Original Contribution

Maternal Thyroid Anomalies and Attention-Deficit Hyperactivity Disorder in Progeny

Ran S. Rotem*, **Gabriel Chodick, Michael Davidovitch, Andrea Bellavia, and Marc G. Weisskopf**

* Correspondence to Dr. Ran S. Rotem, Department of Environmental Health, Harvard T. H. Chan School of Public Health, 665 Huntington Avenue, Boston, MA 02115 (e-mail: ran.rotem@mail.harvard.edu).

Previous epidemiologic investigations suggested that maternal thyroid anomalies are a possible causal factor in attention-deficit hyperactivity disorder (ADHD) in progeny, yet clinical trials indicated that levothyroxine treatment was ineffective in preventing neurodevelopmental impairments. We used an Israeli cohort of 385,542 singleton births from 1999–2012 to explore the interrelated roles of maternal thyroid conditions, laboratory gestational thyroid hormone measurements, use of thyroid medications, and offspring ADHD. Analyses were performed using Cox proportional hazards models. Results indicated that maternal hypothyroidism diagnosis was associated with an elevated progeny ADHD hazard (adjusted hazard ratio = 1.14, 95% confidence interval = 1.10, 1.18). However, this association was unmitigated by gestational use of levothyroxine and was unexplained by maternal gestational thyroid hormone levels. Associations with gestational thyrotropin values and hypothyroxinemia were also observed but were robust only in mothers without other records indicative of a thyroid problem. Results indicated that maternal thyroid hypofunction was associated with progeny ADHD but possibly not due to a direct causal relationship. Instead, maternal thyroid hypofunction may serve as a proxy indicator for other factors that affect neurodevelopment through thyroid hormone independent pathways, which are thus unaffected by pharmaceutical treatments for thyroid hypofunction. Factors known to disrupt thyroid functioning should be examined for their independent ADHD-related effects.

attention-deficit hyperactivity disorder; endocrine disruptors; hypothyroidism; levothyroxine; thyroid stimulating hormone; thyrotropin; thyroxine

Attention-deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by inattention, impulsivity and hyperactivity that impede normal functioning. Prevalence of the disorder has been increasing worldwide, with recent estimates suggesting that up to 14% of children are diagnosed by age 17 years (1–3). This makes ADHD the most common childhood psychiatric disorder, with substantial long-term consequences (4). Children with ADHD have reduced psychosocial health, restricted social participation, and lower quality of life compared with typically developing children (5–9). These outcomes frequently persist into adulthood (10), leading to job insecurity, social isolation, increased tendency to engage in criminal activities and substance abuse, psychiatric comorbidities, and worse quality of

life (8, 11–16). Understanding the role of potentially modifiable risk factors in ADHD could thus have tremendous individual and societal impacts.

The etiology of ADHD is unclear, with genetic, environmental, and societal factors likely playing contributing roles. One specific area of interest is fetal gestational exposure to abnormal thyroid hormones levels. Thyroid hormones play key roles in numerous neurodevelopmental processes, and disruption of these processes could lead to permanent alterations in brain structure and function, with possible implications for ADHD (17–19). Involvement of thyroid hormones in the etiology of ADHD, if confirmed, will have important implications. First, the mother is the sole source of thyroid hormones to the fetus in early pregnancy,

and remains an important source throughout gestation (20). Medications can effectively control thyroid hormone levels in mothers with thyroid disorders, thus potentially mitigate progeny ADHD risk. Second, recent evidence has linked ADHD with perinatal exposures to several environmental toxicants that are also known to interfere with normal thyroid functioning, including certain classes of endocrine disruptors such as phthalates and polyfluoroalkyl substances (21–28). If thyroid hormones mediate or modify the effects of such environmental factors, screening and treatment of pregnant women for thyroid anomalies could be one way to mitigate the risks downstream of the culprit environmental exposures.

Previous epidemiologic studies observed associations between maternal thyroid hormone anomalies and progeny ADHD risk, although the results have been inconsistent (17, 29–35). These epidemiologic investigations often advocated for gestational screening and treatment of thyroid hormone dysfunction, although direct assessment of gestational thyroid hormone medications use was not performed. In contrast, 2 randomized clinical trials found that gestational treatment with thyroid hormone replacement medications (levothyroxine) of mothers with a thyroid hormone deficiency did not result in improved behavior, cognitive function, or intelligence-test scores in progeny and did not reduce the risks for adverse neonatal and pregnancy complications, although treatment only began in the second trimester (36, 37). To further explore the interrelated roles of maternal clinical thyroid condition diagnoses, laboratory gestational thyroid hormone measurements, use of thyroid medications, and offspring ADHD, we used data from a large Israeli birth cohort with detailed clinical and demographic information.

METHODS

Study population

Maccabi Health Services (MHS) is Israel's second largest (2.5 million members) integrated health fund. It provides medical services under universal coverage mandated by the Israeli National Health Insurance Law. In 1999–2012, 445,477 singleton births occurred to mothers who were MHS members throughout the year preceding the date of birth of their child. Since ADHD is rarely and unreliably diagnosed at very young ages (38), our analyses excluded 17,258 children who left MHS or were diagnosed with ADHD before age 3. The study was approved by the MHS institutional review board and by the Office of Human Research Administration at the Harvard T. H. Chan School of Public Health.

ADHD case ascertainment

Data on ADHD diagnosis and medication use were obtained from children's electronic medical records through 2019, allowing for at least 7 years of follow-up for even the youngest children. While an initial indication for suspected ADHD and a first course of treatment can be recorded

and prescribed by any clinician, the Israeli Ministry of Health guidelines require that a definitive ADHD diagnosis and any subsequent treatment recommendations be made only by trained specialists (neurologists, psychiatrists, or pediatricians with specialized training). The diagnosis must include in-person clinical evaluations and incorporate diagnostic questionnaires for parents/caregivers and teachers (39). Thus, for primary analyses, we relied on a strict ascertainment definition for ADHD, defining cases as children who had both an ADHD diagnosis record based on the *International Classification of Diseases, Ninth Revision* (ICD-9), code group 314.x, and at least 2 dispensing records for ADHD medications from the following anatomical therapeutic chemical (ATC) categories (all sold solely as prescription drugs in Israel): dexamphetamine (N06BA02), methylphenidate (N06BA04), pemoline (N06BA05), dexmethylphenidate (N06BA11), amphetamine (N06BA01), atomoxetine (N06BA12), and lisdexamfetamine (N06BA12). More than one-third of children with an ADHD diagnosis in our cohort did not use medications, similar to estimates reported in other cohorts (2). Because ADHD case-status validation in such children is challenging (3), we excluded from the main analyses children diagnosed with ADHD who had fewer than 2 dispensing records for ADHD medications ($n = 38{,}446$). Additionally, ADHD medications may sometimes be used for other conditions, such as sleep problems (40). Therefore, in main analyses we also excluded 4,231 children with dispensing records for ADHD medications who did not have an ADHD diagnosis record. Thus, main analyses included 385,542 children (217,892 mothers). All excluded children were included as cases in sensitivity analyses. In all analyses, the first date of ADHD recognition was defined as the first date of diagnosis or medication purchase, whichever occurred first.

