Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort

David Gyllenberg, Andre Sourander, Heljä-Marja Surcel, Susanna Hinkka-Yli-Salomäki, Ian W. McKeague, and Alan S. Brown

ABSTRACT

BACKGROUND: Evidence from animal and human studies indicates that thyroid hormone deficiency during early gestation alters brain development. As schizophrenia is associated with prenatal brain insults and premorbid cognitive deficits, we tested the a priori hypothesis that serologically defined maternal thyroid deficiency during early gestation to mid-gestation is associated with schizophrenia in offspring.

METHODS: The investigation is based on the Finnish Prenatal Study of Schizophrenia, a nested case-control study that included archived maternal sera from virtually all pregnancies since 1983 (N = >1 million). We identified all offspring in the cohort with a diagnosis of schizophrenia based on the national inpatient and outpatient register and matched them on sex, date of birth, and residence in Finland at time of onset of the case to comparison subjects (1:1) from the cohort. Maternal sera of 1010 case-control pairs were assessed for free thyroxine, and sera of 948 case-control pairs were assessed for thyroid-stimulating hormone.

RESULTS: Maternal hypothyroxinemia (free thyroxine ≤10th percentile, normal thyroid-stimulating hormone) was associated with an increased odds of schizophrenia (odds ratio = 1.75, 95% confidence interval = 1.22–2.50, p = .002). When adjusted for maternal psychiatric history, province of birth, and maternal smoking during pregnancy, the association remained significant (odds ratio = 1.70, 95% confidence interval = 1.13–2.55, p = .010).

CONCLUSIONS: In a large, national birth cohort, prospectively documented hypothyroxinemia during early gestation to mid-gestation was associated with increased odds of schizophrenia in offspring. This information can inform translational studies of maternal hypothyroxinemia examining molecular and cellular deviations relevant to schizophrenia.

Keywords: Biomarker, Cohort, Neurodevelopment, Prenatal, Schizophrenia, Thyroid

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Methods and Materials

The investigation was based on the Finnish Prenatal Study of Schizophrenia (FiPS-S), which used a nested case-control design (13). The sampling frame was defined so that the members of the birth cohort were within the age of risk for schizophrenia. Nationwide registers were used to identify
cases born between 1983 (the first birth year of the cohort) and 1998 and diagnosed with schizophrenia or schizoaffective disorder before December 31, 2009 (see Case and Control Identification). The maximum age was 26 years.

**Description of Cohort and Biobank**

All subjects in FiPS-S were derived from the Finnish Maternity Cohort (FMC). The FMC consisted of all offspring with archived maternal sera drawn during pregnancy in Finland since 1983 (N = >1 million). Sera were drawn during the first trimester or the early second trimester (5th–95th percentile = months 2–4 of pregnancy) from >98% of the gravidae, following informed consent, for screening of human immuno-deficiency virus, syphilis, and hepatitis. One maternal serum sample was obtained for each pregnancy. After the screening, the remainder of each sample was stored as 1 aliquot at −25°C in a single, centralized biorepository (National Institute of Health and Welfare). All of the serum samples in the FMC can be linked with offspring by the unique personal identification number that has been assigned to all residents of Finland by the Finnish Population Registry since 1971. The personal identification numbers of the mothers of case subjects and matched control subjects were linked to the FMC sera biobank and to other registers discussed subsequently.

**Finnish Population Register**

The computerized nationwide Finnish Population Register was established in 1971. It includes comprehensive data on place of birth, twinning, date of emigration, date of death, and biological parents, including their dates of births.

**Case and Control Identification**

The Finnish Hospital and Outpatient Discharge Register (FHDR), maintained by the National Institute of Health and Welfare, was used to identify all recorded diagnoses for psychiatric hospital admissions and psychiatric outpatient treatment visits among members of the FMC. The FHDR was established in 1963, and computerized data are available from 1987 to the present. The register contains the personal and hospital identification codes and primary and secondary psychiatric diagnoses.

