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Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort

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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 to mid-gestation is associated with offspring schizophrenia.

Methods—The investigation is based on the Finnish Prenatal Study of Schizophrenia (FiPS-S), a nested case-control study that included archived maternal sera from virtually all pregnancies since 1983 (total N over 1 million). We identified all offspring in the cohort diagnosed with schizophrenia based on the national inpatient and outpatient register and matched them to comparison subjects (1:1) from the cohort on sex, date of birth, and residence in Finland at time of onset of the case. Maternal sera on 1010 case-control pairs were assessed for free thyroxine (fT4) and 948 for thyroid stimulating hormone (TSH).

Results—Maternal hypothyroxinemia (fT4 10th percentile, normal TSH) was associated with an increased odds of schizophrenia (OR=1.75, 95% CI=1.22 – 2.50; p=0.002). When adjusted for maternal psychiatric history, province of birth and maternal smoking during pregnancy, the association remained significant (OR=1.70, 95%CI 1.13 – 2.55; p=0.010).

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Conflict of Interest Disclosures: All the authors report no biomedical financial interests or potential conflicts of interest.

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

Keywords

schizophrenia; thyroid; prenatal; neurodevelopment; biomarker; cohort

INTRODUCTION

Exposure to low thyroid hormone levels *in utero* alters offspring brain development in both animal models and humans (¹⁻³). Experimental rodent studies have shown that maternal thyroxine (T4) deficiency, even in the mild range, causes aberrant prenatal neurodevelopment (¹⁻³). One such outcome, based on studies of rat dams, is abnormal distribution of neurons in the hippocampus; this can be prevented by replacement of maternal T4 in early pregnancy (⁴).

In humans, the fetus is completely dependent on maternal T4 during early gestation, as fetal T4 production commences during gestational weeks 12-14 (⁵). Maternal T4 crosses the placenta and fetal T4 correlates well with maternal T4 (⁶). Clinical hypothyroidism during pregnancy is an established risk factor for offspring cognitive dysfunction (⁷) and neuroanatomic abnormalities including reduced hippocampal volume (⁸). Low maternal fT4 in the absence of clinical hypothyroidism is termed hypothyroxinemia and defined as fT4 below the 10th percentile with normal levels of thyroid stimulating hormone (TSH). Notably, an emerging literature has yielded intriguing evidence that hypothyroxinemia is also associated with delayed cognitive, motor (⁹⁻¹¹) and speech development in offspring (¹¹).

Because schizophrenia is associated with disrupted prenatal neurodevelopment, and impaired cognitive function (¹²), we tested the hypothesis that maternal hypothyroxinemia, and low, continuously defined maternal fT4 levels during early to mid-gestation are associated with offspring schizophrenia. In a supplemental aim, we examined whether offspring schizophrenia is associated with maternal hypothyroidism, and with other maternal clinical thyroid disorders (see "Methods, Laboratory assays and classification of thyroid disorders", for definitions).

METHODS AND MATERIALS

The investigation was based on the Finnish Prenatal Study of Schizophrenia (FiPS-S) which utilized 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. Therefore, 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 the cohort and the biobank

All subjects in the FiPS-S study 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 (total N is over one million). Sera were drawn during the first trimester or the early second trimester (5th to 95th percentile=months 2-4 of pregnancy) from over 98% of the gravidae, following informed consent, for screening of HIV, syphilis, and hepatitis. One maternal serum sample was obtained for each pregnancy. After the screening, the remainder of each sample was stored as one aliquot at -25°C in a single, centralized biorepository (THL). All of the serum samples in the FMC can be linked with offspring by the unique personal identification number (PIN), which has been assigned to all residents of Finland by the Finnish Population Registry since 1971. The PINs of the mothers of cases and matched controls were linked to the FMC sera biobank and to other registers discussed below.

Finnish Population Register

The computerized nationwide Finnish Population Register (FPR) 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 THL, 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/secondary psychiatric diagnoses.

In order 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 1,514 (¹³). A sufficient amount of maternal sera was available in the study to measure fT4 on 1,010 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 controls drawn from the FMC who were without schizophrenia, other non-affective psychotic disorders and bipolar disorder on the date of birth (+/- 1 month), sex and being a resident of Finland at the time of case diagnosis. The controls for the study were randomly drawn from all controls fulfilling these criteria, since there were many controls 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, IL). The lower limits of detection for fT4 and TSH were 5.1 pmol/l and 0.0025 mIU/l, respectively. The intra- and interassay variation, respectively, were 3.6% and 7.8% for fT4, and 1.7% and 5.3% for TSH.

