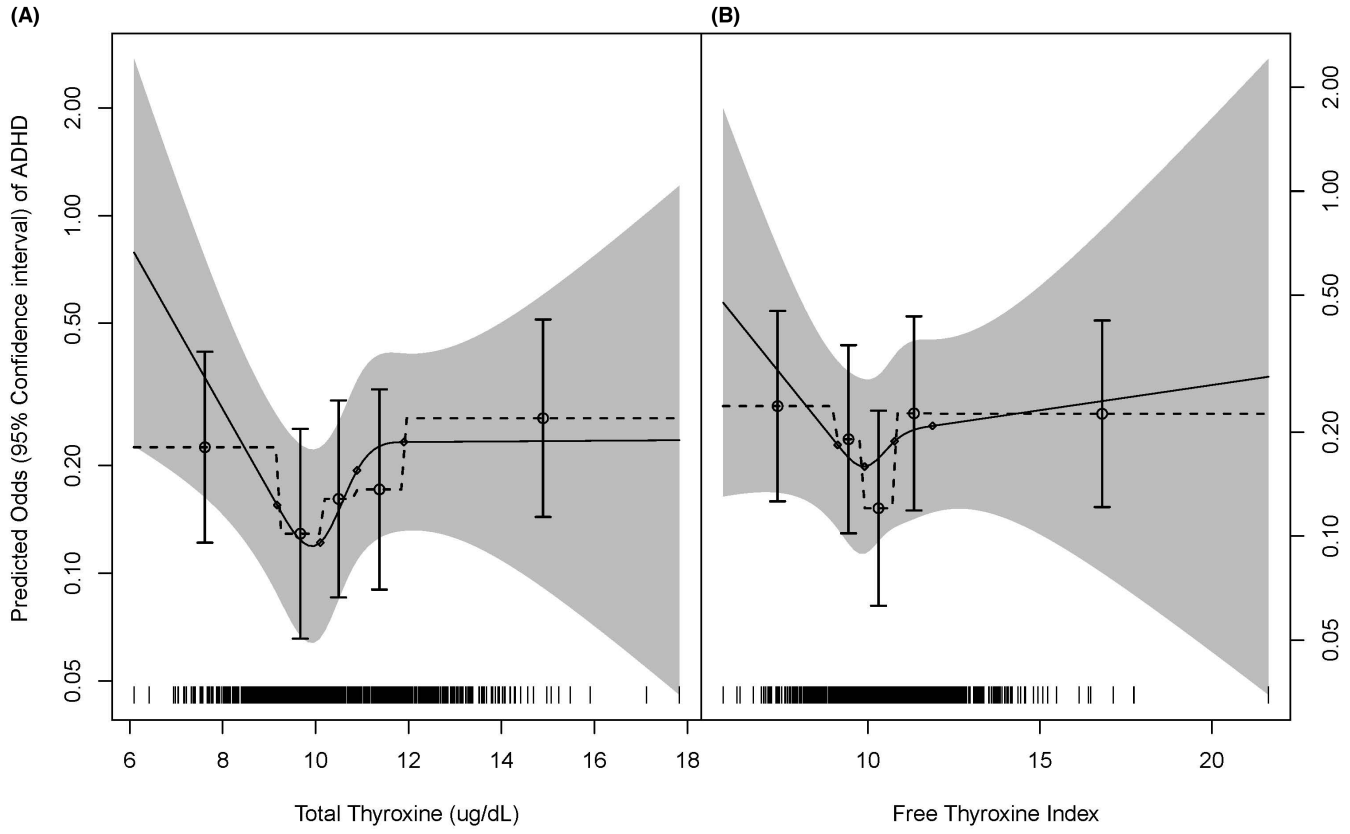

FIGURE 2 Predicted odds of ADHD as a function of Maternal Prenatal Thyroxine and Free Thyroxine Index. Predicted odds (solid line) and 95% confidence intervals (CI) (grey shading) of ADHD as a function of maternal thyroid hormone concentrations, using restricted cubic splines with knots at the 20th, 40th, 60th and 80th percentiles (open circles) are presented for (A) total thyroxine (T4) and (B) free thyroxine index (FT4i). Data points are depicted in tick marks on the bottom of the plot to illustrate data density as a function of concentration. Predicted odds (dotted line) and 95% CIs (solid error bars) of ADHD from the corresponding quintile model, plotted at the medians of the quintiles, are presented for comparison. All models were adjusted for child sex, maternal age, education, marital status and prenatal smoking. The dose–response function of T4 was significantly non-linear ($P \leq 0.01$). Predicted odds of ADHD were elevated at the 20th, 60th and 80th percentiles, relative to the 40th percentile based on the spline model (OR 1.27, 95% CI 1.01, 1.60; OR 1.59, 95% CI 1.08, 2.35; and OR 1.91, 95% CI 1.21, 3.01 respectively).