To identify the cases for the present study, we linked the FMC and the FHDR. All cases with schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25) in the FHDR were identified. Hereinafter schizophrenia and schizoaffective disorder are referred to as schizophrenia. The age at first treatment was recorded by the first contact with a psychiatric facility with a diagnosis of schizophrenia. The diagnostic validity of schizophrenia in the FHDR was very good; in a previous study, 93% of subjects with a diagnosis of schizophrenia in the FHDR were assigned a consensus diagnosis of schizophrenia (14). The total number of schizophrenia cases was 1514 (13). A sufficient amount of maternal sera was available in the study to measure fT4 on 1010 case-control pairs and TSH on 948 pairs; 903 pairs were assayed for both fT4 and TSH. The schizophrenia cases were matched 1:1 to control subjects drawn from the FMC without schizophrenia, other nonaffective psychotic disorders, or bipolar disorder on the date of birth (± 1 month) for sex and residency of Finland at the time of case diagnosis. The control subjects for the study were randomly drawn from all control subjects fulfilling these criteria because there were many control subjects with all of these characteristics.

**Laboratory Assays and Classification of Thyroid Disorders**

Measurements of maternal fT4 and TSH were performed blind to case/control status using chemiluminescent microparticle immunoassays with the Architect i2000 automatic analyzer (Abbott Diagnostics, Abbott Park, Illinois). The lower limits of detection for fT4 and TSH were 5.1 pmol/L and .0025 mIU/L, respectively. The intra-assay and interassay variation were 3.6% and 7.8% for fT4 and 1.7% and 5.3% for TSH, respectively.

To facilitate the clinical interpretation of the data, we conducted additional analyses of maternal serologically defined thyroid disorders in relation to schizophrenia. Given that fT4 varies during pregnancy (15,16), the lack of trimesterspecific reference values from the manufacturer, and the fact that the sera had been frozen and stored for up to several years (17), we defined the cutoff points to categorize these groups based on percentiles in the control population. Maternal hypothyroxinemia was classified as fT4 ≤10th percentile and TSH >5th–95th percentile, consistent with percentiles used in clinical guidelines for thyroid disorders (15) and other thyroid studies (9,11). In a sensitivity analysis, we used an alternative cutoff point to define hypothyroxinemia—fT4 ≤5th percentile and TSH >5th–95th percentile. The cutoff points for the other maternal clinical thyroid disorders were also consistent with a general population subsample of the current biobank (16). Hypothyroidism was defined as fT4 ≤5th percentile and TSH >95th percentile; subclinical hypothyroidism, as fT4 >5th–95th percentile and TSH >50th percentile; hyperthyroidism, as fT4 >95th percentile and TSH ≤5th percentile; and subclinical hyperthyroidism, as fT4 >5th–95th percentile and TSH ≤5th percentile. Table 1 lists the cutoff values for fT4 in pmol/L and for TSH in mIU/L.

**Covariates**

The covariates in the study were selected based on the literature on schizophrenia (18–20) and outcomes of maternal thyroid hormone disorders (9–11,21–25). These included maternal educational level; previous births; maternal age; maternal history of schizophrenia, affective disorders, or any psychiatric disorder; urbanicity of birth; birth province; twinning; and the gestational week of blood draw (classification shown in Table 2). Gestational week of the blood draw was obtained from the FMC, whereas all other covariates were derived from the Finnish Population Register. The degree of urbanization of the birth municipalities was classified based on national standards used by Statistics Finland (26): a densely populated area was defined as a 250 m² area with >200 inhabitants. Municipalities with ≥90% of the population living in densely populated areas were classified as urban; with 60%–89%, as semirurban; and with <60%, as rural. Urbanicity and province of birth were highly correlated in control subjects (χ² = 134.7, df = 6, p < .0001), and 50.8% of the controls born in Southern Finland were born in an urban area.
Table 1. Categorical Measures of Maternal fT4 and TSH in Relation to Offspring Schizophrenia

