Original Investigation

Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children

Thiago Modesto, MSc; Henning Tiemeier, MD, PhD; Robin P. Peeters, MD, PhD; Vincent W. V. Jaddoe, MD, PhD; Albert Hofman, MD, PhD; Frank C. Verhulst, MD, PhD; Akhgar Ghassabian, MD, PhD

IMPORTANCE Maternal thyroid hormone insufficiency during pregnancy can affect children's cognitive development. Nevertheless, the behavioral outcomes of children exposed prenatally to mild thyroid hormone insufficiency are understudied.

OBJECTIVE To examine whether exposure to maternal mild thyroid hormone insufficiency in early pregnancy was related to symptoms of attention-deficit/hyperactivity disorder (ADHD) in children at 8 years of age.

DESIGN, SETTING, AND PARTICIPANTS The study was embedded within the Generation R, a population-based birth cohort in the Netherlands. Children in the Generation R Study are followed up from birth (April 1, 2002, through January 31, 2006) until young adulthood. Of the 4997 eligible mother-child pairs with data on maternal thyroid levels (excluding twins), 3873 pairs of children and caregivers (77.5%) visited the Generation R research center for in-depth assessments and were included in the main analyses. Data collection in Generation R started December 1, 2001 (enrollment of pregnant women), and is ongoing. For this study, we used the data that were collected until January 1, 2014. Data analyses started on January 31 and finished June 30, 2014.

MAIN OUTCOMES AND MEASURES Maternal hypothyroxinemia, characterized by low levels of free thyroxine coexisting with reference thyrotropin levels, and children's symptoms of ADHD. Maternal thyroid hormone levels (thyrotropin, free thyroxine, thyroid peroxidase antibodies) were measured at a mean (SD) of 13.6 (1.9) weeks of gestation. Children's ADHD symptoms were assessed at 8 years of age using the Conners' Parent Rating Scale–Revised Short Form; higher scores indicate more ADHD symptoms (possible range, 0-36).

RESULTS Maternal hypothyroxinemia (n = 127) in early pregnancy was associated with higher scores for ADHD symptoms in children at 8 years of age after adjustments for child and maternal factors (ie, sex, ethnicity, maternal age, maternal educational level, and income) (increase in ADHD scores, 7% [95% CI, 0.3%-15%]). The results remained essentially unchanged when women with elevated levels of thyroid peroxidase antibodies were excluded from the analyses (increase in ADHD scores, 8% [95% CI, 1%-16%]). Additional adjustment for children's IQ or comorbid autistic symptoms attenuated the association (increase in ADHD scores adjusted for autistic symptoms, 7% [95% CI, 1%-15%]; increase in ADHD scores adjusted for IQ, 6% [95% CI, 1%-14%]).

CONCLUSIONS AND RELEVANCE Children exposed to maternal hypothyroxinemia in early pregnancy had more ADHD symptoms, independent of confounders. This finding suggests that intrauterine exposure to insufficient thyroid hormone levels influences neurodevelopment in offspring.

JAMA Pediatr. 2015;169(9):838-845. doi:10.1001/jamapediatrics.2015.0498
Published online July 6, 2015.

Supplemental content at jamapediatrics.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Akhgar Ghassabian, MD, PhD, Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Centre–Sophia Children's Hospital, PO Box 2060, 3000 CB Rotterdam, the Netherlands (a.ghassabian@erasmusmc.nl).

Early stages of fetal life are characterized by fundamental processes that occur in the central nervous system, including cell migration, differentiation, and induction of neural tissue in the neocortex.[1] Thyroid hormones are crucial for neural migration and differentiation in the cerebral cortex and hippocampus.[2,3] Before the onset of thyroid hormone production by the fetus in midgestation, fetal brain development relies on maternal thyroid hormones.[2,3]

Women with normal thyroid function often have a transient and mild decrease in free thyroid hormone levels during pregnancy, without a rise in the thyrotropin level.[4] This condition is known as *hypothyroxinemia*. Many epidemiologic studies have shown that maternal hypothyroxinemia is associated with adverse neurocognitive outcomes in children, such as language delay,[4] delayed cognitive function,[4,5] reduced performance in psychomotor skills[5] in toddlers, and autistic traits[6] and lower IQ[7] in older children. Furthermore, recent reports show that the presence of hypothyroxinemia in early pregnancy might be related to behavioral problems of the offspring, in particular symptoms of attention-deficit/hyperactivity disorder (ADHD).[4,8] In a previous publication of the Generation R Study, Ghassabian et al[4] showed that higher levels of maternal thyrotropin in early pregnancy were associated with higher scores of externalizing problems. In addition, Päkkilä et al[9] found that maternal thyrotropin levels during early pregnancy were associated with ADHD symptoms, but only in girls. Nevertheless, previous studies[4-9] faced methodological issues, such as small sample size, lack of power, retrospective design, relatively short follow-up, and nonspecific outcomes.