Thyroid status definitions

Data on maternal thyroid conditions, laboratory tests, and medication dispensing were available from 1998 through 2016 from electronic medical records. Maternal hypothyroidism was defined as either: 1) an ICD-9 record for hypothyroidism (243.x–244.x) and at least 1 dispensing record for thyroid hormone replacement medications (anatomical therapeutic chemical group H03AA), or 2) at least 2 dispensing records for these medications. Similarly, hyperthyroidism was defined as either: 1) an ICD-9 record for hyperthyroidism (242.x) and at least 1 dispensing record for thiouracils (H03BA) or sulfur-containing imidazole derivatives (H03BB) medications, or 2) at least 2 dispensing records. Thyroid medications are sold solely as prescription drugs in Israel. Children of mothers with some indication of a thyroid anomaly but who did not meet the specific ascertainment definitions above—including mothers who were diagnosed with goiter (240.x–241.x), thyroiditis (245.x), or thyroid cysts or other thyroid anomalies (246.x); who received radiologic or histologic evaluations of the thyroid gland; who underwent radiation treatments of the head or neck or treatment with radioactive iodine; or who

received a diagnosis of hyper- or hypothyroidism based on ICD-9 codes but were never medicated for the condition—were considered as a separate group, termed "other thyroid disorders". This was done to create, for all analyses, a truly unexposed reference group.

To confirm that our results were not sensitive to the strict ascertainment criteria for hyper- and hypothyroidism, we conducted sensitivity analyses using broader ascertainment definitions, which included having any diagnoses or medication dispensing records for these conditions. For all analyses, first date of thyroid condition recognition was defined as the first date of drug dispensing or diagnosis record, whichever occurred first. Since thyroid abnormalities often develop without clinical symptoms or with nonspecific symptoms, diagnosis and onset of treatment may be delayed. This can possibly explain why a previous analysis using the Danish registries observed positive associations between maternal thyroid conditions diagnosed postnatally and adverse neurodevelopmental outcomes (17). Thus, to ensure complete ascertainment of maternal gestational thyroid status, our main analyses considered all maternal thyroid conditions regardless of when they were first recognized, but in additional analyses we specifically examined conditions first recognized before or after delivery. Additionally, since patients with hyperthyroidism may develop chronic hypothyroidism (41), we excluded mothers with a history of both conditions from main analyses, but included them in secondary analyses.

For analyses that examined gestational hormone levels, we calculated normal reference ranges for maternal thyroid stimulating hormone (TSH) and free thyroxine (fT4) for each gestational week based on the distribution of all available laboratory results among the unexposed group (i.e., mothers who were never diagnosed, treated, or underwent a histologic or radiologic evaluation for a thyroid abnormality; Web Table 1, available at https://doi.org/10.1093/aje/kwab272). We defined abnormal results as those with values in the lower or upper 2.5% of the normal gestation week-specific distribution (as a sensitivity analysis, a 5% cutoff was used). We then used these definitions to create mutually exclusive specific subcategories of maternal thyroid hormone anomalies: subclinical hypothyroidism (high TSH, normal fT4), hypothyroxinemia (normal TSH, low fT4), overt hypothyroidism (high TSH, low fT4), subclinical hyperthyroidism (low TSH, normal fT4), overt hyperthyroidism (low TSH, high fT4), and other rarer classes of thyroid hormone anomalies. We examined hormone levels measured through gestational week 19 since the fetus is completely dependent on maternal thyroid supply during this period before fetal synthesis commences (20, 42–44). Most mothers (94.4%) who were tested for fT4 were also simultaneously tested for TSH. In the rare situations where both tests were not done together, we took the TSH test result closest to the fT4, but we excluded these pregnancies in sensitivity analyses to confirm the results' consistency. Additionally, in 24.9% of pregnancies, several fT4 tests were available. In these cases, we relied on the first abnormal fT4 result, or the earliest fT4 result if all tests were normal, to define anomaly categories. In sensitivity analyses, we restricted to pregnancies with only 1 fT4 test result, and also

considered all sets of fT4 and TSH results by examining non–mutually exclusive thyroid anomaly categories.

Covariate information

We obtained information on the following covariates at time of delivery: calendar year, maternal age, residential district, and socioeconomic status (on a scale of 1 to 10, based on a poverty index assigned for each residential enumeration area—a homogeneous geographical unit of approximately 3,000 people; the Israeli census smallest unit of analysis). We also obtained information on enumeration areas with high proportions of Israeli Arab, Jewish Orthodox, and immigrant populations, since these factors may influence the nature of contact with the medical system and thus the likelihood of having a diagnosis record. Information on infant birth weight and gestational age was obtained from hospital birth records. For children with missing gestational age (1.5%) or birth weight (0.8%) data, we assigned the mean value in our study population, but we excluded this group in sensitivity analyses to confirm the results' consistency. Established clinical reference thresholds for thyroid autoantibodies were used to define thyroid autoimmunity, which was considered with other autoimmune conditions in secondary analyses (Web Table 1 and Web Appendix 1). ICD-9 codes 240.x–246.x were used to collect information on thyroid conditions in all children.

To mitigate potential selection issues in analyses of gestational TSH and fT4 levels, we additionally considered predictors of receiving a thyroid-related test during gestation, which could also be related to thyroid function and ADHD hazard (see Web Appendix 2 for definitions). Specifically, history of diabetes, preeclampsia, autoimmune conditions, use of assisted reproductive therapies, or pregnancy loss; maternal overweight before conception; prior pregnancies ending in premature delivery (<37 weeks) or resulting in a low-birth-weight infant (<2.5 kg); and number of interactions with the medical system in the year before conception. We also obtained information on dispensing of medications that may interfere with thyroid hormone homeostasis.