<table>
<thead>
<tr>
<th>Maternal Condition</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroxinemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>649 (71.9)</td>
<td>672 (74.4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107 (11.8)</td>
<td>78 (8.6)</td>
<td>1.75 (1.22–2.50)</td>
<td>.002</td>
</tr>
<tr>
<td>Clinical Thyroid Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>740 (81.9)</td>
<td>746 (82.6)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6 (7.7)</td>
<td>8 (9.9)</td>
<td>.80 (0.47–1.37)</td>
<td>.424</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>29 (3.2)</td>
<td>36 (4.0)</td>
<td>.47 (0.41–0.80)</td>
<td>.009</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>15 (1.7)</td>
<td>16 (1.8)</td>
<td>.95 (0.53–1.69)</td>
<td>.924</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>50 (5.5)</td>
<td>29 (3.2)</td>
<td>1.91 (1.14–3.20)</td>
<td>.014</td>
</tr>
</tbody>
</table>

CI, confidence interval; fT4, free thyroxine; OR, odds ratio; TSH, thyroid-stimulating hormone.

Defined as fT4 $>14.03$ pmol/L ($>10$th percentile) and TSH $>24$–$3.38$ mIU/L ($>5$th–$95$th percentile).

Defined as fT4 $>14.03$ pmol/L ($>10$th percentile) and TSH $>24$–$3.38$ mIU/L ($>5$th–$95$th percentile).

Defined as fT4 $>13.43$–$21.84$ pmol/L ($>5$th–$95$th percentile) and TSH $>24$–$3.38$ mIU/L ($>5$th–$95$th percentile).

Defined as fT4 $>13.43$ pmol/L ($>5$th percentile) and TSH $>3.38$ mIU/L ($>95$th percentile).

Adjusted for degree of urbanization of birth municipality.

Defined as fT4 $>13.43$–$21.84$ pmol/L ($>5$th–$95$th percentile) and TSH $>3.38$ mIU/L ($>95$th percentile).

Adjusted for birth province.

Defined as fT4 $>21.84$ pmol/L ($>5$th percentile) and TSH $<24$ mIU/L ($<5$th percentile).

Defined as fT4 $>13.43$–$21.84$ pmol/L ($>5$th–$95$th percentile) and TSH $<24$ mIU/L ($<5$th percentile).

Adjusted for twinning.

(n = 292/575). In accord with standard epidemiologic practice, covariates were included in the final model if they were associated at $p < .1$ with case-control status and the designated maternal thyroid hormone exposure (27–29). In further analyses, we adjusted for maternal smoking by serum cotinine, a reliable nicotine metabolite, which was assayed from maternal sera.

In addition to these potential confounders, we examined whether preterm birth and low birth weight, derived from abstracted maternity records and the medical birth registry, mediated the association. To test for mediation criteria, we first examined relationships between these variables and exposure/outcome status, as for potential confounders (see previous paragraph). Preterm birth and low birth weight are presumed to be in a causal pathway between hypothyroxinemia and schizophrenia because, by definition, preterm birth occurred several months after the blood draw, maternal hypothyroidism has an impact on preterm birth (25), and preterm birth has been related to schizophrenia (20).

Ethical Approval
The study was approved by the ethical committees of the Hospital District of Southwestern Finland, the National Institute of Health and Welfare, and the institutional review board of the New York State Psychiatric Institute.

Statistical Analyses
The analysis was based on a nested case-control design. The controls were selected from the population at risk (the FiPS-S birth cohort) and matched to cases on selected characteristics (see Case and Control Identification). To evaluate relationships between each covariate, thyroid hormones, and schizophrenia, $\chi^2$, Fisher’s exact, and t tests were used. Because of the skewness of the data, fT4 levels were log transformed before being analyzed as continuous variables. This variable was normally distributed after transformation to log-fT4. To facilitate the interpretation of the data we examined maternal thyroid disorders as categorical variables (Table 1 footnote lists classifications). Appropriate to the nested case-control design, point and 95% confidence intervals (CIs) of odds ratios (ORs) were obtained by fitting conditional logistic regression models. After examining the main effects, we investigated whether the effect of maternal fT4 on schizophrenia differed between male and female subjects. For this purpose, we analyzed the association between fT4 and schizophrenia stratified by sex and tested for interaction by adding the sex-by-fT4 interaction term into the statistical model. Associations were considered statistically significant at $p < .05$. All statistical analyses were conducted using SAS version 9.2 software (SAS Institute, Cary, North Carolina).

