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BRIEF REPORT

Neonatal thyroid-stimulating hormone and association with attention-deficit/hyperactivity disorder

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Abstract

Background: Normal brain development is dependent on maternal, fetal and neonatal thyroid function. Measuring neonatal thyroid-stimulating hormone (TSH) 48-72 hours after birth screens for congenital hypothyroidism, allowing early treatment to avoid serious impairment. However, even within sub-clinical ranges, disrupted thyroid homeostasis during brain development has been linked to adverse neurodevelopmental outcomes, including attention-deficit/hyperactivity disorder (ADHD).

Objectives: To estimate the association between neonatal TSH below threshold for potential congenital hypothyroidism and subsequent ADHD diagnosis using a population-based birth cohort.

Methods: Children with a diagnosis of ADHD in the Norwegian Mother, Father and Child Cohort Study (MoBa) were identified through linkage with the Norwegian Patient Registry using ICD-10 codes for hyperkinetic disorders. The study included 405 ADHD cases and 1,092 controls (born 2003-2008) with available neonatal TSH concentrations below 10 mU/L (cut-off for potential congenital hypothyroidism) measured in dried blood spots sampled 48-72 hours after birth.

Results: In multivariable, quintile models the relationship appeared to follow a U-shaped pattern with elevated odds ratios (OR) at lower and higher TSH levels. Among children with TSH in the lowest quintile, odds of ADHD was approximately 1.5-fold higher than children in the middle quintile (OR 1.60, 95% CI 1.09, 2.34), which was driven by substantially elevated risk among girls, with no association among boys ($P_{interaction}$ = 0.02; girls OR 3.10, 95% CI 1.53, 6.30; boys OR 1.16, 95% CI 0.73, 1.84).

Conclusions: ADHD risk appeared to be elevated among newborns with low TSH levels (i.e. with hyperthyroid status), and this association was mainly found among girls. Because our findings are suggestive of increased risk at very low TSH concentrations, where analytical accuracy is low, future studies should employ highly sensitive assays capable of accurate quantitation at very low concentrations. Also, larger studies are needed to investigate these associations at higher neonatal TSH concentrations where data are more widely distributed.

KEYWORDS

ADHD, brain development, MoBa, neonate, the Norwegian Mother, Father and Child Cohort study, TSH

1 | INTRODUCTION

Thyroid hormones, thyroxine (T4), and triiodothyronine (T3), are essential for prenatal and early postnatal neurodevelopment.[1] Thyroid-stimulating hormone (TSH) regulates production and release of thyroid hormones from the thyroid gland.[2] It is released from the pituitary under control of the hypothalamus and by negative feedback from circulating T3 and T4.[2] Measuring neonatal TSH concentrations 48-72 hours after birth screens for congenital hypothyroidism (CH), allowing early treatment to avoid serious impairment.[3] However, even within subclinical ranges, disrupted thyroid hormone homoeostasis during brain development has been linked to adverse neurodevelopmental outcomes, including attention-deficit/hyperactivity disorder (ADHD).[4-6] ADHD is the most common neurodevelopmental disorder during childhood, affecting 3.4% of children worldwide.[7] Although ADHD is highly heritable, there is limited knowledge of specific environmental risk factors.[7,8] Several studies indicate that especially maternal thyroid hypothyroidism (elevated TSH and low T4) but also hyperthyroidism (suppressed TSH and elevated T4 and/or T3) during pregnancy is linked to the aetiology of ADHD or related behavioural or cognitive problems in the child[4-6]; however, few studies investigate this relationship in neonates.[4] The majority of studies on newborns have compared cases of early-treated CH to non-CH controls.[9-12] Findings indicate associations with ADHD-related behaviour in children and adolescents, especially lowered attention and memory.[9-12] CH is relatively rare and occurs sporadically in about one in 1000-4000 newborns.[13] Thus, CH case-control studies end up small and lacking representativeness of the general population. There have been no previous investigations of TSH levels in the normal range in a population-based study using clinical ADHD diagnosis as the outcome.

The objective of this study was to estimate the association between neonatal TSH below threshold for potential congenital hypothyroidism and subsequent ADHD diagnosis using a population-based birth cohort.

Synopsis

Study question

This study examines the association between newborn concentrations of thyroid-stimulating hormone (TSH) within normal ranges and childhood attention-deficit/hyperactivity disorder (ADHD) using a population-based birth cohort.