To facilitate the clinical interpretation of the data, we conducted supplemental analyses of maternal serologically defined thyroid disorders in relation to schizophrenia. Given that fT4 varies during pregnancy (¹⁵, ¹⁶), the lack of trimester-specific 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, namely 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 >95th percentile; hyperthyroidism as fT4 >95th percentile and TSH 5th percentile; and subclinical hyperthyroidism as fT4 >5th - 95th percentile and TSH :55th percentile. See Table 2 for 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 1). Gestational week of the blood draw was obtained from the FMC, while all other covariates were derived from the Finnish Population Register. The degree of urbanization of the birth municipalities were classified based on national standards used by Statistics Finland (²⁶): a densely populated area was defined as a 250 meter² area with > 200 inhabitants. Municipalities with 90% of the population living in densely populated areas were classified as urban, those with 60-89% as semi-urban and those with <60% as rural. Urbanicity and province of birth were highly correlated in controls ($\chi^2 = 134.7$, df = 6; $p < 0.0001$), and 50.8% of the controls born in Southern Finland were born in an urban area (n=292/575). In accord with standard epidemiologic practice, covariates were included in the final model if they were associated at $p < 0.1$ with both 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 it occurred several months after the blood draw, maternal hypothyroidism has an impact on it (³⁰), has been associated with hypothyroxinemia during the first trimester (²⁵) and has been related to schizophrenia (²⁰).

Ethical approval

The study was approved by the ethical committees of the Hospital District of Southwestern Finland, by the National Institute of Health and Welfare (THL), 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').

Chi square, Fisher exact and t-tests were used to evaluate relationships between each covariate, thyroid hormones, and schizophrenia. Because of the skewness of the data, fT4 levels were log transformed before being analyzed as continuous variables. This variable was normally distributed following transformation to log-fT4. In order to further facilitate the interpretation of the data, we then examined maternal thyroid disorders as categorical variables (see Table 2, footnote for classifications). Appropriate to the nested case-control design, point and 95% confidence intervals (CI) of odds ratios (OR) 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 males and females. For this purpose, we analyzed the association between fT4 and schizophrenia stratified by sex and also tested for interaction by adding the sex-by-fT4 interaction term into the statistical model. Associations were considered statistically significant at $p < 0.05$. All statistical analyses were conducted using SAS software (SAS 9.2, SAS Institute, Cary, NC, USA).

RESULTS

As shown in Table 1, case-control status was associated with twinning, maternal psychiatric history of schizophrenia spectrum disorders, affective disorders and any psychiatric disorder, degree of urbanization and province of birth. None of these potential confounders were associated with fT4 or hypothyroxinemia (Table 1). Preterm birth was associated with case-control status, fT4 under the median and hypothyroxinemia at $p < 0.1$. There were also associations between birth province and hypothyroidism, between degree of urbanization and subclinical hypothyroidism and between twinning and subclinical hyperthyroidism (Supplemental Table 1).

We first analyzed schizophrenia in relation to maternal hypothyroxinemia as shown in Table 2 (defined as fT4 < 10th percentile and normal TSH). The proportion of subjects with

maternal hypothyroxinemia was 11.8% among schizophrenia subjects compared to 8.6% among controls, yielding a significant association (OR=1.75, 95% CI=1.22 – 2.50, $p=0.002$). In a sensitivity analysis, we defined hypothyroxinemia as fT4 under the 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 controls, and the OR was 1.62 (95% CI=0.99 – 2.63, $p=0.055$).

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 offspring schizophrenia. In the conditional logistic regression analysis, the odds of schizophrenia decreased by almost 50% per log unit increase of maternal fT4 (OR=0.54, 95% CI=0.31-0.94, $p=0.028$). The association between log-transformed TSH and schizophrenia was not significant (OR=0.93, 95% CI=0.84 – 1.02, $p=0.108$).

While none of the potential confounders were associated with both schizophrenia and fT4 or hypothyroxinemia (Table 1), we conducted additional adjustments for variables that are strongly related to schizophrenia. Following adjustment of hypothyroxinemia for maternal psychiatric history, province of birth and maternal cotinine, a biomarker of smoking, the OR's 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 non-significant (Table 3).

We considered the possibility that mothers of cases might have failed to adequately increase TSH 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 cases ($r^2 = 0.029$, $p = 0.079$) than controls ($r^2 = 0.014$, $p = 0.299$).