Attention-deficit/hyperactivity disorder is a childhood psychiatric disorder consisting of problems in behavior, cognition, and social abilities. If not properly managed, ADHD can lead to numerous complications. Reduced attention and poor organizational skills in school can lead to academic underperformance and even failure. Individuals are more likely to experience accidents (eg, driving accidents). Attention-deficit/hyperactivity disorder represents a risk factor for self-medication or experimentation with drugs, which might lead to their abuse or addiction. Patients are also more likely to present with pathologic gambling and Internet addictions.[10] Although genetic factors are involved, many environmental factors are also shown to increase the risk for ADHD in children (eg, prematurity or smoking in the mother).[11]

In this study, we examined the relation between maternal hypothyroxinemia in early pregnancy and the parental rating of ADHD symptoms in children at 8 years of age, controlling for maternal and child characteristics. We hypothesized that maternal hypothyroxinemia in early pregnancy increases the risk for ADHD symptoms in their children.

At a Glance

- We examined whether exposure to maternal mild thyroid hormone insufficiency in early pregnancy was related to symptoms of attention-deficit/hyperactivity disorder (ADHD) in children at 8 years of age.
- Maternal hypothyroxinemia in early pregnancy, characterized by low levels of free thyroxine coexisting with reference thyrotropin levels, was associated with a 7% increase in ADHD symptom scores in children at 8 years of age.
- Additional adjustment for a child's IQ or comorbid autistic symptoms did not influence the association of maternal hypothyroxinemia and children's ADHD symptoms.

Methods

Participants

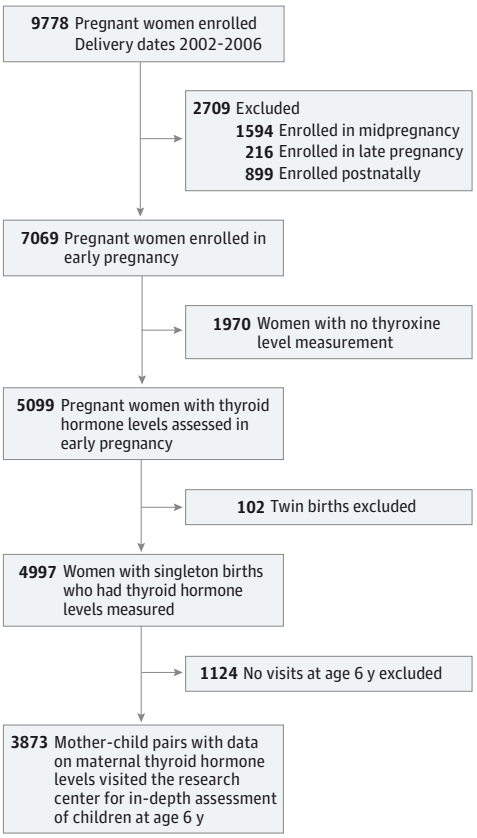
This study was embedded in the Generation R Study, a population-based birth cohort in Rotterdam, the Netherlands.[12] The Generation R Study follows up children from fetal life onward. Pregnant women with a predicted delivery date from April 1, 2002, through January 31, 2006, were invited to participate. The Medical Ethics Committee of the Erasmus Medical Centre approved the study. All adult participants provided written informed consent, and confidentiality was guaranteed. Data collection in Generation R started December 1, 2001 (enrollment of pregnant women), and is ongoing. For this study, we used the data collected until January 1, 2014. Data analyses started on January 31 and finished June 30, 2014.

In total, 9778 pregnant women were enrolled in the study (participation rate, 61.0%), of whom 8879 were enrolled in pregnancy (7069 in early pregnancy, 1594 in midpregnancy, and 216 in late pregnancy). The remaining women were enrolled in the postnatal period and were not eligible for this study. Data on thyroid hormone levels were available in 5099 participants. We excluded 102 women who gave birth to twins owing to possible differences in the neurodevelopment of children born to singleton vs twin pregnancies. This exclusion left 4997 participant pairs eligible for follow-up. Of these, 3873 children (77.5%) and their caregivers visited the Generation R research center for in-depth assessments when the children were aged 5 to 8 years. The remaining 1124 participant pairs were not followed up (**Figure**). Thyroid hormone levels were not different between mother-child pairs included in the study and those who were excluded because of missing child data (free thyroxine [FT_4] levels, 1.19 vs 1.18 ng/dL [P = .33; to convert to picomoles per liter, multiply by 12.871]; thyrotropin levels, 1.60 vs 1.62 mIU/L [P = .78]).

Maternal Thyroid Hormone Levels

Maternal blood samples were collected at the first prenatal visit (mean [SD] gestational age, 13.6 [1.9] weeks; range, 6.6-17.9 weeks). Within 24 hours of collection, the plasma was stored at −70°C and processed in batches during 6 months. The samples were analyzed for levels of FT_4 and thyrotropin using chemiluminescence assays (Vitros ECi immunodiagnostic system; Ortho Clinical Diagnostics). In our laboratory, the reference range for FT_4 levels in nonpregnant women is 0.85 to 1.94 ng/dL; interassay and intra-assay coefficients of variation range from 4.7% to 5.4% and 1.4% to 2.7%, respectively. The reference range for maternal thyrotropin levels in pregnancy was defined as 0.1 to 2.5 mIU/L, as recommended by the Endocrine Society[13] and the American Thyroid Association

Figure. Flowchart of Study Participants



Data were obtained from the Generation R Study, a population-based birth cohort in Rotterdam, the Netherlands.