Statistical analysis

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for ADHD in progeny according to maternal thyroid condition status, employing robust variance estimators to account for multiple births per mother (45). An assumption of this marginal modeling approach is that given the model covariates, the cluster size (i.e., number of progeny/siblings) is uninformative (i.e., independent of the outcome). To test this, we repeated the above analyses using weights (inverse of maternal parity in 1999–2012) (46–48), and results were similar, suggesting uninformative clustering (48, 49). Age (in months) was used as the time scale in the models, with follow-up starting at the child's third birthday and ending at the first date of ADHD recognition, leaving MHS, death, the child's 18th birthday, or end of follow-up (January 1, 2019), whichever occurred first. The proportional hazards

assumption was verified by examining the Schoenfeld residuals. Stratification or interaction with the time scale were used for covariates that did not meet the proportionality assumption. Effect modification by child's sex was evaluated by including terms for interaction with maternal thyroid conditions.

In analyses of gestational fT4 and TSH measurements, we simultaneously evaluated the association between each specific subcategory of gestational thyroid hormone anomaly and ADHD hazard using the same Cox model depicted above. We additionally flexibly examined the change in HR for ADHD per unit change in mean log maternal gestational TSH and fT4 concentrations using mutually adjusted additive Cox models with penalized splines. For analyses of gestational hormones, we excluded 532 children whose mothers were periconceptionally treated with antithyroid medications since use of these medications may result in fetal thyroid insufficiency even in euthyroid mothers (50), but we considered them in sensitivity analyses to confirm the results' consistency. We used R, version 4.0 (R Foundation for Statistical Computing, Vienna, Austria), and SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), for all analyses.

Sensitivity analyses

As described above, we conducted several sensitivity analyses to test the results' consistency to the use of different ascertainment definitions and inclusion criteria. These included using broader ascertainment definitions for ADHD and thyroid conditions; excluding children with missing gestational age or whose mothers used antithyroid medications periconceptionally or had a history of thyroid-related medical procedures, and including children exposed to both maternal hypo- and hyperthyroidism. We also explored models with additional adjustments for maternal thyroid autoimmunity, child thyroid conditions, and possible mediators of the maternal thyroid-ADHD association. Additionally, in analyses of gestational hormones levels, we examined the results' consistency after excluding pregnancies with multiple gestational fT4 tests, with TSH and fT4 tests collected separately, or with records indicative of gestational use of thyroid-interfering medications.

RESULTS

Overall, 27,300 (7.1%) children in our cohort were born to mothers with hypothyroidism, 2,673 (0.7%) to mothers with hyperthyroidism, and 1,462 (0.4%) to mothers who experienced both conditions. Mothers who had thyroid problems had a higher prevalence of metabolic, reproductive, and autoimmune comorbidities compared with mothers without these conditions (Table 1).

We observed that maternal hypothyroidism was associated with a modestly elevated ADHD hazard (adjusted HR = 1.14, 95% CI: 1.10, 1.18; Table 2). Results for hyperthyroidism trended in the opposite direction, but the 95% CI included the null (adjusted HR = 0.93, 95% CI: 0.84,

1.04). Children born to mothers with other thyroid conditions not meeting the hyperthyroidism or hypothyroidism ascertainment definitions also had an elevated ADHD hazard (adjusted HR = 1.07, 95% CI: 1.05, 1.10). We did not find strong evidence for effect modification by child's sex for either hyperthyroidism (P = 0.27) or hypothyroidism (P = 0.14). Effect estimates were overall similar when we specifically examined thyroid conditions first recognized before or after birth (Table 2).

All sensitivity analyses involving additional adjustments and exclusions yielded consistent findings (Web Table 2). No statistically significant association was observed with maternal thyroid autoimmunity nor effect modification by it. Of mothers ever diagnosed with hyperthyroidism, only 20.7% were medicated for the condition (required for our main ascertainment definition), compared with 71.2% of the mothers diagnosed with hypothyroidism. When using the broader ascertainment definitions for these conditions, which included having any diagnosis or medication records, the results were consistent for hypothyroidism (n = 32,697; adjusted HR = 1.14, 95% CI: 1.11, 1.18) but attenuated for hyperthyroidism (n = 11,304; adjusted HR = 0.99, 95% CI: 0.94, 1.05). Similarly, considering all ADHD cases regardless of ADHD medication use resulted in slightly attenuated effect estimates, yet the results for hypothyroidism remained statistically significant (Web Table 3). The HR for ADHD among children of mothers with hypothyroidism who started treatment with levothyroxine preconceptionally and continued receiving this treatment in pregnancy was similar to the main analyses (n = 7,780; adjusted HR = 1.15, 95% CI: 1.08, 1.22). The result was also similar when the above analysis was further restricted to include only children of mothers medicated for hypothyroidism who had normal TSH and fT4 laboratory test results during the first half of pregnancy (n = 1,561; adjusted HR = 1.14, 95% CI: 0.99, 1.32).

TSH results from the first half of gestation were available for 154,969 (40.3%) of the births, of which 42,964 (27.7%) also had fT4 results. An additional 197 births only had a fT4 result. Repeating the analyses of thyroid conditions in the subgroup of children with available TSH and fT4 results yielded effect estimates for hypothyroidism (adjusted HR = 1.19, 95% CI: 1.11, 1.27) and hyperthyroidism (adjusted HR = 0.96, 95% CI: 0.79, 1.17) that were consistent with those observed in the full cohort. Analysis of specific subcategories of maternal thyroid hormone anomaly based on gestational hormone levels indicated an elevated effect estimate for hypothyroxinemia but not the other thyroid hypofunction categories, while effect estimates for hyperfunction anomalies were slightly below 1 (Table 3). Excluding mothers treated periconceptionally with thyroid-hormone-interfering medications, those who had more than 1 available fT4 test result, and those with TSH and fT4 tests collected separately resulted in consistent findings. Consistent results were also obtained when mothers treated periconceptionally with antithyroid medications were included, and when non–mutually exclusive thyroid anomaly categories were considered based on all available sets of fT4 and TSH results. Attenuated effect estimates were observed when a 5% cutoff was used to define abnormal test results (Web Table 4), and when all suspected ADHD cases were considered,

Table 1. Characteristics of Singleton Births According to Maternal Thyroid Status, Maccabi Health Services, Israel, 1999–2012