RESULTS
As shown in Table 2, case-control status was associated with twinning; maternal psychiatric history of schizophrenia spectrum disorder, affective disorder, or any psychiatric disorder; degree of urbanization; and province of birth. None of these potential confounders were associated with fT4 or hypothyroxinemia (Table 2). Preterm birth was associated with case-control status; fT4 under the median, and hypothyroxinemia at $p < .1$. There were also associations between birth province and hypothyroidism, between degree of urbanization and subclinical hypothyroidism, and between twinning and subclinical hyperthyroidism (Supplemental Table S1).

We first analyzed schizophrenia in relation to maternal hypothyroxinemia as shown in Table 1 (defined as fT4 $<10$th percentile and normal TSH). The proportion of subjects with maternal hypothyroxinemia was 11.8% among schizophrenia subjects compared with 8.6% among control subjects, yielding
### Table 2. Covariates in Relation to Schizophrenia and to Maternal Early Gestational ft4 Levels and Hypothyroxinemia in Control Subjects

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Cases (n = 1010)</th>
<th>Controls (n = 1010)</th>
<th>ft4 &lt; Median (n = 503)</th>
<th>ft4 ≥ Median (n = 507)</th>
<th>Hypothyroxinemia (n = 78)</th>
<th>Hypothyroxinemia (n = 672)</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Mother at Birth</td>
<td>28.5 (5.5)</td>
<td>28.2 (5.1)</td>
<td>28.2 (5.1)</td>
<td>28.3 (5.1)</td>
<td>29.2 (4.9)</td>
<td>28.2 (5.1)</td>
<td>.240</td>
</tr>
<tr>
<td>Gestational Week of Blood Draw</td>
<td>11.0 (4.0)</td>
<td>10.8 (4.1)</td>
<td>11.2 (4.5)</td>
<td>10.3 (3.5)</td>
<td>12.3 (5.7)</td>
<td>10.8 (4.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Previous Births (≤ 1)</td>
<td>626 (62.0)</td>
<td>624 (61.8)</td>
<td>313 (62.2)</td>
<td>311 (61.3)</td>
<td>50 (64.1)</td>
<td>410 (61.0)</td>
<td>.359</td>
</tr>
<tr>
<td>Twin</td>
<td>20 (2.0)</td>
<td>42 (4.2)</td>
<td>17 (3.4)</td>
<td>25 (5.0)</td>
<td>2 (2.6)</td>
<td>27 (4.0)</td>
<td>.005</td>
</tr>
<tr>
<td>Maternal History of Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia and other nonaffective psychoses²</td>
<td>104 (10.3)</td>
<td>14 (1.4)</td>
<td>8 (1.6)</td>
<td>6 (1.2)</td>
<td>0 (0)</td>
<td>11 (1.6)</td>
<td>.616</td>
</tr>
<tr>
<td>Affective disorders²</td>
<td>216 (21.4)</td>
<td>83 (8.2)</td>
<td>45 (9.0)</td>
<td>38 (7.5)</td>
<td>8 (10.3)</td>
<td>55 (8.2)</td>
<td>.532</td>
</tr>
<tr>
<td>Any psychiatric disorder²</td>
<td>332 (32.9)</td>
<td>140 (13.9)</td>
<td>78 (15.5)</td>
<td>62 (12.2)</td>
<td>11 (14.1)</td>
<td>91 (13.3)</td>
<td>.891</td>
</tr>
<tr>
<td>No education after secondary school</td>
<td>.259</td>
<td>.959</td>
<td>.85</td>
<td>.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocational degree or secondary school graduate</td>
<td>568 (56.5)</td>
<td>574 (57.1)</td>
<td>284 (56.6)</td>
<td>290 (57.5)</td>
<td>42 (53.9)</td>
<td>384 (57.3)</td>
<td></td>
</tr>
<tr>
<td>College or university bachelor degree</td>
<td>120 (11.9)</td>
<td>141 (14)</td>
<td>73 (14.5)</td>
<td>68 (13.5)</td>
<td>9 (11.5)</td>
<td>95 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Master degree or Ph.D.</td>
<td>57 (5.7)</td>
<td>62 (6.2)</td>
<td>30 (6.0)</td>
<td>32 (6.4)</td>
<td>5 (6.4)</td>
<td>45 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Birth Province</td>
<td>.0001</td>
<td>.001</td>
<td>.112</td>
<td>.150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>254 (25.2)</td>
<td>300 (29.7)</td>
<td>147 (29.2)</td>
<td>153 (30.2)</td>
<td>22 (28.2)</td>
<td>203 (30.2)</td>
<td></td>
</tr>
<tr>
<td>Gestational Age at Birth³</td>
<td>.073</td>
<td>.073</td>
<td>.088</td>
<td>.116</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Weight</td>
<td>.524</td>
<td>.324</td>
<td>.116</td>
<td>.116</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ft4, free thyroxine; TSH, thyroid-stimulating hormone.