Guideline.[14] The interassay and intra-assay coefficients of variation ranged from 2.5% to 4.1% and 1.0% to 1.2%, respectively. Maternal hypothyroxinemia (n = 127) was defined as thyrotropin levels of 0.1 to 2.5 mIU/L coexisting with FT_4 levels below the 5th percentile of the sample (ie, <0.85 ng/dL).[14] Maternal levels of thyroid peroxidase antibodies were measured using a commercially available immunoassay (Phadia 250; Thermo Scientific); results were defined as positive when plasma concentrations were 100 IU/mL or greater. According to these international guidelines,[13,14] we also calculated reference ranges for levels of thyrotropin (0.03-4.04 mIU/L) and FT_4 (0.81-1.71 ng/dL) based on our own study sample to define maternal subclinical hypothyroidism and hypothyroxinemia and examined whether the associations were independent of the cutoff choice. Thyroid hormone levels were evaluated after the children's birth, and the parents were not informed about the results, with the exception of 1 clinical case that was excluded from the study.

Children's ADHD Symptoms

When the children were 8 years of age (mean [SD] age, 8.1 [0.2] years; range, 7.5-10.5 years), mothers reported on their children's ADHD symptoms using the Conners' Parent Rating Scale-Revised Short Form (CPRS-R:S). The CPRS-R:S is a 27-item questionnaire that provides a standard measure for the assessment of behavioral problems in children, including symptoms of ADHD and oppositional defiant disorder. The CPRS-R:S includes the following 4 scales: Cognitive Problems/Inattention (6 items), Hyperactivity (6 items), Oppositional (6 items), and the ADHD index (ADHDi; 12 items).[15] The items in the Cognitive Problems/Inattention, Hyperactivity, and Oppositional scales were derived by Conners et al[15] from exploratory factor analyses of the items in the long form and were used in the short form if the item loadings were higher than 0.40. The selection of items on the ADHDi scale specifically discriminated children with ADHD from matched control individuals.[16] The scales are shown to have a good reliability and internal consistency and have been used previously in the Dutch population.[17,18] In our sample, the internal consistency coefficients for the scales were as following: 0.89 for the Cognitive Problems/Inattention scale, 0.79 for the Hyperactivity scale, 0.81 for the Oppositional scale, and 0.92 for the ADHDi scale. Possible scores for the Cognitive Problems/Inattention scale, Hyperactivity scale, and Oppositional scale range from 0 to 18; for the ADHDi scale, 0 to 36. Higher scores indicate more problems.

In a subsample of the Generation R Study, trained research assistants interviewed the parents when the children were a mean (SD) age of 6.7 (0.6) years (n = 689; age range, 5.5-9.5 years) using the Diagnostic Interview Schedule for Children-Young Child version.[19] This subsample consisted of the children who scored in the top 15th percentile of the Child Behavior Checklist for Toddlers total score and a random selection of controls. In this subsample, we compared the CPRS-R:S scores of children with a diagnosis of ADHD or oppositional defiant disorder (defined by findings on the Diagnostic Interview Schedule for Children-Young Child version) and children with no ADHD or oppositional defiant disorder. Children classified as positive for ADHD had a mean (SD) ADHDi score of 23 (8.6) and those classified as negative had a mean (SD) ADHDi score of 10 (7.6). This difference was statistically significant ($P < .001$).

Covariates

The choice of potential confounders was performed a priori and on the basis of background knowledge about the study question.[4-7] Information on maternal age at enrollment, parity, educational level, marital status, and family income and on child age, ethnic background, and sex were obtained from questionnaire and medical records. The child's ethnic background was based on the country of birth of both parents. Maternal educational level was defined as the highest completed schooling. Maternal smoking was assessed using questionnaires at enrolment, in midpregnancy, and in late pregnancy. Family income was defined by the total net monthly income of the household. Maternal body mass index in early pregnancy was calculated based on maternal height and weight at enrolment. Maternal psychopathologic symptoms were assessed during pregnancy using the Dutch version of the Brief Symptom Inventory.[20]

Various test batteries and rating scales were used to further evaluate other aspects of behavior and cognition in children to 8 years of age (eTable 1 in the Supplement). Parents re-

ported on their children's autisticlike behaviors at 6 years of age using a short form of the Social Responsiveness Scale.[21] Children's nonverbal IQ was assessed using 2 subsets of a well-validated Dutch nonverbal intelligence test.[22]