Characteristic	Hypothyroidism (n = 27,300)		Hyperthyroidism (n = 2,673)		Both Conditions (n = 1,462)		Other Thyroid Disorders (n = 63,297)		Normal Thyroid Function (n = 290,810)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sex										
Male	13,741	50.3	1,349	50.5	765	52.3	31,709	50.1	146,995	50.5
Female	13,559	49.7	1,324	49.5	697	47.7	31,588	49.9	143,815	49.5
District										
North	4,048	14.8	496	18.6	280	19.2	10,946	17.3	47,161	16.2
Sharon	5,213	19.1	538	20.1	270	18.5	12,335	19.5	52,694	18.1
South	3,973	14.6	380	14.2	247	16.9	9,665	15.3	46,562	16.0
Central	7,186	26.3	628	23.5	337	23.1	15,158	24.0	74,190	25.5
Jerusalem and Shfela	6,880	25.2	631	23.6	328	22.4	15,193	24.0	70,203	24.1
Assisted reproductive therapy										
Ovarian stimulation only	2,348	8.6	206	7.7	122	8.3	4,600	7.3	18,472	6.4
In vitro fertilization	1,205	4.4	105	3.9	56	3.8	2,333	3.7	9,428	3.2
Gestational diabetes	2,380	8.7	213	8.0	143	9.8	4,998	7.9	17,893	6.2
Preconception diabetes	251	0.9	14	0.5	15	1.0	341	0.5	849	0.3
Preeclampsia and hypertension	792	2.9	80	2.3	47	3.2	1,814	2.9	6,285	2.2
Preconception excess weight	4,361	16.0	277	10.4	193	13.2	7,837	12.4	29,976	10.3
Preconception autoimmune condition	4,122	15.1	362	13.5	277	19.0	8,551	13.5	32,581	11.2
Tested for thyroid autoimmunity	21,679	79.4	2,270	84.9	1,326	90.7	23,133	36.6	19,122	6.6
Positive thyroid autoimmunity	14,701	53.9	1,540	57.6	1,090	74.7	5,500	8.7	1,645	0.6
Maternal age, years[a]	32.0 (5.1)		32.0 (5.1)		32.0 (4.8)		31.6 (5.1)		30.9 (5.2)	
Socioeconomic status[a,b]	6.1 (2.0)		6.1 (1.9)		6.2 (2.0)		6.1 (1.9)		5.9 (2.0)	
Gestational age, weeks[a,c]	39.2 (1.8)		39.1 (1.8)		39.1 (1.7)		39.2 (1.7)		39.2 (1.7)	
Birth weight, kg[a,d]	3.3 (0.5)		3.3 (0.5)		3.2 (0.5)		3.3 (0.5)		3.3 (0.5)	

[a] Values are expressed as mean (standard deviation).
[b] On a scale of 1 to 10 based on residential enumeration area, as defined in the main text.
[c] Excluding 5,706 children (1.5%) with missing values.
[d] Excluding 3,232 children (0.8%) with missing values.

regardless of ADHD medication use (Web Table 5). When restricting the analysis only to children whose mothers were clinically diagnosed with hypothyroidism, only 188 experienced gestational hypothyroxinemia, and in this group the HR for the association between hypothyroxinemia and ADHD was attenuated (adjusted HR = 1.10, 95% CI: 0.71, 1.71).

In analyses of continuous hormone levels, a weak positive association between TSH levels and ADHD hazard was observed among children of mothers never diagnosed or treated for any thyroid condition. However, when the analysis was similarly restricted to mothers with a hypothyroidism diagnosis, there was no indication for such an association. Analysis of fT4 levels in both groups did not indicate statistically significant associations (Figure 1). Similar observations were made when all suspected ADHD cases were considered, regardless of ADHD medication use (Web Figure 1).

DISCUSSION

Our analysis provides additional evidence concerning a possible link between maternal thyroid dysfunction and progeny ADHD. We observed that children born to mothers with hypothyroidism had an elevated ADHD hazard, while results for maternal hyperthyroidism were less conclusive. However, and importantly, our results also suggest that the observed associations between maternal thyroid hypofunction and ADHD may operate, at least in part, through thyroid-hormone-independent pathways, which are consequently unaffected by treatment with thyroid hormone medications. The above conclusion is supported by several lines of evidence: 1) use of levothyroxine did not attenuate the observed association between maternal hypothyroidism and progeny ADHD; 2) an association with ADHD was still observed, specifically for mothers with predelivery hypothyroidism who were continuously medicated for
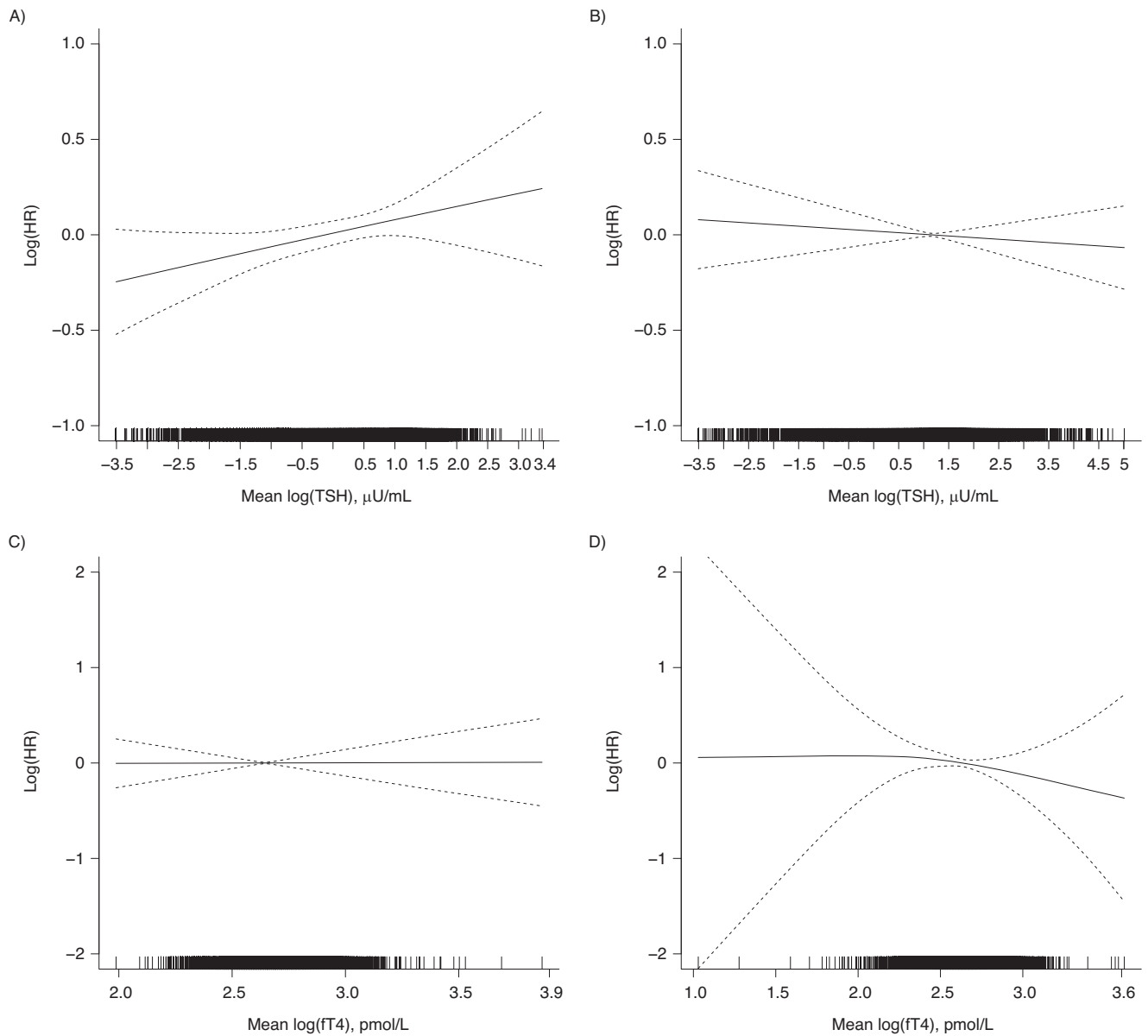
Figure 1. Partial effect plots from an additive Cox proportional hazards model using penalized splines, showing the associations between mean log maternal thyroid stimulating hormone (TSH) (A, B) and free thyroxine (fT4) (C, D) values from early pregnancy (gestational week ≤19) and log HR for progeny attention-deficit hyperactivity disorder (ADHD), Maccabi Health Services, Israel, 1999–2012. Results are shown for children whose mothers were never diagnosed or treated, or never underwent a procedure, for a thyroid condition (A, C; n = 22,069); and for children of mothers diagnosed with hypothyroidism (B, D; n = 11,967). Solid line represents the centered log HRs with confidence intervals represented by the dashed lines. Tick marks along the x-axis indicate mean log laboratory value for individual pregnancies with available test results. All models mutually adjusted for fT4 and TSH levels and excluded 532 children whose mothers used antithyroid medications periconceptionally or during pregnancy. The following covariates were included in the models, either by means of stratification or adjustment: calendar year, maternal age, socioeconomic status, district of residence at birth, residence in enumeration areas with a high proportion of minority or immigrant subpopulations, or prior history of diabetes, preeclampsia, autoimmune conditions, use of assisted reproductive therapies and pregnancy loss/termination; maternal overweight before conception; any prior pregnancies ending in premature delivery (<37 weeks) or resulting in a low-birth-weight infant (<2.5 kg); and number of interactions with the medical system in the year preceding conception. A) Mean log maternal TSH in mothers without thyroid conditions (P value<0.01, estimated DF = 1.1). B) Mean log maternal TSH in mothers with hypothyroidism (P value = 0.48, estimated degrees of freedom (df) = 1.0). C) Mean log maternal fT4 in mothers without thyroid conditions (P value = 0.99, estimated df = 1.0). D) Mean log maternal fT4 in mothers with hypothyroidism (P value = 0.24, estimated df = 1.6).

