Maternal and Birth Characteristics Are Determinants of Offspring Thyroid Function

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Background: Intrauterine adaptation to the outside environment is an important mechanism via which the fetus increases its chance to thrive after birth. Therefore, various maternal-, pregnancy-, and labor-related factors are potential determinants of thyroid function of the offspring. Animal studies suggest that very high maternal thyroid hormone levels during pregnancy can alter the development of the hypothalamic-pituitary-thyroid axis set point of the child. However, to what extent maternal and birth characteristics (including maternal thyroid function, smoking, and birth weight) are associated with thyroid function of the offspring is currently unknown.

Methods: We selected 4273 mother-child pairs from a large population-based prospective cohort with data available on maternal gestational TSH and free T4 (FT4) levels and newborn TSH and FT4 (n = 3339; at birth) or childhood TSH and FT4 (n = 2523; median age, 6 y). We used multivariable (non)linear regression models to study the association of potential determinants (including maternal TSH, FT4, thyroid peroxidase antibodies, iodine excretion, age, body mass index, smoking status, parity, pre-eclampsia, fetal distress, gestational age at birth, birth weight, mode of delivery, and thyroid function-associated single nucleotide polymorphisms) with newborn and childhood TSH and FT4.

Results: There was a strong association of maternal TSH and FT4 levels during pregnancy with newborn and childhood TSH and FT4 levels, respectively (for both, \( P < .0001 \)). Maternal FT4 was also associated with newborn TSH levels (\( P < .0009 \)). Birth weight, fetal distress, gestational age at birth and maternal parity were all associated with newborn TSH and/or FT4 (\( P < .0001 \)), but these associations did not persist into childhood. Genetic risk scores for TSH and FT4 were strongly associated with newborn and childhood thyroid function (\( P < .0005 \)). The association between maternal and offspring thyroid function did not change after correction for genetic risk scores.

Conclusions: In this study, childhood thyroid function was predominantly determined by maternal TSH or FT4 levels and thyroid-specific single nucleotide polymorphisms. Effects of stress-related changes in thyroid function at birth were transient. Other potential factors were not associated with offspring thyroid function. (J Clin Endocrinol Metab 101: 206–213, 2016)

As a key regulator of metabolism, thyroid hormone (TH) plays an important role in the growth and maturation of many target tissues. To meet tissue requirements, the production of TH is regulated via the hypothalamic-pituitary-thyroid (HPT) axis with a TH set point that is specific for each individual. During intrauterine development of the HPT axis, the fetal thyroid gland is not functionally matured, and therefore the fetus predominantly depends on the placental transfer of maternal T4 (1, 2). Animal as well as human studies have suggested that very high or very low maternal TH levels during development may induce a shift in the HPT axis set point of the offspring (3–10). We have previously shown that maternal thyroid function is positively associated with offspring thyroid function at birth (11). However, it

Abbreviations: BMI, body mass index; FT4, free T4; GRS, genetic risk score; hCG, human chorionic gonadotropin; HPT, hypothalamic-pituitary-thyroid; SNP, single nucleotide polymorphism; TH, thyroid hormone; TPOAb, thyroid peroxidase antibody.
remains unknown whether differences within the normal maternal thyroid function spectrum are associated with thyroid function of the offspring later in life and whether other factors, including genetics and birth characteristics, may underline the association of maternal thyroid function with newborn or childhood thyroid function.

Developmental adaptivity refers to the process by which the fetus is prepared for the environment it is about to enter, and this adaptivity plays an essential role in providing the optimal chances of survival and reproductive success for the offspring (12). Developmental adaptivity can lead to fetal programming of adult disease via, for example, endocrine changes in insulin, androgen, glucocorticoid, and/or IGF-1 levels (12). As such, prolonged exposure to slightly higher or lower TH levels may also affect maturation, metabolic state, and eventually the risk of adverse clinical outcomes via an intra-uterine shift in the HPT axis set point. However, it remains unknown to what extent maternal and birth characteristics are associated with childhood thyroid function.

Clinical data on the association of maternal thyroid function and characteristics, birth characteristics, and common genetics variants with offspring thyroid function are sparse, whereas this type of data may increase our knowledge on mechanisms that lead to interindividual differences in thyroid function. Therefore, we investigated the association of maternal and fetal characteristics with thyroid function in newborn and school-aged children in a large population-based prospective cohort study.