Statistical Analysis

Children were included in the analysis if data on maternal FT_4 levels in pregnancy were available and they had visited the research center from 5 to 8 years of age (includes 3873 active pairs of respondents). The percentage of missing data for covariates was less than 10%, except for maternal psychopathologic symptoms in pregnancy (607 pairs [15.7%]), autistic symptoms (1045 pairs [27.0%]), and household income (677 pairs [17.5%]). One thousand three hundred forty-five pairs (34.7%) were missing data for the ADHDi and Oppositional scores in the CPRS-R:S. Missing values in covariates and outcome measures (ADHDi and Oppositional scores) were imputed using multiple imputations only if another behavioral measure was available (eTable 1 in the Supplement). All covariates were used as predictors in the multiple imputations, and we used additional behavioral information from previous assessment waves. We created 30 copies of the original data set, with missing values replaced by ones randomly generated from predictive distribution on the basis of the correlation between the variables. Effect size and confidence intervals were estimated by taking the mean effect size of the 30 imputed sets (pooled data set). The results of a complete case analysis are presented in eTable 2 in the Supplement.

Maternal thyroid function was the determinant in all analyses. Continuous measures of thyrotropin and FT_4 levels were divided by their SDs so that their associations with the outcome can be compared easily. We included maternal hypothyroxinemia as a categorical determinant in the analyses. We examined associations of maternal thyroid function with children's ADHDi and Oppositional scores using linear regression. The ADHDi and Oppositional scores were transformed using natural logarithm to satisfy the assumption of normality. Regression coefficients were exponentiated and converted to percentage differences.

Models were adjusted for the child's age, sex, ethnic background, and parity and for maternal educational level, history of smoking, psychopathologic symptoms in pregnancy, age, marital status, household income, body mass index, and gestational age at the time of blood sampling in pregnancy. These models were additionally adjusted for children's autistic symptoms, nonverbal IQ, or Oppositional scores (or ADHDi scores in case the Oppositional scores were the outcomes) in separate steps to test the specificity of the findings.

Sex differences are well established in ADHD symptoms[23]; also, a recent study reported a sex-specific relation between maternal thyroid insufficiency during pregnancy and ADHD symptoms in the offspring.[9] Therefore, we explored an interaction between children's sex and maternal thyroid function in relation to ADHDi or Oppositional scores. We also reran the analyses in a subsample excluding women with positive thyroid peroxidase antibody findings (n = 288) and separately excluding pregnant women who received medication for any thyroid-related condition (n = 30) to explore the effect of maternal thyroid function on a child's behavior independently of these factors. Furthermore, we performed a sensitivity analysis in a sample of women with FT_4 values measured in the first trimester of pregnancy (n = 1733). In the subsample of children with data on the Diagnostic Interview Schedule for Children–Young Child version and CPRS-R:S, we performed an independent-sample *t* test to compare the ADHDi or Oppositional scores between children with a diagnosis of ADHD (or oppositional defiant disorder) and healthy controls. Statistical analyses were performed using commercially available software (SPSS, version 22.0; IBM Statistics).

Table 1. Maternal Characteristics

Characteristic	No. Valid for Observation	Data[a]
Age, mean (SD), y	3873	30.0 (5.0)
Married or cohabitating	3659	3251 (88.8)
BMI during pregnancy, median (IQR)	3851	23.5 (21.5-26.3)
Parity, primipara	3851	2286 (59.4)
Educational level	3689	
Primary		738 (20.0)
Secondary		1976 (53.6)
Higher		975 (26.4)
Family income, €	3196	
<1200		200 (6.3)
1200-2000		508 (15.9)
>2000		2488 (77.8)
Smoking during pregnancy	3806	
Never		2893 (76.0)
Until pregnancy was known		333 (8.7)
Continued during pregnancy		580 (15.2)
Maternal prenatal psychopathologic symptom score, median (IQR)[b]	3266	0.2 (0.1-0.3)
Gestational age at blood sampling, median (IQR), wk	3873	13.4 (12.2-14.9)
Thyrotropin level, median (IQR), mIU/L	3644	1.4 (0.9-2.1)
Free T_4 level, ng/dL	3873	15.3 (3.7)
Hypothyroxinemia present[c]	3687	127 (3.4)
TPO-Abs, positive finding[d]	3627	183 (5.0)
Thyroid medication used	3873	30 (0.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; T_4, thyroxine; TPO-Abs, thyroid peroxidase antibodies.

SI conversion factor: To convert free T_4 to picomoles per liter, multiply by 12.871.

[a] Unless otherwise indicated, data are expressed as number (percentage) of participants (including 3873 participant pairs). Percentages have been rounded and may not total 100.

[b] Calculated using the Dutch version of the Brief Symptom Inventory.[20] Possible scores range from 0 to 1; higher scores indicate more problems.

[c] Defined as free T_4 concentrations below the fifth percentile (ie, <0.85 ng/dL) and thyrotropin levels within the reference range.

[d] Levels of greater than 100 IU/mL were defined as positive.