Table 2. Hazard Ratios for Attention-Deficit Hyperactivity Disorder According to Maternal Thyroid Status Based on Clinical Diagnoses and Medication Use, Maccabi Health Services, Israel, 1999–2012

Thyroid Condition	Total No. in Category	ADHD Cases		Crude Analysis		Adjusted Analysis[a]	
		No.	%	HR	95% CI	HR	95% CI
Normal thyroid	290,810	42,549	14.6	1.00	Referent	1.00	Referent
Ever diagnosed or treated							
Hypothyroid	27,300	4,829	17.7	1.16	1.12, 1.20	1.14	1.10, 1.18
Hyperthyroid	2,673	398	14.9	0.94	0.84, 1.05	0.93	0.84, 1.04
Other thyroid conditions	63,297	10,870	17.2	1.11	1.08, 1.13	1.07	1.05, 1.10
Diagnosed or treated before delivery							
Hypothyroid	15,650	2,464	15.7	1.16	1.11, 1.21	1.16	1.11, 1.21
Hyperthyroid	1,183	148	12.5	0.92	0.78, 1.09	0.94	0.79, 1.11
Other thyroid conditions	13,250	1975	14.9	1.11	1.06, 1.17	1.11	1.05, 1.16
Diagnosed or treated after delivery							
Hypothyroid	11,650	2,365	20.3	1.16	1.11, 1.21	1.11	1.06, 1.16
Hyperthyroid	1,490	250	16.8	0.95	0.83, 1.09	0.93	0.81, 1.06
Other thyroid conditions	50,047	8,895	17.8	1.10	1.08, 1.13	1.07	1.04, 1.10

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; HR, hazard ratio.

[a] Accounting, though stratification or adjustments, for the following covariates as recorded at time of birth: calendar year, maternal age, socioeconomic status, district of residence at birth, and residence in enumeration areas with a high proportion of minority or immigrant subpopulations.

their condition during pregnancy and also had normal TSH and fT4 lab results in early gestation; 3) among mothers diagnosed with hypothyroidism, there was no association between gestational TSH levels and ADHD hazard; and 4) the effect estimate observed for hormone concentration-based hypothyroxinemia was attenuated when the analysis was restricted to mothers with a hypothyroidism diagnosis. The reason these last 2 observations suggest that thyroid hormones may not play a direct role in ADHD etiology is that if hormone levels were the causal factor, then the associations with ADHD should have been observed in all mothers, including those diagnosed with hypothyroidism. The fact that these associations were nullified or substantially attenuated in mothers clinically diagnosed with hypothyroidism suggests that anomalies in maternal gestational thyroid hormones concentrations do not causally affect ADHD hazard but rather serve as proxy indicators for factors related to ADHD via other mechanisms. The observed associations are attenuated in mothers with a hypothyroidism diagnosis because the diagnosis itself is possibly a better proxy for those other ADHD-related factors than are the gestational hormone measurements (that, in the absence of a clinical diagnosis, can similarly act as a proxy, which is possibly why associations with TSH and hypothyroxinemia were more robust among mothers without known thyroid problems). A directed acyclic graph depicting this proposed mechanism is shown in Figure 2. We note that the positive association with ADHD observed for the "other thyroid conditions" group may also support the above hypothesis of an indirect mechanism, as mothers in this group were clinically deemed

not to require treatment with levothyroxine, and thus the observed association is less likely to have been caused by a thyroid hormone insufficiency. Additionally, it may suggest that the latent causal factors possibly causing ADHD can induce other thyroid abnormalities in otherwise euthyroid mothers.