¹There were no missing values on any covariate except for those noted in footnotes d, f, g, k, l, m, and n.
²p value based on pooled t test assuming equality of variances except for those noted in footnote c.
³p value based on Satterthwaite’s t test assuming inequality of variances.
⁴Frequency missing = 139 cases, 142 controls.
⁵p value based on $\chi^2$ test except for those noted in footnote h.
⁶Frequency missing = 4 cases, 4 controls.
⁷ICD-10 codes F20–25, F28–29; ICD-9 codes 295, 297, 298.9X, 301.2C; and ICD-8 codes 295, 297, 298.20, 298.99, 299.
⁸p value based on Fisher’s exact test.
⁹ICD-10 codes F30–34, F38–39; ICD-9 codes 296, 290, 298.8A; and ICD-8 codes 296, 298.00, 298.10, 300.41.
¹¹Frequency missing = 4 cases, 4 controls.
¹²Frequency missing = 282 cases, 294 controls.
¹³Frequency missing = 282 cases, 300 controls.
a significant association (OR = 1.75, 95% CI = 1.22–2.50, p = .002). In a sensitivity analysis, we defined hypothyroxinemia as fT4 <5th percentile in controls and normal TSH. Using that alternative definition, the respective proportions with maternal hypothyroxinemia were 6.6% (n = 52) among schizophrenia subjects and 5.0% (n = 39) among control subjects, and the OR was 1.62 (95% CI = .99–2.63, p = .055).

We next analyzed maternal fT4 defined as a continuous variable. The distribution of maternal fT4 in cases and controls is shown in Figure 1A. As shown in Figure 1B, there was a linear association between log units of maternal fT4 and log odds of schizophrenia in offspring. In the conditional logistic regression analysis, the odds of schizophrenia decreased by almost 50% per log unit increase of maternal fT4 (OR = .54, 95% CI = .31–.94, p = .028). The association between log-transformed TSH and schizophrenia was not significant (OR = .93, 95% CI = .84–1.02, p = .108).

Although none of the potential confounders were associated with both schizophrenia and fT4 or hypothyroxinemia (Table 2), we conducted additional adjustments for variables that are strongly related to schizophrenia. After adjustment of hypothyroxinemia for maternal psychiatric history, province of birth, and maternal cotinine, a biomarker of smoking, the ORs remained similar, and the associations between hypothyroxinemia and schizophrenia were statistically significant (Table 3). When fT4 was treated as a continuous variable (log-fT4), and adjusted for cotinine, the OR increased by 23.1%, and the p value became nonsignificant (Table 3).