Results

The characteristics of the study population are presented in **Table 1** and **Table 2**. In this sample, 738 mothers (20.0%) had only

Table 2. Child Characteristics

Characteristic	No. Valid for Observation	Data[a]
Male sex	3873	1935 (50.0)
Ethnicity	3820	
Dutch		2301 (60.2)
Other Western		350 (9.2)
Non-Western		1169 (30.6)
Birth weight, mean (SD), g	3870	3436 (546)
Gestational age at birth, median (IQR), wk	3873	40.0 (39.3-41.0)
CPRS-R:S data[b]		
Age, median (IQR), y	2588	8.1 (8.0-8.3)
ADHDi score, median (IQR)	2528	6.0 (2.0-10.0)
Oppositional scale score, median (IQR)	2534	3.0 (1.0-5.0)
Social Responsiveness Scale[c]		
Age, median (IQR), y	2888	6.0 (5.8-6.3)
Total score, median (IQR)	2828	0.2 (0.1-0.3)
Nonverbal IQ[d]		
Age, median (IQR), y	3873	6.0 (5.8-6.3)
IQ score	3576	101.7 (14.9)
Diagnostic Interview Schedule for Children-Young Child version[e]		
Age, median (IQR), y	689	6.5 (6.3-7.0)
ADHD, %	689	39 (5.7)
ODD, %	686	119 (17.3)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHDi, ADHD index; CPRS-R:S, Conner's Parent Rating Scale–Revised Short Form; IQR, interquartile range; ODD, oppositional defiant disorder.

[a] Unless otherwise indicated, data are expressed as number (percentage) of participants (including 3873 participant pairs). Percentages have been rounded and may not total 100.

[b] Possible scores for the ADHDi range from 0 to 36; for Oppositional scale, 0 to 18; higher scores indicate more problems.

[c] Possible scores range from 0 to 1; higher scores indicate more problems.

[d] Possible IQ scores range from 50 to 150.

[e] Scored as pass or fail.

primary education, 200 (6.3%) were from low-income families, and 580 (15.3%) continued to smoke during pregnancy. In total, 2301 children (60.2%) were Dutch. On average, children were born at term (median gestational age, 40.0 [interquartile range, 39.3-41.0] weeks). Based on the criteria described above, 127 women (3.4%) had hypothyroxinemia and 183 (5.0%) had positive findings for thyroid peroxidase antibodies.

The children exposed to maternal hypothyroxinemia during early pregnancy had higher ADHDi scores at 8 years of age compared with nonexposed children (β = 0.07 [95% CI, 0.003-0.14]; percentage increase in ADHD scores, 7% [95% CI, 3%-15%]) (**Table 3**). Additional adjustments for children's autistic symptoms or Oppositional scores did not affect the association. When we additionally adjusted the models for the children's nonverbal IQ, the association between maternal hypothyroxinemia and the children's ADHDi scores was slightly attenuated (percentage increase in ADHDi scores, 6% [95% CI, 1%-14%]). The results of the association analyses with hypothyroxinemia using an alternative cutoff of thyrotropin levels are presented in eTable 3 in the Supplement.

We found no association between maternal subclinical hypothyroidism and ADHDi score in children (eTable 4 in the Supplement). In addition, we found no relation between maternal thyroid function in early pregnancy and the children's Oppositional scores at 8 years of age (**Table 4**).

The exclusion of mothers with positive findings for thyroid peroxidase antibodies also changed the association between maternal hypothyroxinemia and children's ADHDi scores only slightly (percentage increase in ADHDi scores, 8% [95% CI, 1%-16%]) (eTable 5 in the Supplement). Likewise, the exclusion of mothers who took thyroid medication only minimally influenced the results. Similar results emerged when the sample was limited to pregnant women with FT_4 levels measured in the first trimester of pregnancy (eTable 6 in the Supplement). We found no interaction between maternal hypothyroxinemia and the children's sex in the association with the ADHDi scores in children at 8 years of age.

Discussion

In our population-based cohort, we observed a modest association between maternal hypothyroxinemia in early gestation and an increased risk for ADHD symptoms in children at 8 years of age, independent of confounders. No association was apparent between maternal thyroid function and children's Oppositional scores. The findings of this large-scale prospective study in school-aged children are in line with those of previous reports from small-scale retrospective studies or studies performed in younger children.[4,8]

The fetal brain predominantly depends on circulating T_4 levels for the intracellular supply of triiodothyronine, which is converted locally by the enzyme type 2 deiodinase. The active hormone then binds to its nuclear receptor and regulates gene expression in the brain.[24] The detrimental effects of hypothyroxinemia on fetal neurologic development have been suggested by studies in animals[2,3] and in humans.[4,6,7] In rats, hypothyroxinemia in pregnancy causes irreversible abnormalities in the cytoarchitecture of the somatosensory cortex and hippocampus.[5] Neuroimaging studies in humans show that maternal thyroid hormone insufficiency in pregnancy is related to a smaller genu and combined anterior section and a larger splenium and combined posterior section in the corpus callosum in the offspring.[25,26]