In a supplemental analysis we examined whether other maternal serologically defined thyroid disorders were associated with schizophrenia (Table 2). Maternal hypothyroidism was not associated with schizophrenia ($p=0.827$). However, the number of subjects was small as clinical hypothyroidism was documented in mothers of only six cases and eight controls. Further, in this exploratory analysis, subclinical hyperthyroidism was significantly associated with offspring schizophrenia (OR=1.91, 95% CI=1.14 – 3.20, $p=0.014$).

Because the risk of schizophrenia varies by sex (¹²), we conducted supplementary sex-stratified analyses of the association between maternal fT4 and schizophrenia: the odds ratio for males was 0.36 (95% CI 0.17 – 0.76) and for females was 0.87 (95% CI 0.40 – 1.94). However, when pooling both sexes, the sex-by-fT4 interaction term was not statistically significant ($p=0.11$).

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 1, 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 0.86 – 2.15, p = 0.184). Though birth weight was not associated with hypothyroxinemia or schizophrenia (Table 1), for the purpose of comparability, we also adjusted for birth weight. The OR was decreased by 22% and the p-value was non-significant (OR=1.43, 95% CI 0.90 – 2.26, p=0.130).

DISCUSSION

We have demonstrated, in a nationwide cohort, that early to mid-gestational serologically defined maternal hypothyroxinemia was associated with an increased odds of offspring schizophrenia. As noted in the introduction, 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), while mixed results were found when the same exposure was measured during the late second trimester or third trimester as noted in a recent 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. Following 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. While we observed an association in the unadjusted analysis, adjustment for maternal smoking resulted in a greater than 20% change in the odds ratio (towards the null) and the finding was no longer statistically significant. This 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 the lowest tenth percent of the distribution. Another possibility is that there was not sufficient power to detect a significant finding when the exposure was defined as continuous fT4. This is supported by the fact that the confidence intervals in the unadjusted and adjusted analyses of log-fT4 overlap considerably though 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 T4 to triiodothyronine (T3), the active form, which regulates gene expression by binding to nuclear thyroid hormone receptors (³³). Many T3-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 T3-regulated gene expression is a mechanism accounting for some histological abnormalities seen in offspring exposed to maternal hypothyroxinemia (³⁵). In rodent studies, experimentally induced

maternal hypothyroxinemia causes offspring histological abnormalities, such as abnormal distributions of neurons in the hippocampus (⁴, ³⁶). This is particularly relevant to schizophrenia, in which morphological and functional abnormalities of the hippocampus have been documented in patients (³⁷).

Another possible explanation for the finding is mediation by preterm birth and/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) and 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); 3) there is a prior literature indicating that preterm birth/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 thus met criteria for a potential mediator. When hypothyroxinemia was adjusted for preterm birth, the OR decreased by 28% and the p-value became non-significant (p=0.19). 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. Following adjustment, for birth weight the association was attenuated though somewhat less than for preterm birth (22%), with p-value 0.13, 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 six mothers of cases had hypothyroidism. Maternal hypothyroxinemia has been related to subtle neurodevelopmental deficits (³), some of which are observed in schizophrenia (¹²), while 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 properly evaluate schizophrenia symptoms, could potentially also explain the lack of an association.

The one result that was not hypothesized *a priori* was the association between subclinical hyperthyroidism 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 schizophrenia patients than among mothers of patients with other psychiatric disorders. Further, 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 a supplemental analysis and no previous study examined subclinical hyperthyroidism necessitates caution in the interpretation.

As noted, a supplemental analysis revealed that the relationship between maternal FT4 and schizophrenia was observed only among males. Differential loss of females 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 ($p=0.11$).

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 body mass index (BMI), given its association with schizophrenia (⁴³) and the previously demonstrated correlations between high BMI and hypothyroxinemia (^{24, 25}). Unfortunately, we were not able to examine the relationship between BMI and hypothyroxinemia in our data.

The 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 controls than in schizophrenia cases. Previous studies have shown instead that twinning is increased in schizophrenia (⁴⁴) or no relation to schizophrenia (⁴⁵). While we have no ready explanation for this, we speculated on the reasons in a previous publication (¹³).

Several methodological 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 to mid-gestation, but not later during pregnancy. Hence, 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 not available on maternal thyroid replacement, such as levothyroxine, for thyroid disorders. However, pregnant mothers of the vast majority 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, due to the fact that the cohort was born relatively recently, the age at the first treatment of the schizophrenia cases in this study was relatively low (mean 19.1; maximum 26). Therefore, the results may not be representative of schizophrenia cases with onset later in life. Finally, though we tested whether several key covariates were associated with both the exposure and the outcome, there is the potential for residual confounding.