We considered the possibility that mothers of case subjects might have failed to increase TSH adequately for the magnitude of their hypothyroxinemia. In an analysis of mothers with hypothyroxinemia, we did not find evidence for this: the correlations between continuous TSH and continuous fT4 were only slightly higher among case subjects (r² = .029, p = .079) than control subjects (r² = .014, p = .299). In an additional analysis, we examined whether other maternal serologically defined thyroid disorders were associated with schizophrenia (Table 1). Maternal hypothyroidism was not associated with schizophrenia (p = .827). However, the number of subjects was small because clinical hypothyroidism was documented in mothers of only six case subjects and eight control subjects. Furthermore, in this exploratory analysis, subclinical hyperthyroidism was significantly associated with schizophrenia in offspring (OR = 1.91, 95% CI = 1.14–3.20, p = .014).

Because the risk of schizophrenia varies by sex (12), we conducted sex-stratified analyses of the association between maternal fT4 and schizophrenia: the OR for male subjects was .36 (95% CI = .17–.76) and for female subjects was .87 (95% CI = .40–1.94). However, when pooling both sexes, the sex-by-fT4 interaction term was not statistically significant (p = .11).

**Analysis of Mediation**

We tested for preterm birth and birth weight as potential mediators of the association between hypothyroxinemia and schizophrenia. As noted in Table 2, preterm birth was related to schizophrenia, fT4 under the median, and hypothyroxinemia. As expected, when the relationship between hypothyroxinemia and schizophrenia was adjusted for preterm birth, the OR decreased by 28%, and the p value was no longer significant (OR = 1.36, 95% CI .86 – 2.15, p = .184). Although birth weight was not associated with hypothyroxinemia or schizophrenia (Table 2), for the purpose of comparability, we also adjusted for birth weight. The OR was decreased by 22%, and the p value was nonsignificant (OR = 1.43, 95% CI .90–2.26, p = .130).

**DISCUSSION**

In a nationwide cohort, we demonstrated that serologically defined maternal hypothyroxinemia in early gestation to midgestation was associated with an increased odds of schizophrenia in offspring. As noted earlier, maternal hypothyroxinemia alters fetal brain development (1,2), supporting its plausibility as a risk factor for schizophrenia, largely considered to be a neurodevelopmental disorder (31,32). Hypothyroxinemia during early gestation, the period during which serum specimens were drawn in this study, has been associated with neurocognitive deficits (9–11), whereas mixed results were found when the same exposure was measured during the late second trimester or third trimester as noted in a review (1). Although none of the covariates met the a priori confounding criteria, for reassurance, we further adjusted for factors that were strongly related to schizophrenia. After adjustment for maternal psychopathology, province of birth, and maternal cotinine, a metabolite of nicotine measured in the sera, the association between hypothyroxinemia and schizophrenia remained similar to the unadjusted analysis and was statistically significant.

We also examined whether continuously defined fT4 was related to risk of schizophrenia. Although we observed an association in the unadjusted analysis, adjustment for maternal smoking resulted in a >20% change in the OR (toward the null), and the finding was no longer statistically significant. This finding suggests that the relationship between maternal fT4 and schizophrenia is present only when fT4 levels are below a particular threshold, which in this study was defined as under the 10th percentile of the distribution. Another possibility is that there was insufficient power to detect a significant finding when the exposure was defined as continuous fT4. This possibility is supported by the fact that the CIs in the unadjusted and adjusted analyses of log-fT4 overlap considerably, although the point estimates are in the same direction.

One potential explanation for the association between maternal hypothyroxinemia and schizophrenia is that hypothyroxinemia contributes to altered fetal gene expression, which adversely affects fetal brain development (2). In neurons, deiodinase-2 converts thyroxine to triiodothyronine, the active form, which regulates gene expression by binding to nuclear thyroid hormone receptors (33). Many triiodothyronine-regulated genes are involved in neurodevelopmental processes, such as circuit formation, neuronal migration, myelination, axon guidance, or synaptogenesis (2,34). It has been suggested that triiodothyronine-regulated gene expression is a mechanism accounting for some histologic abnormalities seen in offspring exposed to maternal hypothyroxinemia (35). In rodent studies, experimentally induced maternal
hypothyroxinemia causes histologic abnormalities in offspring, such as abnormal distributions of neurons in the hippocampus (4,36). This finding is particularly relevant to schizophrenia, in which morphologic and functional abnormalities of the hippocampus have been documented in patients (37).