Dysfunctions of frontal and prefrontal lobes, which are involved in impulsivity and motor activity control, and in those of the cortical and subcortical striatal areas, which are involved in inhibition of irrelevant responses and executive function, are hypothesized to underlie symptoms of ADHD.[8] Langevin et al[27] demonstrated that children with ADHD have microstructural abnormalities in the frontal regions of the corpus callosum and abnormalities in white matter connections underlying the primary and somatosensory motor cortices. The similarity between neuroimaging findings in children with ADHD and abnormalities in children exposed to thyroid hormone insufficiency in prenatal life suggests a plausible explanation for the findings of the present study.[28] Furthermore, the normal development of the monoaminergic and cholinergic

Table 3. Maternal Thyroid Function in Early Pregnancy and Children's ADHDi Scores at 8 Years of Age

Thyroid Function Variable	Parent-Reported ADHDi Score[a,b] β Coefficient (95% CI)	*P* Value	Change in Scores, % (95% CI)
Maternal hypothyroxinemia[c]			
Unadjusted	0.08 (0.01 to 0.15)	.03	8 (1 to 16)
Adjusted for age and sex	0.08 (0.01 to 0.15)	.03	8 (1 to 16)
Fully adjusted model[d]	0.07 (0.003 to 0.14)	.04	7 (3 to 15)
Free T_4 level per SD[e]			
Unadjusted	−0.01 (−0.02 to 0.01)	.22	−1 (−2 to 1)
Adjusted for age and sex	−0.01 (−0.02 to 0.01)	.32	−1 (−2 to 1)
Fully adjusted model[d]	−0.01 (−0.02 to 0.01)	.41	−1 (−2 to 1)
Thyrotropin level per SD[f]			
Unadjusted	−0.01 (−0.02 to 0.01)	.29	−1 (−2 to 1)
Adjusted for age and sex	−0.01 (−0.02 to 0.003)	.16	−1 (−2 to 0.3)
Fully adjusted model[d]	−0.01 (−0.02 to 0.01)	.28	−1 (−2 to 1)

Abbreviations: ADHDi, attention-deficit/hyperactivity disorder index; T_4, thyroxine.

SI conversion factor: to convert free T_4 to picomoles per liter, multiply by 12.871.

[a] Derived from the Conners' Parent Rating Scales–Revised Short Form. Data are from 3873 maternal-child pairs from the Generation R Study.[12] Possible scores range from 0 to 36; higher scores indicate more problems.

[b] Values are not easily interpretable because the mathematically transformed scores were used in the analyses. Therefore, the β coefficients were exponentiated and converted to percentage differences. Negative values indicate a decrease in scores.

[c] Defined as thyrotropin levels within the reference range and free T_4 levels below the 5th percentile (ie, <0.85 ng/dL) (n = 127).

[d] Adjusted for child age, sex, and ethnic background and maternal educational level, age, history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, body mass index, and time of blood sampling in pregnancy.

[e] The SD for free T_4 is 0.29 ng/dL.

[f] The SD for thyrotropin is 1.3 mIU/L.

Table 4. Maternal Thyroid Function in Early Pregnancy and Children's Oppositional Scale Score at 8 Years of Age

Thyroid Function Variable	Parent-Reported Oppositional Score[a,b] β Coefficient (95% CI)	*P* Value	Change in Scores, % (95% CI)
Maternal hypothyroxinemia[c]			
Unadjusted	0.02 (−0.04 to 0.08)	.63	2 (−4 to 8)
Adjusted for age and sex	0.02 (−0.04 to 0.08)	.66	2 (−4 to 8)
Fully adjusted model[d]	0.02 (−0.04 to 0.08)	.49	2 (−4 to 8)
Free T_4 level per SD[e]			
Unadjusted	0.00 (−0.01 to 0.01)	.97	0 (−1 to 1)
Adjusted for age and sex	0.00 (−0.01 to 0.01)	.99	0 (−1 to 1)
Fully adjusted model[d]	0.00 (−0.01 to 0.01)	.93	0 (−1 to 1)
Thyrotropin level per SD[f]			
Unadjusted	−0.01 (−0.02 to 0.003)	.16	−1 (−2 to 0.3)
Adjusted for age and sex	−0.01 (−0.02 to 0.002)	.13	−1 (−2 to 0.2)
Fully adjusted model[d]	−0.01 (−0.02 to 0.004)	.21	−1 (−2 to 0.4)

Abbreviation: T_4, thyroxine.

SI conversion factor: To convert free T_4 to picomoles per liter, multiply by 12.871.

[a] Derived from the Conners' Parent Rating Scales–Revised Short Form. Data are from 3873 maternal-child pairs from the Generation R Study.[12] Possible scores range from 0 to 18; higher scores indicate more problems.

[b] Values are not easily interpretable because the mathematically transformed scores were used in the analyses. Therefore, the β coefficients were exponentiated and converted to percentage differences. Negative values indicate a decrease in scores.

[c] Defined as thyrotropin levels within the reference range and free T_4 levels below the 5th percentile (ie, <0.85 ng/dL) (n = 127).

[d] Adjusted for child age, sex, and ethnic background and maternal educational level, age, history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, maternal body mass index, and time of blood sampling in pregnancy.

[e] The SD for free T_4 is 0.29 ng/dL.