Further, it is unlikely that maternal hypothyroxinemia is a risk factor that is specific to schizophrenia. As noted above, 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 therefore suggest future studies of maternal hypothyroxinemia as a risk factor for other psychiatric disorders. Likewise, it would be of interest 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 (MIA) as a risk factor for schizophrenia, a "two-hit" model has been suggested⁽⁵⁰⁾. In a rodent study, an initial insult of MIA interacted synergistically with later stress during adolescence to cause neuropathological 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.

To conclude, we found an association between low maternal thyroxine and increased odds of offspring schizophrenia. The finding is biologically plausible as it is consistent with an extensive literature on maternal hypothyroxinemia as a disruptor of offspring neurodevelopment^(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 level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Previous presentation: An oral presentation of the work was given at the Annual Meeting of the Society of Biological Psychiatry in New York, NY, in May 2014 and as poster presentations at the 104th Annual Conference of the American Psychopathological Association, New York, March 2014, and at the 61st Annual Meeting of the American Academy of Child and Adolescent Psychiatry, San Diego, October 2014.

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Figure 1.

The proportion of schizophrenia cases and controls by maternal free thyroid hormone (fT4) units (panel A) and the odds of schizophrenia by maternal fT4 (panel B). The categorization of fT4 units in panel B correspond to the categorization of fT4 in panel A. Because conditional logistic regression used in the main analyses of matched pairs does not provide an intercept, the fitted line in panel B is derived from standard logistic regression of log-transformed fT4 predicting schizophrenia in the data without considering the matching ($N_{\text{cases}} = 1,010$; $N_{\text{controls}} = 1,010$; intercept = 1.60, slope = -0.57 , standard error of slope = 0.27, equaling odds ratio = 0.57, 95% confidence interval = 0.34 – 0.96, $p = 0.034$).

Table 1

Covariates in relation to schizophrenia and to maternal early gestational free thyroxine (fT4) levels and hypothyroxinemia in controls.

Covariates ^a	Cases (n=1,010) Mean (SD)	Controls (n=1,010) Mean (SD)	p ^j	fT4 <median (n=503) Mean (SD)	fT4 median (n=507) Mean (SD)	p ^j	Hypothyroxine mia (n=78) Mean (SD)	No hypothyroxinem a (n=672) Mean (SD)	p ^j
Age of mother at birth	28.5 (5.5)	28.2 (5.1)	0.240 _k	28.2 (5.1)	28.3 (5.1)	0.81 ₈	29.2 (4.9)	28.2 (5.1)	0.08 ₆
Gestational week of blood draw ^b	11.0 (4.0)	10.8 (4.1)	0.368	11.2 (4.5)	10.3 (3.5)	0.00 ₁	12.3 (5.7)	10.8 (4.0)	0.00 ₄
	N (%)	N (%)	p ^l	N (%)	N (%)	p ^l	N (%)	N (%)	p ^l
Previous births (1)	626 (62.0)	624 (61.8)	0.927	313 (62.2)	311 (61.3)	0.77 ₂	50 (64.1)	410 (61.0)	0.59 ₆
Twin ^c	20 (2.0)	42 (4.2)	0.005	17 (3.4)	25 (5.0)	0.21 ₂	2 (2.6)	27 (4.0)	0.75 ₉
Maternal history of psychiatric disorders									
Schizophrenia and other nonaffective psychoses ^d	104 (10.3)	14 (1.4)	<0.00 ₀₁	8 (1.6)	6 (1.2)	0.58	0 (0.0)	11 (1.6)	0.61 _{6m}
Affective disorders ^e	216 (21.4)	83 (8.2)	<0.00 ₀₁	45 (9.0)	38 (7.5)	0.40 ₁	8 (10.3)	55 (8.2)	0.53 _{2m}
Any psychiatric disorder ^f	332 (32.9)	140 (13.9)	<0.00 ₀₁	78 (15.5)	62 (12.2)	0.13 ₂	11 (14.1)	91 (13.5)	0.89 ₁
Maternal education level ^g			0.259			0.95 ₉			0.61 ₈
No education after secondary school	261 (25.9)	229 (22.8)		115 (22.9)	114 (22.6)		22 (28.2)	146 (21.8)	
Vocational degree or secondary school graduate	568 (56.5)	574 (57.1)		284 (56.6)	290 (57.5)		42 (53.9)	384 (57.3)	
College degree or bachelor university degree	120 (11.9)	141 (14)		73 (14.5)	68 (13.5)		9 (11.5)	95 (14.2)	
Master degree or PhD	57 (5.7)	62 (6.2)		30 (6.0)	32 (6.4)		5 (6.4)	45 (6.7)	
Degree of urbanization of birth municipality			0.033			0.19 ₄			0.58
Urban	631 (62.5)	575 (56.9)		279 (55.5)	296 (58.4)		43 (55.1)	385 (57.3)	
Semi-Urban	125 (12.4)	135 (13.4)		77 (15.3)	58 (11.4)		13 (16.7)	84 (12.5)	
Rural	254 (25.2)	300 (29.7)		147 (29.2)	153 (30.2)		22 (28.2)	203 (30.2)	
Birth province			<0.00 ₀₁			0.20 ₁			0.17 ₁
Southern Finland Province	488 (48.3)	376 (37.2)		195 (38.8)	181 (35.7)		30 (38.5)	259 (38.5)	
Eastern Finland Province	126 (12.5)	153 (15.2)		84 (16.7)	69 (13.6)		10 (12.8)	98 (14.6)	