Our results agree with several previous epidemiologic investigations. A large population-based study using data from the Danish registers observed a positive association between maternal hypothyroidism diagnoses and progeny ADHD hazard. A positive association was also reported for hyperthyroidism (51), although, similar to our finding, it was not seen for overt hyperthyrodism in a subsequent analysis using a subgroup of the original cohort with stored gestational serum samples (33). Other analyses that focused on hormone measurements in maternal sera from early gestation specifically linked elevated TSH levels and hypothyroxinemia with worse scores on scales of hyperactivity, externalizing behavior, and inattention, as well as with an increased hazard of receiving a clinical ADHD diagnosis (29, 31–34). This is also consistent with our observations, since these analyses primarily examined mothers without known thyroid conditions, among whom we similarly observed these associations. Our results also agree with findings of 2 randomized clinical trials, which, while not specifically examining ADHD, reported that gestational levothyroxine treatment did not result in improved behavior, cognitive function, or intelligence-test scores in progeny (36, 37). These observations are consistent with our hypothesis that these risks are not directly caused by
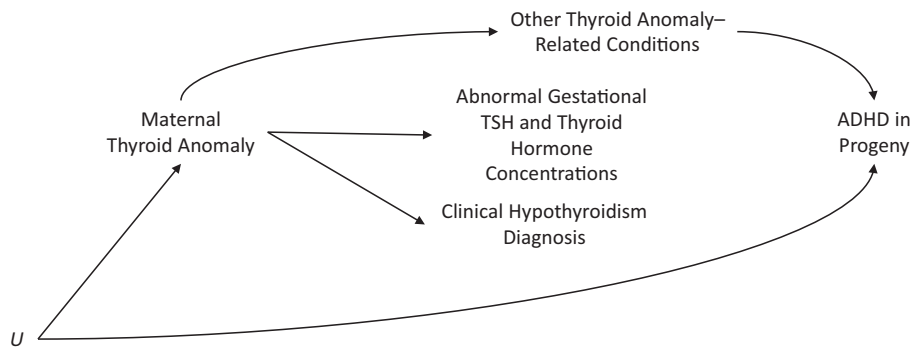
Figure 2.   Proposed simplified causal structure (directed acyclic graph) of the association between maternal thyroid abnormalities and progeny attention-deficit hyperactivity disorder (ADHD). We assume that maternal gestational thyroid stimulating hormone (TSH) and thyroid hormone concentrations are not causally related to ADHD in progeny in most cases. Under this assumption, associations between maternal thyroid anomalies and progeny ADHD are driven either by some latent factor *U*, which affects maternal thyroid function and progeny ADHD through independent mechanisms, or by other, non–thyroid-hormone-mediated effects of the maternal thyroid anomaly. Since the association between abnormal maternal gestational thyroid hormone levels and progeny ADHD is not causal, pharmaceutical treatment effective at mitigating hormone levels would be ineffective at mitigating the risk of ADHD in progeny.

anomalies in gestational thyroid hormone levels, and thus treatments effective at normalizing thyroid hormone levels would still be ineffective at mitigating potential adverse neurodevelopmental risks. Instead, anomalies in thyroid hormone levels indicate the presence of other factors affecting neurodevelopment, which are themselves unaltered by pharmaceutical treatments.

Our results did not change when accounting for thyroid conditions in children, suggesting that shared mother-child genetics linked with thyroid abnormalities do not drive the observations, although other shared genetics could. Alternatively, recent evidence has linked several environmental exposures known to affect thyroid abnormalities with adverse neurodevelopmental outcomes including ADHD

Table 3.   Hazard Ratios for Attention-Deficit Hyperactivity Disorder According to Maternal Thyroid Hormone Anomaly Categories Based on Gestational Laboratory Results (*n* = 42,964), Maccabi Health Services, Israel, 1999–2012

Thyroid Hormone Anomaly Category[a]	No.	ADHD		Minimally Adjusted Model[b]		Fully Adjusted Model[c]	
		No.	%	HR	95% CI	HR	95% CI
Normal lab results	28,678	3,483	12.2	1.00	Referent	1.00	Referent
Subclinical hypothyroidism (high TSH, normal fT4)	6,010	797	13.3	1.05	0.97, 1.14	1.03	0.94, 1.12
Hypothyroxinemia (normal TSH, low fT4)	782	132	16.9	1.35	1.13, 1.61	1.28	1.06, 1.54
Overt hypothyroidism (high TSH, low fT4)	1,299	190	14.6	1.01	0.87, 1.18	0.99	0.84, 1.16
Subclinical hyperthyroidism (low TSH, normal fT4)	3,416	418	12.2	0.92	0.83, 1.02	0.97	0.87, 1.08
Overt hyperthyroidism (low TSH, high fT4)	1,514	185	12.2	0.90	0.78, 1.05	0.91	0.79, 1.06
Other classes of thyroid hormone anomalies[d]	1,265	174	13.8	0.93	0.79, 1.09	0.92	0.78, 1.08

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; HR, hazard ratio; TSH, thyroid stimulating hormone; fT4, free thyroxine.

[a] See methods and Web Table 1 for definitions of abnormal TSH and fT4.

[b] Accounting, though stratification or adjustments, for the following covariates as recorded at time of birth: calendar year, maternal age, socioeconomic status, district of residence at birth, and residence in enumeration areas with a high proportion of minority or immigrant subpopulations.

[c] Additionally accounting, though stratification or adjustments, for predictors of receiving a thyroid-related test during gestation, which could also relate to thyroid function and ADHD hazard, to mitigate possible selection effects (prior history of: diabetes, preeclampsia, autoimmune conditions, use of assisted reproductive therapies and pregnancy loss/termination; maternal overweight before conception; any prior pregnancies ending in premature delivery (<37 weeks) or resulting in low-birth-weight infant (<2.5 kg); and number of interactions with the medical system in the year preceding conception).

[d] Low TSH and low fT4 (e.g., secondary hypothyroidism), high TSH and high fT4 (e.g., thyroid resistance), and high fT4 and normal TSH (e.g., hyperthyroxinemia).

(52–63), and some preliminary evidence suggests that these neurodevelopmental effects may operate through thyroid-hormone-independent pathways (27). Such environmental factors could also result in the pattern of our findings.