[f] The SD for thyrotropin is 1.3 mIU/L.

neurotransmitter system are thyroid dependent, and dysfunctions in these transmitter systems have been linked to attention deficits and hyperactivity.[28] A high prevalence of ADHD has been reported in children with generalized resistance to thyroid hormones, a disease caused by mutations in the thyroid hormone receptor-β (*THRB*) gene (OMIM 190160) and characterized by reduced responsiveness of peripheral and pituitary tissues to the activation of the thyroid hormones.[29] The

strikingly high prevalence of ADHD in these individuals suggests that common mechanisms downstream of *THRB* may be responsible for manifestation of the behavioral phenotypes in both disorders.

We found no relation between maternal hypothyroxinemia in early pregnancy and children's Oppositional scores. A possible explanation for this null finding is that some specific subregions of the brain, which are related to ADHD symptoms, are more severely affected by thyroid hormone insufficiency, despite a global insult to the brain. Considering that the insult resulted from thyroid hormone insufficiency that occurred in early gestation, this exposure would most likely have a global effect on the neurodevelopment of the fetus. In this study, further adjustment of the models for IQ only attenuated the association of maternal mild thyroid insufficiency and children's ADHD. This finding suggests that the adverse effects on the brain of thyroid hormone insufficiency in early pregnancy might not be only global; rather, some areas of the brain are more susceptible to the lack of these hormones.

Our study has several strengths, including a large population-based sample, prospective design, available information on numerous maternal and child confounders, long-term follow-up of children (which allows a valid assessment of behavior in school-aged children[30]), and the assessment of maternal thyroid function in early pregnancy, as recommended.[14] Furthermore, to reduce bias due to a selective response to questionnaires, we applied multiple imputations to replace the missing values of the ADHDi scores using a vast range of different behavioral measures. We also faced some limitations. First, no information was available regarding the clinical diagnosis of ADHD in children or their history of ADHD-related medication use. In large-scale studies, diagnosis based on interviews and direct observations is not feasible. Instead, parental reports of children's behavior have been widely used in epidemiologic studies.[4,17,18] In this study, we found a strong relation between the diagnosis of ADHD by a structured interview and ADHD symptoms reported by mothers. This finding further supports the validity of the maternal report of ADHD symptoms (CPRS-R:S scores). Second, maternal thyroid hormone levels were measured only once during pregnancy; therefore, any analysis of how the effect of thyroid hormone deficiencies depends on gestational age was not possible.

Conclusions

The adverse cognitive outcomes of prenatal exposure to thyroid hormone insufficiency have been known for decades. Our findings provide further support of the possible role of maternal mild thyroid hormone insufficiency during early gestation in the behavioral development of the offspring, in particular ADHD. Neuroimaging and animal studies are needed to address the underlying mechanism of the association between maternal mild thyroid insufficiency and ADHD in children.

ARTICLE INFORMATION

Accepted for Publication: February 24, 2015.

Published Online: July 6, 2015. doi:10.1001/jamapediatrics.2015.0498.

Author Affiliations: Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Centre–Sophia Children's Hospital, Rotterdam, the Netherlands (Modesto, Tiemeier, Verhulst, Ghassabian); The Generation R Study Group, Erasmus Medical Centre, Rotterdam, the Netherlands (Modesto, Jaddoe, Ghassabian); Department of Psychiatry, Erasmus Medical Centre, Rotterdam, the Netherlands (Tiemeier); Department of Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands (Tiemeier, Jaddoe, Hofman); Division of Endocrinology, Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands (Peeters); Rotterdam Thyroid Centre, Erasmus Medical Centre, Rotterdam, the Netherlands (Peeters); Department of Pediatrics, Erasmus Medical Centre–Sophia Children's Hospital, Rotterdam, the Netherlands (Jaddoe).

Author Contributions: Dr Ghassabian had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data.
Study concept and design: Tiemeier, Peeters, Hofman, Verhulst, Ghassabian.
Acquisition, analysis, or interpretation of data: Modesto, Tiemeier, Peeters, Jaddoe, Verhulst, Ghassabian.
Drafting of the manuscript: Modesto, Ghassabian.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Modesto, Tiemeier, Ghassabian.
Obtained funding: Tiemeier, Jaddoe.
Study supervision: Tiemeier, Peeters, Hofman, Verhulst, Ghassabian.

Conflict of Interest Disclosures: Dr Verhulst is the contributing editor of the *Achenbach System of Empirically Based Assessment*, from which he receives remuneration. No other disclosures were reported.

Funding/Support: The Generation R Study is supported by the Erasmus Medical Center, Rotterdam; Erasmus University Rotterdam; Netherlands Organization for Health Research and Development; Netherlands Organisation for Scientific Research; Ministry of Health, Welfare, and Sport; and Ministry of Youth and Families. Measurements of thyroid hormone levels have been made possible by a generous financial gift from Ortho Clinical Diagnostics and Jan Dekker/Ludgardine Bouwman Foundation, Fa Merck, and Foundation Zeist. This study was also supported by research grant FP7/2008–2013 from the European Community's Seventh Framework Programme under grant agreement 212652 (NUTRIMENTHE project, The Effect of Diet on the Mental Performance of Children) (Drs Tiemeier and Ghassabian).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the general practitioners, hospitals, midwives, and pharmacies in Rotterdam who contributed to this study.