Covariates ^a	Cases (n=1,010) Mean (SD)	Controls (n=1,010) Mean (SD)	p ^j	ft4 <median (n=503) Mean (SD)	ft4 median (n=507) Mean (SD)	p ^j	Hypothyroxine mia (n=78) Mean (SD)	No hypothyroxinem a (n=672) Mean (SD)	p ^j
Western Finland Province	266 (26.3)	348 (34.5)		159 (31.6)	189 (37.3)		22 (28.2)	237 (35.3)	
Northern Finland Province	130 (12.9)	133 (13.2)		65 (12.9)	68 (13.4)		16 (20.5)	78 (11.6)	
Gestational age at birth ^b			0.073			0.07 3 ^m			0.08 8 ^m
31 weeks or less	9 (1.2)	3 (0.4)		3 (0.8)	0 (0.0)		1 (1.6)	1 (0.2)	
32-36 weeks	43 (5.9)	32 (4.5)		19 (5.0)	13 (3.9)		5 (8.2)	16 (3.4)	
37-40 weeks	508 (69.8)	532 (74.9)		271 (71.5)	261 (78.9)		43 (70.5)	350 (75.1)	
41 weeks or more	168 (23.1)	143 (20.1)		86 (22.7)	57 (17.2)		12 (19.7)	99 (21.2)	
Birth weight ⁱ			0.524			0.32 4 ^m			0.11 6 ^m
Under 1500 grams	11 (1.5)	6 (0.8)		5 (1.3)	1 (0.3)		2 (3.3)	3 (0.6)	
1500-2499 grams	20 (2.8)	19 (2.7)		9 (2.3)	10 (3.0)		2 (3.3)	11 (2.3)	
Over 2500 grams	697 (95.7)	691 (96.5)		371 (96.4)	320 (96.7)		57 (93.4)	458 (97.0)	

Abbreviations: ft4, free thyroxine; TSH, thyroid stimulating hormone; SD, standard deviation; SSD, schizophrenia spectrum disorder or other non-affective psychoses.

^aThere were no missing values on any covariate, except for those noted in footnotes b, c, d, g, h and i.

^bFrequency missing = 139 cases, 142 controls.

^cFrequency missing = 4 cases, 4 controls.

^dICD-10 codes F20-25, F28-29, ICD-9 codes 295, 297, 298.9X, 301.2C, and ICD-8 codes 295, 297, 298.20, 298.30, 298.99, 299.

^eICD-10 codes F30-34, F38-39, ICD-9 codes 296, 300.4, 298.8A, and ICD-8 codes 296, 298.00, 298.10, 300.41.

^fIn addition to the above this includes ICD-10 codes F84, F40-45, F48, F50-53, F55, F59-66, F68-69, F99, F10-19, ICD-9 codes 299, 300-300.3, 300.5-301.1, 301.2 excluding 301.2C, 301.3-301.9, 302, 307.1A, 307.4A, 307.4F, 307.4H, 307.5A, B, C & E, 307.8A, 307.9X, 309-309.1, 309.2 excluding A&B, 309.2D, E & F, 309.3-309.9 excluding 309.3A & 309.4A, 312.0A, 312.1-312.2, 312.3 excluding 312.3D, 312.4-312.9, 291-292, 303-305, and ICD-8 codes 308, 300.0-300.3, 300.4, 300.5-302.9, 305, 306.40, 306.50, 306.98, 307.99, 291, 303-304.