Another possible explanation for the finding is mediation by preterm birth or low birth weight. We considered preterm birth and low birth weight as potential mediators rather than as confounders based on the following rationale: 1) hypothyroxinemia is measured early in gestation, and these variables are defined at a considerably later time point; 2) the prevailing view from prior studies is that hypothyroidism has an impact on these outcomes (30,38), and hypothyroxinemia during the first trimester has also been associated with preterm birth (25); and 3) previous literature indicates that preterm birth and low birth weight are risk factors for schizophrenia (20). In accord with standard epidemiologic texts (29), we first tested for relationships between these covariates and hypothyroxinemia/ fT4 and schizophrenia, respectively. Preterm birth was related to schizophrenia, fT4 under the median, and hypothyroxinemia, and met criteria for a potential mediator. When hypothyroxinemia was adjusted for preterm birth, the OR decreased by 28%, and the p-value became nonsignificant (p = .19); this suggests partial mediation by preterm birth. Low birth weight was not related to schizophrenia, fT4 under the median, and hypothyroxinemia, suggesting that it did not mediate the association. After adjustment for birth weight, the association was attenuated, although somewhat less than for preterm birth.
(22%), with \( p \) value = .13, which may reflect the fact that birth weight is highly correlated with the mediator preterm birth.

We did not find an association for maternal hypothyroidism, a more severe condition than hypothyroxinemia. The lack of association between maternal hypothyroidism and schizophrenia is due to low statistical power, as only 6 mothers of case subjects had hypothyroidism. Maternal hypothyroxinemia has been related to subtle neurodevelopmental deficits (3), some of which are observed in schizophrenia (12), whereas maternal hypothyroidism has been associated with more substantial developmental disturbances in offspring, such as mental retardation, stunted growth, and deafness (3). The presence of these more severe disorders, which may have made it difficult to evaluate schizophrenia symptoms properly, potentially could also explain the lack of an association.

The one result that was not hypothesized a priori was the association between subclinical hypothyroidism and schizophrenia. Maternal hyperthyroidism in relation to schizophrenia has been reported previously (39). In that study, the proportion of retrospectively reported thyroid disease during pregnancy was higher among mothers of patients with schizophrenia than among mothers of patients with other psychiatric disorders. Furthermore, among mothers of schizophrenia subjects who had a thyroid disorder, hyperthyroidism was more common than hypothyroidism (39). The fact that our result was derived from an additional analysis and no previous study examined subclinical hyperthyroidism necessitates caution in the interpretation.

As noted, an additional analysis revealed that the relationship between maternal fT4 and schizophrenia was observed only among male subjects. Differential loss of female fetuses in gestation should be considered as an explanation. However, the findings should be interpreted with caution because the sex-by-fT4 interaction term did not reach statistical significance (\( p = .11 \)). It is also worth considering the potential relationships of hypothyroxinemia with iodine deficiency and body mass index (BMI). Hypothyroxinemia is common in areas of iodine deficiency (40). Nonetheless, in iodine-sufficient areas, controlled trials have not found any evidence that additional iodine supplementation reduces the risk of maternal hypothyroxinemia (40,41). In Finland, pregnant women have adequate iodine levels because this nutrient is routinely supplemented in dietary salt (42). Another factor to consider is BMI, given its association with schizophrenia (43) and the previously demonstrated correlations between high BMI and hypothyroxinemia (24,25). However, we were unable to examine the relationship between BMI and hypothyroxinemia in our data.

This study has several strengths, including the nationwide cohort, the large sample size, the prospective and systematic collection of maternal sera, the comprehensive ascertainment of nearly all pregnancies and schizophrenia cases in Finland born beginning in 1983, and data on many prospectively measured covariates that allowed for adjustment of confounding and testing of mediation. One unexpected finding to emerge from this analysis was that twinning was greater in control subjects than in schizophrenia cases. Previous studies showed twinning increased in schizophrenia (44) or no relation to schizophrenia (45). Although we have no ready explanation for this unexpected finding, we speculated on the reasons in a previous publication (13).