What's already known?

Thyroid hormones are essential for normal brain development. Severe hypothyroidism in neonates causes mental retardation if not treated early. Maternal thyroid dysfunction during pregnancy is linked to adverse neurodevelopment in offspring, including ADHD or related behavioural problems. Few studies investigate this in neonates, and none has investigated TSH levels in the normal range with ADHD diagnosis in a population-based study.

What this study adds

Attention-deficit/hyperactivity disorder risk appeared to be elevated among newborns with low TSH levels, and this was mainly found among girls. This calls for further investigation of conditions of hyperthyroidism as potential risk factors for ADHD.

2 | METHODS

Our study is nested within the Norwegian Mother, Father and Child Cohort study (MoBa), a population-based, longitudinal prospective birth cohort of almost 113 000 women giving birth in Norway between 1999 and 2008 (41% participation rate)[14] (Appendix 1). We used a pooled analysis of two nested case-cohort sub-studies within MoBa that included children born between 2003 and 2008. In both studies, we identified children with ADHD (ICD-10 F90 hyperkinetic disorder)[15] through linkage with the Norwegian Patient Registry (NPR) (Appendix 1). The NPR is an administrative database containing activity data from all Norwegian government-owned hospitals and outpatient clinics with diagnoses available from 2008 and onwards. We required a minimum of two ADHD-diagnoses registered in order to exclude erroneous single registrations. All subjects were singletons, had no serious malformations at birth or Down's syndrome, returned the first MoBa questionnaire, and births were registered in the Medical Birth Registry of Norway (MBRN). They also had available maternal biospecimens. Nationwide data on neonatal TSH were available starting in approximately 2003 from the National newborn screening of Norway, which routinely measure TSH in dried blood spots sampled ~48-72 hours after birth by immunoassay (AutoDELFIA Neonatal TSH kit'; Perkin Elmer). The limit of detection (LOD) for this current assay is 1.3 mU/L.[16] While the specific kits have changed, the National newborn screening programme has routinely quantified TSH values «1mU/L, the lowest value on the calibration curve. We chose

only participants with neonatal TSH concentrations below 10 mU/L (cut-off for potential congenital hypothyroidism). In the first study, we selected 506 ADHD cases and 657 controls, frequency matched on birth year and sex to the case group. The second study included 199 ADHD cases and 529 controls matched on birth year but not sex (see Engel et al[17]). Because of this slight difference in selection methods, all analyses were adjusted for or stratified by child sex. After excluding subjects where TSH data from the newborn screening's central record were missing/not recorded (n = 293) and those with TSH >10 mU/L (n = 2), and accounting for study overlap (187 cases and 6 controls), the merged sample consisted of 405 ADHD case and 1092 control children and their mothers (Table S1). This study was approved by The Regional Committee for Medical Research Ethics (ref. no. 2012/985-1).

The current study is based on version 9 of the MoBa quality-assured data files. We conducted multivariable-adjusted logistic regression with ADHD as outcome, analysing TSH concentrations (exposure variable) both in quintiles and using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles. Zero values (n = 8) were replaced with a low number close to zero (0.001 mU/L). Initial analyses indicated non-linearity (data not presented), and consequently, quintile three was chosen as reference. Covariates were obtained from MoBa questionnaires and MBRN (Appendix S1), and adjustment set was selected a priori using a Directed Acyclic Graph approach.[18] All models were adjusted for MoBa sub-study (study 1 or 2), child sex and sampling time (hours after birth), maternal age and parity, as well as maternal smoking, maternal thyroid disease and intake of thyroid medication during pregnancy. Missing values for sampling time (n = 270) were replaced using single imputation based on the natural log-normal distribution of sampling time (see Appendix S1). We also tested for interaction by sex of the child, overall interaction effect and for Q1, Q2, Q4, and Q5 separately, and in the restricted cubic spline. We also assessed whether the functional form in restricted cubic splines differed from linearity including stratification by sex of the child (Appendix S1).

We performed several sensitivity analyses. In quintile models, we investigated the potential for residual confounding by covariates for which the association between exposure and outcome is more uncertain[4,19] including birth year, maternal education level, pre-pregnancy BMI, and maternal iodine intake during pregnancy. We also examined the impact of excluding preterm children (<37 weeks) or small for gestational age (SGA), excluding children of mothers with thyroid disease and thyroid medication during pregnancy, excluding children with TSH values of zero, and excluding children where sampling time was missing. Finally, we re-ran restricted cubic spline models by child sex, replacing zero values for TSH (n = 8) with the lowest value (0.01 mU/L) divided by square root of 2, as well as excluding children of mothers with thyroid disease and thyroid medication during pregnancy.