^gFrequency missing = 4 cases, 4 controls.

^hFrequency missing = 282 cases, 294 controls.

ⁱFrequency missing = 282 cases, 300 controls.

^jP-value based on pooled t-test assuming equality of variances, except for those noted in footnote k.

^kP-value based on Satterthwaite t-test assuming inequality of variances.

^lP-value based on chi-square test, except for those noted in footnote m.

^mP-value based on Fisher's exact test.

Table 2

Categorical measures of maternal free thyroxine (fT4) and thyroid stimulating hormone (TSH) in relation to offspring schizophrenia

Maternal condition	Cases	Controls	OR (95% CI)	p
	N (%)	N (%)		
Hypothyroxinemia				
No ^a	649 (71.9)	672 (74.4)	1	-
Yes ^b	107 (11.8)	78 (8.6)	1.75 (1.22 - 2.50)	0.002
Clinical thyroid disorders				
Reference ^c	740 (81.9)	746 (82.6)	1	-
Hypothyroidism ^{d,e}	6 (0.7)	8 (0.9)	0.86 (0.23 - 3.24)	0.827
Subclinical hypothyroidism ^{f,g}	29 (3.2)	36 (4.0)	0.80 (0.47 - 1.37)	0.424
Hyperthyroidism ^h	15 (1.7)	16 (1.8)	0.87 (0.41 - 1.82)	0.706
Subclinical hyperthyroidism ^{i,j}	50 (5.5)	29 (3.2)	1.91 (1.14 - 3.20)	0.014

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

^aDefined as fT4 >14.03 - 19.96 pmol/l (>10th - 90th percentile) and TSH >0.24 - 3.38 mIU/l (>5th - 95th percentile)

^bDefined as fT4 <14.03 pmol/l (<10th percentile) and TSH >0.24 - 3.38 mIU/l (>5th - 95th percentile)

^cDefined as fT4 >13.43 - 21.84 pmol/l (>5th - 95th percentile) and TSH >0.24 - 3.38 mIU/l (>5th - 95th percentile)

^dDefined as fT4 <13.43 pmol/l (<5th percentile) and TSH >3.38 mIU/l (>95th percentile)

^eAdjusted for degree of urbanization of birth municipality.

^fDefined as fT4 >13.43 - 21.84 pmol/l (>5th - 95th percentile) and TSH >3.38 mIU/l (>95th percentile)

^gAdjusted for birth province.

^hDefined as fT4 >21.84 pmol/l (>95th percentile) and TSH <0.24 mIU/l (<5th percentile)

ⁱDefined as fT4 >13.43 - 21.84 pmol/l (>5th - 95th percentile) and TSH <0.24 mIU/l (<5th percentile)

^jAdjusted for twinning.

Table 3

Additional adjustments of the association between maternal hypothyroxinemia and offspring schizophrenia.

Model	OR (95% CI)	p
Categorical hypothyroxinemia ^a during early gestation		
Unadjusted	1.75 (1.22 - 2.50)	0.002
Individually adjusted for maternal psychiatric history ^b	1.92 (1.30 - 2.83)	0.001
Individually adjusted for province of birth	1.78 (1.23 - 2.57)	0.002
Individually adjusted for maternal smoking during early gestation ^c	1.62 (1.12 - 2.37)	0.012
Adjusted for maternal psychiatric history, province of birth and maternal smoking	1.70 (1.13 - 2.55)	0.010
Log transformed fT4 during early gestation		
Unadjusted	0.54 (0.31 - 0.94)	0.028
Individually adjusted for maternal psychiatric history ^b	0.53 (0.30 - 0.94)	0.029
Individually adjusted for province of birth	0.57 (0.33 - 0.999)	0.049
Individually adjusted for maternal smoking during early gestation ^c	0.71 (0.39 - 1.27)	0.243
Adjusted for maternal psychiatric history, province of birth and maternal smoking	0.74 (0.40 - 1.38)	0.342

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

^aDefined as fT4 < 14.03 pmol/l (< 10th percentile) and TSH > 0.24 - 3.38 mIU/l (> 5th - 95th percentile).^bMaternal history of any psychiatric disorder. See footnote of Table 1 for complete list of ICD-codes.^cBased on log transformed cotinine levels, a metabolite of nicotine and biomarker of smoking, in maternal sera from the Finnish Maternity Cohort.