There are several limitations to our analysis. While our hypothesis of no causal relationship between maternal thyroid hormone concentrations and progeny ADHD fits the pattern of our results and helps explain the discrepancy between the epidemiologic observations and those of the clinical trials, we cannot completely rule out the possibility that thyroid hormones do have etiological roles in some situations. For example, while attenuated, an elevated effect estimate for hypothyroxinemia was still observed when restricting the analysis to mothers clinically diagnosed with hypothyroidism. Additionally, since TSH tests are often the primary screening tool for thyroid anomalies, we likely missed some mothers with abnormal fT4 levels who had normal TSH test results. That said, results of our main analysis were consistent when models were restricted to only pregnancies with available test results for both TSH and fT4, and our findings were also consistent with those reported in other epidemiologic investigations. Also, while we observed that levothyroxine treatment was ineffective at mitigating ADHD hazard, it is possible that the lack of treatment effect was due to inadequate dosage. However, effect estimates remained elevated even when we restricted the analysis to mothers whose treatment efficacy was confirmed by gestational laboratory measurements. That said, it is still possible that treatment could be effective for some specific thyroid hormone anomalies, such as hypothyroxinemia. However, similar to other previous investigations (29, 33), measured hypothyroxinemia was relatively uncommon in our cohort, suggesting that even if treatment is effective for this condition, its attributable risk reduction could be minimal. Finally, as is often true for analyses examining possible risk factors for developmental outcomes, our results are conditional on a live birth. That is, if the likelihood of a live birth is affected by maternal thyroid disorders, then the effect estimates we observed for ADHD among children who were born could be different from the effect estimates we would have observed in the pseudopopulation where thyroid disease had no effect on the probability of a live birth (64, 65).

Overall, our study has important implications. Maternal thyroid hypofunction may serve as an indicator for children who have a higher likelihood of developing ADHD. However, the underlying mechanisms driving these associations appear to operate independently of maternal gestational thyroid hormone concentrations, and thus be unaffected by pharmaceutical treatments. Exogenous and endogenous factors known to disrupt thyroid function should be examined for possible independent effects on ADHD.

REFERENCES

1. Bloom B, Jones LI, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2012. *Vital Health Stat 10*. 2013;(258):1–81.
2. Danielson ML, Bitsko RH, Ghandour RM, et al. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. *J Clin Child Adolesc Psychol*. 2018;47(2):199–212.
3. Davidovitch M, Koren G, Fund N, et al. Challenges in defining the rates of ADHD diagnosis and treatment: trends over the last decade. *BMC Pediatr*. 2017;17(1):218.
4. Birnbaum HG, Kessler RC, Lowe SW, et al. Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. *Curr Med Res Opin*. 2005;21(2):195–205.
5. Loe IM, Feldman HM. Academic and educational outcomes of children with ADHD. *J Pediatr Psychol*. 2007;32(6):643–654.
6. Marques JC, Oliveira JA, Goulardins JB, et al. Comparison of child self-reports and parent proxy-reports on quality of life of children with attention deficit hyperactivity disorder. *Health Qual Life Outcomes*. 2013;11(1):186.
7. Das D, Cherbuin N, Butterworth P, et al. A population-based study of attention deficit/hyperactivity disorder symptoms and associated impairment in middle-aged adults. *PLoS One*. 2012;7(2):e31500.
8. Fletcher J, Wolfe B. Long-term consequences of childhood ADHD on criminal activities. *J Ment Health Policy Econ*. 2009;12(3):119–138.
9. Knecht C, de Alvaro R, Martinez-Raga J, et al. Attention-deficit hyperactivity disorder (ADHD), substance use disorders, and criminality: a difficult problem with complex solutions. *Int J Adolesc Med Health*. 2015;27(2):163–175.
10. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. *Acta Paediatr*. 2007;96(9):1269–1274.

11. Agarwal R, Goldenberg M, Perry R, et al. The quality of life of adults with attention deficit hyperactivity disorder: a systematic review. *Innov Clin Neurosci*. 2012;9(5–6):10–21.

12. Skoglund C, Chen Q, Franck J, et al. Attention-deficit/ hyperactivity disorder and risk for substance use disorders in relatives. *Biol Psychiatry*. 2015;77(10):880–886.

13. Charach A, Yeung E, Climans T, et al. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. *J Am Acad Child Adolesc Psychiatry*. 2011;50(1):9–21.

14. Lee SS, Humphreys KL, Flory K, et al. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev*. 2011;31(3): 328–341.

15. Groenman AP, Oosterlaan J, Rommelse N, et al. Substance use disorders in adolescents with attention deficit hyperactivity disorder: a 4-year follow-up study. *Addiction*. 2013;108(8):1503–1511.

16. McGough JJ, Smalley SL, McCracken JT, et al. Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. *Am J Psychiatry*. 2005; 162(9):1621–1627.

17. Andersen SL, Laurberg P, Wu CS, et al. Attention deficit hyperactivity disorder and autism spectrum disorder in children born to mothers with thyroid dysfunction: a Danish nationwide cohort study. *BJOG*. 2014;121(11):1365–1374.

18. Andersen SL, Olsen J, Laurberg P. Foetal programming by maternal thyroid disease. *Clin Endocrinol (Oxf)*. 2015;83(6): 751–758.

19. Moog NK, Entringer S, Heim C, et al. Influence of maternal thyroid hormones during gestation on fetal brain development. *Neuroscience*. 2017;342:68–100.

20. Morreale de Escobar G, Obregon M, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol*. 2004;151(suppl 3):U25–U37.

21. Janssen BG, Saenen ND, Roels HA, et al. Fetal thyroid function, birth weight, and in utero exposure to fine particle air pollution: a birth cohort study. *Environ Health Perspect*. 2017;125(4):699–705.

22. Park C, Choi W, Hwang M, et al. Associations between urinary phthalate metabolites and bisphenol a levels, and serum thyroid hormones among the Korean adult population—Korean National Environmental Health Survey (KoNEHS) 2012-2014. *Sci Total Environ*. 2017;584-585: 950–957.

23. Colborn T. Neurodevelopment and endocrine disruption. *Environ Health Perspect*. 2004;112(9):944–949.

24. Hartoft-Nielsen ML, Boas M, Bliddal S, et al. Do thyroid disrupting chemicals influence Foetal development during pregnancy? *J Thyroid Res*. 2011;2011:342189.

25. Kajta M, Wojtowicz AK. Impact of endocrine-disrupting chemicals on neural development and the onset of neurological disorders. *Pharmacol Rep*. 2013;65(6): 1632–1639.

26. Ozzola G. Pollution, the thyroid and neurodevelopment. *Clin Ter*. 2016;167(6):191–197.

27. Engel SM, Villanger GD, Nethery RC, et al. Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian mother and child cohort. *Environ Health Perspect*. 2018; 126(5):057004.