3.1 | Comment

3.1.1 | Principal findings

In this nested case–control study, we found associations between maternal thyroid function at mid-pregnancy and risk of ADHD, even after excluding individuals with clinical or subclinical thyroid disorders. These results suggest that variability in maternal thyroid function within a normal range alters risk of ADHD. High maternal T3 during pregnancy was associated with increased risk of ADHD, as was the highest quintile of the FT3i/FT4i ratio. However, the relationships between T4 and FT4i with ADHD were U-shaped such that both low and high concentrations were associated with increased risk of ADHD. For FT4i, this trend was especially pronounced in the strata of subjects with low iodine intake.

3.1.2 | Strengths of study

We nested our study within a large-scale, population-based birth cohort. Thyroid hormone concentrations were measured in early pregnancy, a time in which maternal thyroid hormones fully support foetal demands.[7] We carefully established the robustness of our hormone measurements in prior studies.[38] Reported iodine intake was validated against a 24-h urinary iodine biomarker in this population.[49] Moreover, dietary intake may be the best estimate of iodine intake for the larger MoBa population, since only spot urines were collected in the MoBa cohort, and there exists substantial diurnal and day-to-day variability in iodide excretion.[51]

3.1.3 | Limitations of study

MoBa, while large and population-based, underrepresents young mothers, those living alone and smokers.[52] A recent study found this self-selection to have little impact on exposure-outcome associations[53]; however, we adjusted for these factors in our analysis. Our study was additionally restricted to a subset of enrolment years and from larger-volume hospitals, thus participants likely represented more urbanicity and higher socioeconomics than MoBa as a whole. While the NPR established strong validity for

TABLE 3 Relationships of thyroid hormone biomarkers with ADHD by iodine and selenium intake