3 | RESULTS

Attention-deficit/hyperactivity disorder cases were more often boys, older and had somewhat lower gestational age and birthweight compared to controls. Mothers of ADHD cases had lower education, younger age at delivery, higher pre-pregnancy BMI, and a larger proportion smoked during pregnancy (Table 1). Median neonatal TSH level was 1.0 mU/L, range 0.001-7.5 mU/L (Table S1). Median TSH concentrations in cases and controls did not differ (Hodges-Lehman's estimate 0.07, 95% CI −0.01, 0.16).

We observed elevated odds ratios (ORs) at low and high TSH quintiles relative to quintile three (reference) indicating a possible non-linear (U-shaped) relationship. These results were only significant among children in the lowest quintile of TSH, where odds of ADHD was approximately 1.5-fold higher than for children in the middle quintile (Table 2), adjusted OR 1.60 (95% CI 1.09, 2.34). We also identified interaction by sex in the lowest quintile of TSH ($P_{interaction}$ = .02), such that higher odds of ADHD was limited to girls (Table 2); girls OR 3.10 (95% CI 1.53, 6.30) and boys OR 1.16 (95% CI 0.73, 1.84). Restricted cubic splines with knots at the 10th, 50th, and 90th percentiles showed similar U-shaped relationship as the quintile models; however, this non-linearity was driven primarily by a strong non-linear response among girls (P < .01; Figure 1; Figures S1 and S2). None of the sensitivity analyses resulted in an important change in the results (Tables S2 and S3; Figures S3 and S4).

3.1 | Comment

Our findings imply that there may be a sex-specific relationship between low neonatal TSH (ie, with hyperthyroid status) and ADHD, with girls having threefold higher odds of ADHD in this concentration range, with very little evidence of increased risk among boys. Also, the U-shaped dose-response relationship indicated in the quintile model was only apparent for girls when modelled in restricted cubic spline by child sex (Figure 1; Figures S1 and S2). The data were much denser in the lower than in the higher part of the TSH distribution, which limited inferences at higher TSH concentrations. Even so, recent studies report inverted U-shaped relationships between *maternal* free T4 concentrations during pregnancy and child IQ,[20,21] suggesting the presence of non-monotonic dose-response relationships between thyroid function biomarkers and neurodevelopmental outcomes. Previous studies using dried blood spots collected 2-3 days after birth investigating T4 and ADHD diagnosis[22,23] or TSH and ADHD-related behaviour[24] found no associations.[22-24] These studies were small (n = 182-310) and not population-based, and did not investigate non-linear relationships or effect modification by child sex. However, a large population-based study using newborn screening data indicated a modest increase in risk of autism spectrum disorders with low neonatal T4 levels, but no association with TSH or any effect modification by sex was reported.[25] Still, two studies report that abnormal maternal thyroid function during pregnancy was more strongly associated with ADHD in girls than in boys.[26,27] As pointed out by the authors,[26] the sex differences might be linked to differences in the aetiology of ADHD for boys and girls. This could imply an interplay between brain sexual differentiation and thyroid function that is related to the aetiology of ADHD. Experimental studies have indicated crosstalk between the thyroid hormone system and sex steroids during brain

TABLE 1 Characteristics of study participants selected from Norwegian Mother, Father and Child Cohort study (MoBa)