28. Forns J, Verner MA, Iszatt N, et al. Early life exposure to perfluoroalkyl substances (PFAS) and ADHD: a meta-analysis of nine European population-based studies. *Environ Health Perspect*. 2020;128(5):057002.

29. Modesto T, Tiemeier H, Peeters RP, et al. Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. *JAMA Pediatr*. 2015;169(9):838–845.

30. Alvarez-Pedrerol M, Ribas-Fito N, Torrent M, et al. TSH concentration within the normal range is associated with cognitive function and ADHD symptoms in healthy preschoolers. *Clin Endocrinol (Oxf)*. 2007;66(6):890–898.

31. Ghassabian A, Bongers-Schokking JJ, Henrichs J, et al. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. *Pediatr Res*. 2011;69(5):454–459.

32. Oostenbroek MHW, Kersten RHJ, Tros B, et al. Maternal hypothyroxinaemia in early pregnancy and problem behavior in 5-year-old offspring. *Psychoneuroendocrinology*. 2017;81: 29–35.

33. Andersen SL, Andersen S, Vestergaard P, et al. Maternal thyroid function in early pregnancy and child neurodevelopmental disorders: a Danish Nationwide case-cohort study. *Thyroid*. 2018;28(4):537–546.

34. Pakkila F, Mannisto T, Pouta A, et al. The impact of gestational thyroid hormone concentrations on ADHD symptoms of the child. *J Clin Endocrinol Metab*. 2014; 99(1):E1–E8.

35. Levie D, Korevaar TIM, Mulder TA, et al. Maternal thyroid function in early pregnancy and child attention-deficit hyperactivity disorder: an individual-participant meta-analysis. *Thyroid*. 2019;29(9):1316–1326.

36. Casey BM, Thom EA, Peaceman AM, et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. *N Engl J Med*. 2017;376(9):815–825.

37. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med*. 2012;366(6):493–501.

38. Wolraich ML, Hagan JF, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144(4):e20192528.

39. Criteria for diagnosing ADHD in children, adolescents, and adults [in Hebrew]. 2010. https://www.health.gov.il/hozer/ mr40_2010.pdf. Accessed Dec 21 2020.

40. Mignot EJ. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. *Neurotherapeutics*. 2012;9(4): 739–752.

41. Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):315–389.

42. Berbel P, Mestre JL, Santamaria A, et al. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid*. 2009;19(5):511–519.

43. Calvo RM, Jauniaux E, Gulbis B, et al. Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. *J Clin Endocrinol Metab*. 2002;87(4):1768–1777.

44. Lavado-Autric R, Auso E, Garcia-Velasco JV, et al. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. *J Clin Invest*. 2003; 111(7):1073–1082.

45. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc*. 1989;84(408): 1074–1078.

46. Seaman SR, Pavlou M, Copas AJ. Methods for observed-cluster inference when cluster size is informative:

a review and clarifications. *Biometrics*. 2014;70(2): 449–456.

47. Williamson JM, Datta S, Satten GA. Marginal analyses of clustered data when cluster size is informative. *Biometrics*. 2003;59(1):36–42.

48. Williamson JM, Kim H-Y, Manatunga A, et al. Modeling survival data with informative cluster size. *Stat Med*. 2008; 27(4):543–555.

49. Yelland LN, Sullivan TR, Pavlou M, et al. Analysis of randomised trials including multiple births when birth size is informative. *Paediatr Perinat Epidemiol*. 2015;29(6): 567–575.

50. Atkins P, Cohen SB, Phillips BJ. Drug therapy for hyperthyroidism in pregnancy: safety issues for mother and fetus. *Drug Saf*. 2000;23(3):229–244.

51. Andersen S, Laurberg P, Wu C, et al. Attention deficit hyperactivity disorder and autism spectrum disorder in children born to mothers with thyroid dysfunction: a Danish nationwide cohort study. *BJOG*. 2014;121(11): 1365–1374.

52. Engel SM, Zhu C, Berkowitz GS, et al. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. *Neurotoxicology*. 2009;30(4):522–528.

53. Cho SC, Bhang SY, Hong YC, et al. Relationship between environmental phthalate exposure and the intelligence of school-age children. *Environ Health Perspect*. 2010;118(7): 1027–1032.

54. Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect*. 2010;118(4): 565–571.

55. Yolton K, Xu Y, Strauss D, et al. Prenatal exposure to bisphenol a and phthalates and infant neurobehavior. *Neurotoxicol Teratol*. 2011;33(5):558–566.

56. Whyatt RM, Liu X, Rauh VA, et al. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. *Environ Health Perspect*. 2012;120(2):290–295.

57. Kobrosly RW, Evans S, Miodovnik A, et al. Prenatal phthalate exposures and neurobehavioral development scores in boys and girls at 6–10 years of age. *Environ Health Perspect*. 2014;122(5):521–528.

58. Gascon M, Valvi D, Forns J, et al. Prenatal exposure to phthalates and neuropsychological development during childhood. *Int J Hyg Environ Health*. 2015;218(6):550–558.

59. Lien YJ, Ku HY, Su PH, et al. Prenatal exposure to phthalate esters and behavioral syndromes in children at 8 years of age: Taiwan Maternal and Infant Cohort Study. *Environ Health Perspect*. 2015;123(1):95–100.

60. Markevych I, Tesch F, Datzmann T, et al. Outdoor air pollution, greenspace, and incidence of ADHD: a semi-individual study. *Sci Total Environ*. 2018;642: 1362–1368.

61. Shih P, Huang CC, Pan SC, et al. Hyperactivity disorder in children related to traffic-based air pollution during pregnancy. *Environ Res*. 2020;188:109588.

62. Huang PC, Kuo PL, Guo YL, et al. Associations between urinary phthalate monoesters and thyroid hormones in pregnant women. *Hum Reprod*. 2007;22(10):2715–2722.

63. Meeker JD, Ferguson KK. Relationship between urinary phthalate and bisphenol a concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES) 2007–2008. *Environ Health Perspect*. 2011;119(10): 1396–1402.

64. Raz R, Kioumourtzoglou M-A, Weisskopf MG. Live-birth bias and observed associations between air pollution and autism. *Am J Epidemiol*. 2018;187(11): 2292–2296.

65. Leung M, Kioumourtzoglou M-A, Raz R, et al. Bias due to selection on live births in studies of environmental exposures during pregnancy: a simulation study. *Environ Health Perspect*. 2021;129(4):047001.