	Iodine <150 μg/day (*N* = 547)	Iodine ≥150 μg/day (*N* = 245)	Iteraction *P* value	Selenium <60 μg/day (*N* = 545)	Selenium ≥60 μg/day (*N* = 247)	Interaction *P* value
	OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)	
Thyroid-stimulating hormone (TSH) (mU/L)						
Q1 (0.01–1.11)	1.00 (Reference)	1.00 (Reference)	0.50	1.00 (Reference)	1.00 (Reference)	0.42
Q2 (>1.11–1.45)	1.17 (0.56, 2.45)	0.57 (0.18, 1.74)		0.68 (0.33, 1.40)	1.93 (0.62, 6.02)	
Q3 (>1.45–1.82)	1.90 (0.92, 3.92)	0.89 (0.32, 2.47)		1.52 (0.76, 3.02)	1.41 (0.47, 4.26)	
Q4 (>1.82–2.37)	0.95 (0.44, 2.03)	1.12 (0.41, 3.06)		0.81 (0.40, 1.67)	1.59 (0.52, 4.90)	
Q5 (>2.37–17.3)	1.26 (0.59, 2.70)	1.16 (0.43, 3.09)		1.09 (0.52, 2.27)	1.70 (0.59, 4.89)	
Triiodothyronine (T3) ng/dl						
Q1 (92–147)	1.00 (Reference)	1.00 (Reference)	0.99	1.00 (Reference)	1.00 (Reference)	0.91
Q2 (>147–161)	1.34 (0.64, 2.82)	1.02 (0.33, 3.16)		1.11 (0.53, 2.31)	1.42 (0.45, 4.46)	
Q3 (>161–177)	1.41 (0.64, 3.12)	1.23 (0.46, 3.30)		1.41 (0.66, 3.00)	1.39 (0.49, 3.94)	
Q4 (>177–194)	1.20 (0.56, 2.57)	1.31 (0.45, 3.77)		1.09 (0.52, 2.28)	1.54 (0.51, 4.71)	
Q5 (>194–284)	2.25 (1.06, 4.74)	1.92 (0.64, 5.79)		1.78 (0.85, 3.72)	3.01 (0.98, 9.26)	
Free triiodothyronine index (FT3i)						
Q1 (108–147)	1.00 (Reference)	1.00 (Reference)	0.93	1.00 (Reference)	1.00 (Reference)	0.34
Q2 (>147–161)	1.05 (0.50, 2.19)	1.16 (0.40, 3.38)		0.74 (0.36, 1.51)	2.54 (0.78, 8.32)	
Q3 (>161–173)	0.95 (0.44, 2.04)	1.55 (0.54, 4.44)		0.73 (0.34, 1.54)	2.74 (0.90, 8.37)	
Q4 (>173–189)	1.14 (0.52, 2.49)	1.26 (0.46, 3.47)		0.85 (0.40, 1.79)	2.53 (0.81, 7.92)	
Q5 (>189–286)	1.61 (0.77, 3.35)	1.50 (0.49, 4.57)		1.12 (0.54, 2.31)	3.32 (1.03, 10.74)	
Thyroxine (T4) ug/dl						
Q1 (6.09–9.18)	2.07 (0.97, 4.40)	0.63 (0.22, 1.78)	0.25	2.09 (0.98, 4.45)	0.66 (0.23, 1.89)	0.20
Q2 (>9.18–10.1)	1.06 (0.50, 2.25)	0.90 (0.31, 2.62)		1.34 (0.65, 2.74)	0.46 (0.14, 1.48)	
Q3 (>10.1–10.9)	1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	1.00 (Reference)	
Q4 (>10.9–11.9)	1.56 (0.74, 3.26)	0.65 (0.23, 1.83)		1.14 (0.55, 2.36)	1.19 (0.42, 3.41)	
Q5 (>11.9–17.8)	2.62 (1.25, 5.50)	0.90 (0.31, 2.63)		2.37 (1.15, 4.90)	1.05 (0.35, 3.13)	
Free thyroxine index (FT4i)						
Q1 (5.79–9.12)	2.86 (1.32, 6.19)	0.94 (0.31, 2.88)	0.04	2.72 (1.29, 5.73)	1.24 (0.36, 4.23)	0.05
Q2 (>9.12–9.91)	1.45 (0.69, 3.07)	2.70 (0.88, 8.30)		1.52 (0.74, 3.13)	3.01 (0.92, 9.81)	
Q3 (>9.91–10.8)	1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	1.00 (Reference)	
Q4 (>10.8–11.8)	2.38 (1.13, 5.02)	1.47 (0.48, 4.54)		1.50 (0.72, 3.12)	4.65 (1.42, 15.18)	
Q5 (>11.8–21.7)	2.73 (1.31, 5.70)	0.95 (0.30, 3.01)		2.01 (0.97, 4.15)	2.20 (0.66, 7.37)	
Thyroid Peroxidase Antibody (TPO-Ab) level above 9 mIU/L	1.11 (0.45, 2.73)	0.49 (0.14, 1.70)	0.30	0.82 (0.31, 2.16)	0.86 (0.28, 2.68)	0.95
FT3i/FT4i Ratio						
Q1 (8.59–14)	1.00 (Reference)	1.00 (Reference)	0.89	1.00 (Reference)	1.00 (Reference)	0.67
Q2 (>14–15.5)	1.71 (0.81, 3.63)	1.34 (0.48, 3.76)		2.07 (0.99, 4.35)	1.00 (0.35, 2.86)	
Q3 (>15.5–16.8)	1.27 (0.60, 2.71)	1.08 (0.36, 3.23)		1.20 (0.56, 2.54)	1.21 (0.40, 3.60)	
Q4 (>16.8–18.4)	1.70 (0.82, 3.53)	0.96 (0.32, 2.87)		1.69 (0.82, 3.48)	0.94 (0.30, 2.92)	
Q5 (>18.4–32.6)	1.67 (0.79, 3.52)	1.75 (0.61, 5.00)		1.76 (0.85, 3.66)	1.63 (0.54, 4.89)	

Note: Models adjusted for child sex, maternal age, maternal education, maternal marital status, smoking during pregnancy and year.

other child neuropsychiatric disorders,[24] a study conducted within the NPR to assess the extent to which the clinical basis for ADHD registrations were appropriately documented revealed that only approximately half of the registered diagnoses contained the appropriate documentation.[54] Among the remaining registrations, some may have been true cases; however, supporting material in the clinical record was not found. Because maternal blood was collected only once during pregnancy, we cannot evaluate

the influence of gestational timing on our reported associations. Endendijk et al. (2017) measured thyroid hormones in each trimester and found that higher first trimester TSH was associated with more attention problems in boys.[55] However, overall there is sparse information on differences in associations across trimesters, with most existing studies measuring thyroid biomarker levels once in the first 20 weeks of pregnancy.[9] While we limited our assessment of interaction to the multiplicative scale, finding evidence of FT4i–iodine interactions, nutrient–thyroid interaction may yet be present on the additive scale for other thyroid hormone biomarkers associated with ADHD, like T3, T4, and FT3i/FT4i ratio; moreover, additive interaction may be more relevant for the design of future public health interventions.[56] Finally, we cannot exclude the possibility of residual confounding by unmeasured covariates.