Several methodologic limitations need to be considered. First, information on maternal thyroid function was available only for one time point for each pregnancy, which was in early gestation to mid-gestation, but not later during pregnancy. It is unclear whether the alterations in thyroid function represent a transient or continuous exposure and whether similar associations would have been found later in pregnancy. Second, data were unavailable on maternal thyroid replacement, such as levothyroxine, for thyroid disorders. However, pregnant mothers of most of the individuals with low fT4 did not have clinical hypothyroidism, and we demonstrated a relationship between maternal fT4 levels across a considerable distribution of levels of this exposure. In addition, low fT4 is not screened for during pregnancy. Therefore, it is unlikely that maternal thyroid replacement confounded the result. Third, owing to the fact that the cohort was born relatively recently, the age at the first treatment of the schizophrenia cases in this study was not considered.
relatively low (mean, 19.1 years; maximum, 26 years). The results may not be representative of schizophrenia cases with onset later in life. Finally, although we tested whether several key covariates were associated with the exposure and the outcome, there is the potential for residual confounding.

Furthermore, it is unlikely that maternal hypothyroxinemia is a risk factor that is specific to schizophrenia. As noted earlier, this exposure has pleiotropic effects on offspring neurodevelopment and cognition (1,2). Schizophrenia, bipolar disorder, autism, and mental retardation share several risk factors (46), and it has been hypothesized that their neurodevelopmental components overlap (47). One study showed that maternal hypothyroxinemia is a risk factor for autistic symptoms as assessed by parental questionnaires (48), but low maternal thyroxine was not related to the diagnosis of childhood autism in work from our group in this same birth cohort (49). We recommend future studies of maternal hypothyroxinemia as a risk factor for other psychiatric disorders. Likewise, it would be interesting to examine whether the association between maternal hypothyroxinemia and schizophrenia is mediated by premorbid cognitive deficits, which have been observed in schizophrenia (12). Furthermore, it is possible that maternal hypothyroxinemia interacts with genetic variants, other endogenous factors, or environmental insults to increase the risk of schizophrenia. In the case of maternal immune activation as a risk factor for schizophrenia, a “two-hit” model has been suggested (50). In a rodent study, an initial insult of maternal immune activation interacted synergistically with later stress during adolescence to cause neuropathologic and behavioral abnormalities in offspring similar to those found in schizophrenia (51). Given that rodent models of maternal hypothyroxinemia have been developed, it would be intriguing to conduct a similarly designed study in which maternal hypothyroxinemia is tested as the initial insult.

In conclusion, we found an association between low maternal thyroxine and increased odds of schizophrenia in offspring. This finding is biologically plausible as it is consistent with an extensive literature on maternal hypothyroxinemia as a disruptor of neurodevelopment in offspring (1,2) and with extensive evidence that schizophrenia is largely a neurodevelopmental disorder (31,32). This finding may lead to translational studies aimed at examining specific mechanisms by which low maternal thyroxine causes neurodevelopmental deviations relevant to schizophrenia at the molecular and cellular levels.

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ARTICLE INFORMATION

From the Department of Psychiatry (DG, AS, ASB), College of Physicians and Surgeons of Columbia University, New York State Psychiatric Institute, New York, New York; Department of Child Psychiatry (DG, AS, SH-Y-S), Faculty of Medicine, University of Turku; Department of Child Psychiatry (AS), Turku University Hospital, Turku; National Institute for Health and Welfare (H-MS), Oulu, Finland; and Departments of Biostatistics (IWM) and Epidemiology (ASB), Columbia University Mailman School of Public Health, New York, New York.

Address correspondence to David Gyllenberg, M.D., Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, Unit 23, New York, NY, 10032; E-mail: david.gyllenberg@utu.fi.

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