	ADHD cases (N = 405)		Controls (N = 1092)	
	N	%	N	%
Maternal				
Age at delivery (y)				
≤24	75	18.5	89	8.2
25-29	152	37.5	377	34.5
30-34	125	30.9	434	39.7
35-39	38	9.4	170	15.6
≥40	15	3.7	22	2.0
Parity				
0	210	51.9	527	48.3
≥1	195	48.1	565	51.7
Education (y)				
≤12	224	55.3	259	23.7
>12	170	41.9	790	72.4
Others/missing	11	2.7	43	3.9
Pre-pregnancy BMI				
<18.5	15	3.7	35	3.2
18.5-29.9	308	76.0	924	84.6
≥30	70	17.3	97	8.9
Missing	12	3.0	36	3.3
Smoking in pregnancy				
Never	325	80.2	1013	92.8
Yes	80	19.8	79	7.2
Iodine intake (dietary) in pregnancy[b]				
<150 µg/d	245	60.5	744	68.1
≥150 µg/d	138	34.1	324	29.7
Missing	22	5.4	24	2.2
Thyroid disease and/or thyroid medication in pregnancy				
Yes	20	4.7	32	2.8
No incl. missing	305	95.3	1060	97.2
Child				
Reference range TSH[a]				
<Ref. range	15	3.7	29	2,7
within ref. range	385	95.1	1035	94.7
>Ref. range	5	1.2	28	2.6
Time of sampling (h)				
<48	2	0.5	2	0.2
48-71	173	42.7	546	50.0
≥72	105	25.9	399	36.5
Missing	125	30.9	145	13.3
Sex of the child				
Boy	291	71.9	641	58.7
Girl	114	28.1	451	41.3
Child birth year				
2003	79	19.5	52	4.8

(Continues)

TABLE 1 (Continued)

	ADHD cases (N = 405)		Controls (N = 1092)	
	N	%	N	%
2004	152	37.5	214	19.6
2005	101	24.9	339	31.0
2006	44	10.9	241	22.1
2007	24	5.9	212	19.4
2008	5	1.2	35	3.2
Gestation age (wk)				
<37	30	7.4	44	4.0
37-42	374	92.4	1043	95.5
>42	1	0.2	5	0.5
Small for gestational age, SGA				
No	393	97.0	1076	98.5
yes	12	3.0	16	1.5

Note: Descriptions of the variables are in the Supporting Information.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; TSH, thyroid-stimulating hormone.

[a]Estimated daily intake based on the maternal food frequency questionnaire at 22 wk' gestation.

[b]Reference range was calculated from 2.5 to 97.5 percentiles of TSH levels in the controls excluding children of mothers with thyroid disease or with intake of thyroid medication during pregnancy: 0.11-3.71 mU/L (n = 1024).

TABLE 2 Odds ratio (OR) with 95% confidence intervals (95% CIs) of neonatal TSH concentrations in quintiles (Q1-Q5, Q3 is reference) for TSH <10 mU/L in relation to ADHD diagnosis

	Unadjusted	Adjusted[a]
TSH (mU/L)	OR (95% CI)	OR (95% CI)
Quintiles		
Q1 (0.001-0.5)	1.57 (1.09, 2.27)	1.60 (1.09, 2.34)
Q2 (>0.5-0.86)	1.24 (0.89, 1.80)	1.22 (0.83, 1.78)
Q3 (>0.86-1.22)	1.00 (Reference)	1.00 (Reference)
Q4(>1.22-1.82)	1.12 (0.77, 1.64)	1.12 (0.76, 1.67)
Q5 (>1.82-7.45)	1.26 (0.87, 1.83)	1.17 (0.79, 1.72)

	Girls	Boys	
By child sex (interaction)	OR (95% CI)	OR (95% CI)	$P_{interaction}$[b]
			.14
Q1 (0.001-0.5)	3.10 (1.53, 6.30)	1.16 (0.73, 1.84)	.02
Q2 (>0.5-0.86)	1.54 (0.71, 3.33)	1.12 (0.71, 1.76)	.48
Q3 (>0.86-1.22)	1.00 (Reference)	1.00 (Reference)	
Q4 (>1.22-1.82)	1.76 (0.83, 3.72)	0.94 (0.59, 1.51)	.16
Q5 (>1.82-7.45)	1.38 (0.63, 3.03)	1.10 (0.76, 1.73)	.62

Abbreviations: ADHD, attention-deficit/hyperactivity disorder;TSH, thyroid-stimulating hormone.

[a]Adjusted for sub-study (study 1 or 2), child sex and sampling time (hours after birth; n = 270 missing was replaced by single imputation by chained equation using natural log-normal distribution of sampling time, see Supporting Information), parity, maternal smoking, maternal age, and maternal thyroid disease and intake of thyroid medication in pregnancy as covariates.

[b]Interaction by sex of the child; overall interaction effect and for Q1, Q2, Q4, and Q5 separately.

development.[28-30] However, ADHD tends to be under-ascertained among girls.[31] Therefore, girls who are identified may represent a more extreme end of the ADHD phenotype,[31] which may partially explain increased risk in this subgroup. How sex can modify the relationship between thyroid function and adverse neurodevelopment remains a relatively unexplored area.