3.1.4 | Interpretation

Iodine and selenium are required for the biosynthesis and metabolism of thyroid hormone.[20] Whereas iodine is an essential component of T3 and T4, selenium deficiency has the effect of impairing thyroid metabolism by interfering with peripheral iodothyronine deiodinase enzymes, which convert T4 to the more biologically active T3.[57] Overall, iodine intake is low in this population,[46] and in the strata of subjects with sufficient iodine intake, most of the associations between FT4i and ADHD attenuate, suggesting that iodine sufficiency during pregnancy may reduce an effect of normal variation in free thyroid hormone concentrations on ADHD risk.

TSH was not associated with increased risk of ADHD in our population, which is in accordance with a recent meta-analysis of three European cohorts,[11] nor was TPO-Ab positivity. It could be that we had very few subjects with values outside of their respective reference ranges ($n = 33$ and $n = 73$ respectively). However, it should also be noted that TSH is a noisy carrier of information about thyroid status during pregnancy, due to the competing activity of human chorionic gonadotropin (hCG).[32,58]

Although thyroid hormones are known to play a critical role in early foetal brain development,[6,7,59] the focus of the literature has largely been on thyroid hormone deficiency.[59] New evidence also implicates excess thyroid hormones during gestation in the occurrence of neurodevelopmental disorders,[16] as well as effects on the developing brains of experimental animals, including the expression of neuronal cytoskeletal proteins,[60] and the development of the visual cortex.[61] Both low and high FT4 concentrations during pregnancy have been associated with reductions in child IQ, as well as grey matter and cortex volumes.[62] The impact of excess thyroid hormones during gestation on foetal brain development needs more experimental and observational research.

One facet of thyroid hormone activity that has not previously been examined in the context of ADHD is differential conversion of T4 to T3. Approximately 80% of circulating T3 is not produced by the thyroid gland directly, but rather from mono-deiodination of T4.[63] Therefore, in euthyroid individuals, the ratio of FT3 to FT4 is an indication of how efficient the body is at converting T4 to T3.[37,64] Larger ratios, indicating more FT3 per unit FT4, suggest higher peripheral deiodinase activity. In hyperthyroid individuals, the thyroid gland takes on a disproportionate share of T3 production—increasing to as much as 57%,[65] which has the result of increasing the T3 to T4 ratio.[66] In addition, preferential secretion of T3 is a biochemical marker of iodine deficiency, which also has the effect of increasing the T3 to T4 ratio.[58,67] Therefore, because multiple physiological factors can contribute to an excess of T3, it is difficult to pinpoint the mechanism underlying our findings.

The clinical significance of our findings is uncertain, because few mothers met clinical criteria for diagnosis or treatment. However, most associations in our study were unaffected by excluding clinically significant thyroid disorders. That excluding subjects on thyroid medications or with thyroid disease did not materially alter associations is interesting in light of recent clinical trials that found screening and treatment for deficits in maternal thyroid function had no beneficial effect on child cognition[68,69]; however, why trials have not observed a benefit is unclear. It is possible that treatment initiation came too late in gestation, that over-treatment inadvertently increased risk in some cases, or that studies were underpowered. Our results are consistent with other investigations that have reported associations with a variety of neurobehavioural and psychiatric outcomes among those within a clinically normal range.[70]

4 | CONCLUSIONS

We found associations between maternal thyroid function and risk of ADHD, suggesting that maternal thyroid hormone concentrations within a clinically normal population may be relevant to the aetiology of ADHD.

AUTHOR CONTRIBUTIONS

SME, GDV, AH, PZ, GPK, TRK, MPL and AH contributed to conceptualisation, validation, analysis, funding acquisition, supervision, drafting and editing of manuscripts. RCN and SSMD contributed to analysis, drafting and editing. RTZ and HMM contributed to conceptualisation and editing.

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CONFLICT OF INTEREST

Financial disclosures and potential conflicts of interest: The authors report no financial or other conflicts of interest.

DATA AVAILABILITY STATEMENT

Data utilized in this research may be requested through application to the Norwegian Mother, Father and Child cohort according to standard requirements. Further information may be found at the MoBa website: https://www.fhi.no/en/studies/moba/for-forskere-artikler/research-and-data-access/.

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SUPPORTING INFORMATION

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