REFERENCES

1. Stiles J, Jernigan TL. The basics of brain development. *Neuropsychol Rev*. 2010;20(4):327-348.

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

3. Ausó E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. *Endocrinology*. 2004;145(9):4037-4047.

4. Ghassabian A, Henrichs J, Tiemeier H. Impact of mild thyroid hormone deficiency in pregnancy on cognitive function in children: lessons from the Generation R Study. *Best Pract Res Clin Endocrinol Metab*. 2014;28(2):221-232.

5. Henrichs J, Ghassabian A, Peeters RP, Tiemeier H. Maternal hypothyroxinemia and effects on cognitive functioning in childhood: how and why? *Clin Endocrinol (Oxf)*. 2013;79(2):152-162.

6. Román GC, Ghassabian A, Bongers-Schokking JJ, et al. Association of gestational maternal hypothyroxinemia and increased autism risk. *Ann Neurol*. 2013;74(5):733-742.

7. Ghassabian A, El Marroun H, Peeters RP, et al. Downstream effects of maternal hypothyroxinemia

in early pregnancy: nonverbal IQ and brain morphology in school-age children. *J Clin Endocrinol Metab*. 2014;99(7):2383-2390.

8. Vermiglio F, Lo Presti VP, Moleti M, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab*. 2004;89(12):6054-6060.

9. Päkkilä F, Männistö 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.

10. Bokor G, Anderson PD. Attention-deficit/hyperactivity disorder. *J Pharm Pract*. 2014;27(4):336-349.

11. Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? *J Child Psychol Psychiatry*. 2013;54(1):3-16.

12. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol*. 2012;27(9):739-756.

13. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(8):2543-2565.

14. Stagnaro-Green A, Abalovich M, Alexander E, et al; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21(10):1081-1125.

15. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol*. 1998;26(4):257-268.

16. Conners CK. *Conners Rating Scales–Revised*. New York, NY: Multi-Health Systems; 2001.

17. Troost PW, Steenhuis MP, Tuynman-Qua HG, et al. Atomoxetine for attention-deficit/hyperactivity disorder symptoms in children with pervasive developmental disorders: a pilot study. *J Child Adolesc Psychopharmacol*. 2006;16(5):611-619.

18. Kuny AV, Althoff RR, Copeland W, et al. Separating the domains of oppositional behavior: comparing latent models of the Conners' oppositional subscale. *J Am Acad Child Adolesc Psychiatry*. 2013;52(2):172-183.e8.

19. Rijlaarsdam J, Stevens GWJM, van der Ende J, et al. Prevalence of *DSM-IV* disorders in a population-based sample of 5-to 8-year-old children: the impact of impairment criteria [published online February 26, 2015]. *Eur Child Adoles Psy*. doi:10.1007/s00787-015-0684-6.

20. de Beurs E. *Brief Symptom Inventory: Handleiding [Dutch Manual]*. Leiden, the Netherlands: PITS; 2004.

21. Constantino J. *Social Responsiveness Scale (SRS)*. Los Angeles, CA: Western Psychological Services; 2007.

22. Tellegen PJ. *SON-R 2 1/2-7: Snijders-Oomen niet-verbale intelligentietest: handleiding en verantwoording*. Amsterdam, the Netherlands: Boom test uitgevers; 2005.

23. Gershon J. A meta-analytic review of gender differences in ADHD. *J Atten Disord*. 2002;5(3):143-154.

24. Bernal J, Guadaño-Ferraz A, Morte B. Perspectives in the study of thyroid hormone action on brain development and function. *Thyroid*. 2003;13(11):1005-1012.

25. Samadi ASJ, Rovet JF. Children born to women with hypothyroidism during pregnancy show abnormal corpus callosum development. *Thyroid*. 2013;23(5):115-121.

26. Willoughby KA, McAndrews MP, Rovet JF. Effects of maternal hypothyroidism on offspring hippocampus and memory. *Thyroid*. 2014;24(3):576-584.

27. Langevin LM, Macmaster FP, Crawford S, Lebel C, Dewey D. Common white matter microstructure alterations in pediatric motor and attention disorders. *J Pediatr*. 2014;164(5):1157-1164.e1. doi:10.1016/j.jpeds.2014.01.018.

28. Siesser WB, Zhao J, Miller LR, Cheng SY, McDonald MP. Transgenic mice expressing a human mutant beta1 thyroid receptor are hyperactive, impulsive, and inattentive. *Genes Brain Behav*. 2006;5(3):282-297.

29. Hauser P, Zametkin AJ, Martinez P, et al. Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. *N Engl J Med*. 1993;328(14):997-1001.

30. Applegate B, Lahey BB, Hart EL, et al. Validity of the age-of-onset criterion for ADHD: a report from the *DSM-IV* field trials. *J Am Acad Child Adolesc Psychiatry*. 1997;36(9):1211-1221.