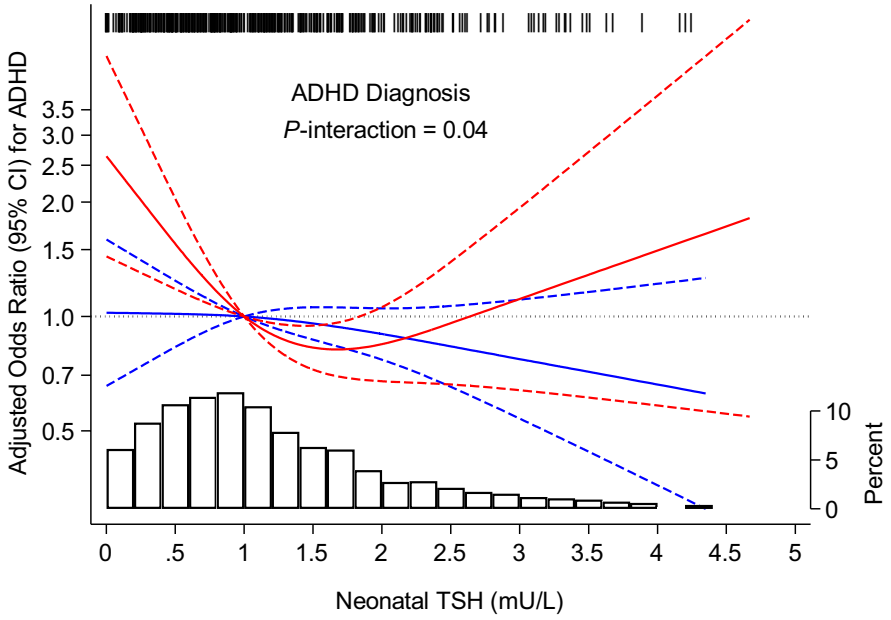

FIGURE 1 Restricted cubic splines (knots at 10th, 50th, and 90th percentile, baseline 1.0 mU/L thyroid-stimulating hormone [TSH]) modelling the association between neonatal TSH concentrations and attention-deficit/hyperactivity disorder (ADHD) with interaction by child sex. The model was adjusted for the following covariates: sub-study, child sex, natural log-sampling time (hours after birth), parity, maternal age, maternal smoking during pregnancy, and thyroid disease and intake of thyroid medication in pregnancy. Odds ratios on the vertical axis are presented on log-scale. Dashed lines represent 95% CIs. Blue lines represent boys, while red lines represent girls. Hashing along the top horizontal axis represents the distribution of ADHD cases [Colour figure can be viewed at wileyonlinelibrary.com]

There is ample literature describing relationships between maternal or severe neonatal hypothyroidism and adverse neurodevelopment including ADHD.[4-6] However, our findings add to emerging evidence that hyperthyroidism could also be a potential risk factor for adverse neurodevelopment.[20,27,32] Specifically, our results point to increased risk at the very low end of the TSH concentration range, which in some cases fall orders of magnitude below the assay LOD. Values below the LOD are measured with less accuracy; however, the TSH distribution among our participants was in accordance with other studies reporting neonatal TSH from dried blood spots using the same analytical method.[33-35] Korada et al[33] investigated the accuracy of TSH measurements at lower concentrations, and reported intra-assay coefficient of variation to be 8% and 16% at 1.3 and 0.5 mU/L, respectively, and that in a population of 65 446 infants, 73% had TSH levels lower than 1.0 mU/L. Newborn screening programmes are geared towards the detection of congenital hypothyroidism; therefore, accurate quantitation of very low values is not of primary concern. Our findings suggest that there may be increased risk for neurodevelopmental disability within this large population of infants with very low TSH values; therefore, accurate quantitation of very low TSH concentrations is desirable in future studies.

4 | CONCLUSIONS

We found that odds of ADHD was elevated among newborns with low TSH levels and that this association was mainly found among girls. Because our findings are suggestive of increased risk at very low TSH concentrations, in a concentration range where analytic accuracy is low for high throughput neonatal screening, future studies should employ highly sensitive assays capable of accurate quantitation at very low concentrations. In addition, larger studies are needed to investigate these associations at higher neonatal TSH concentrations where data are more widely distributed.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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