**Subjects and Methods**

**Study design and participants**

This study was embedded in the Generation R Study, a population-based prospective cohort from early fetal life onward in Rotterdam, The Netherlands (13). Maternal TSH or free T4 (FT4) levels were determined in 6065 mothers; in their offspring, TSH and FT4 were measured in cord blood samples at birth (n = 3388) and during childhood at a median age of 6 years (n = 4306). Women with twin pregnancies (n = 128), pre-existing thyroid disease (n = 85), thyroid-interfering medication usage (n = 4), or fertility treatment (n = 76) and children with thyroid disease or chronic illness (endocrine, inflammatory, autoimmune, cancer, or kidney disease; n = 12) or thyroid (interfering) medication usage (levothyroxine or GH; n = 7) were excluded. The final study population comprised 4273 mother and child pairs with data on maternal gestational TSH and FT4 levels and newborn TSH or FT4 (n = 3339) or childhood TSH or FT4 (n = 2523). As compared to mother-child pairs for which data were available for both newborn and childhood thyroid function, mother-child pairs with data availability for only newborn thyroid function were more likely to have a spontaneous delivery, and the mothers were slightly younger; this was opposite for mother-child pairs with data availability for only childhood thyroid function. There was no difference in maternal TSH and FT4 levels or thyroid peroxidase antibody (TPOAb) positivity between the mother-child pairs based on data availability.

**Determinants and covariates**

We selected potential determinants based on current knowledge on maternal, pregnancy, or birth characteristics and associations with other outcomes (14), biological plausibility, and data availability. These included maternal TSH, FT4, TPOAbs, age, body mass index (BMI), smoking status, parity, pre-eclampsia, fetal distress, gestational age at birth, birth weight (standardized to gestational age at birth), mode of delivery, and thyroid function-associated single nucleotide polymorphism (SNPs). Gestational age at blood sampling was defined using fetal ultrasound data on crown-rump length or biparietal diameter for pregnancy dating. Information on maternal age and smoking status was obtained by questionnaires during pregnancy. Maternal weight and length were measured at intake and used to calculate BMI. Maternal smoking status was classified as no smoking, smoking until known pregnancy, and continued smoking during pregnancy. Information on fertility treatment, delivery, pregnancy outcome, date of birth, birth anthropometrics, and the gender of the child was obtained from community midwives, obstetricians, and hospital registries. Pre-eclampsia was defined according to international criteria that were described in detail previously (15); this diagnosis was cross-checked by certified doctors. Medical and obstetrical history were assessed by questionnaires, and answers were cross-checked by certified medical doctors. Models were adjusted for maternal education level and child ethnicity, BMI, and age, which were obtained by questionnaires and measurement at a visit to our research center (the same time as blood sampling), respectively. Maternal education levels consisted of three categories: no education finished/primary school/secondary phase one; secondary phase two/higher education phase one; and higher education phase two. Child ethnicity was determined by country of origin of the child and/or parents and was defined according to the classification of Statistics Netherlands and categorized according to the major ethnic groups in Rotterdam. In a subset of women, urinary iodine/creatinine ratios were available (overlapping n = 1095 with newborn and n = 502 with childhood thyroid function data availability), details of which have been described previously (16). Although we have previously described the linear association of maternal thyroid function with cord blood thyroid function, these analyses did not take into account the potential effect of important potential confounders/mediators, and therefore we believe that new analyses on this association and also on the investigation of maternal and birth characteristics as determinants of cord blood thyroid function measurements will add significantly to the previous analyses (11).

Data on SNPs were obtained with the Illumina 670 K platform and subsequent imputation using phase 2 of the CEPH HapMap project. These data were only available for a subset of children: n = 3111 for children with data on newborn TSH or FT4; and n = 1833 for children with data on childhood TSH or FT4. We calculated a genetic risk score (GRS) for each child according to SNPs that have been associated with thyroid function in adult populations (17–20). Of the total 67 SNPs that have been identified to be associated with thyroid function (18), we were able to obtain data from 56 SNPs that were either the original SNP or an SNP in high linkage disequilibrium (R2 > 0.9) with the original SNP. Of these 56 SNPs, the SNPs that were in high linkage disequilibrium with each other (R2 > 0.3) and the SNPs that had an opposite effect estimate, compared to the reported effect estimates in adult GWAS studies, were excluded. This resulted in a final selection of 20 SNPs for TSH and six for FT4 that were used for construction of the GRS. The GRS was calculated by multiplying the reported adult effect size and the
copy number of effect alleles for each person (0, 1, or 2). Due to the
ethnic heterogeneity of our study population, we performed a sen-
sitivity analysis for all GRS analyses by excluding non-Caucasian
children. Further details on genetic data determination, quality con-
trols, and infrastructure used have been described previously (13).

Cord blood thyroid function is notoriously influenced by
stress-related factors, and therefore the variability according to
genetics may be lower as compared to later childhood. We in-
vestigated this by assessing the difference in standardized effect
size estimates of the association between the GRS and either
newborn or childhood TSH or FT4.

Procedures
Maternal serum samples were obtained in early pregnancy (me-
dian, 13.2 wk; 95% range, 9.8–17.5), cord blood samples were
obtained directly after birth (median gestational age at birth, 40.1
wk; 95% range, 35.9–42.3), and child serum samples were ob-
tained at the time of visiting our research center (median age, 6 y;
95% range, 5.6–7.9). Plain tubes were centrifuged, and serum was
stored at −80°C. TSH and FT4 were determined in maternal and
cord blood serum samples using chemiluminescence assays (Vitros
ECI; Ortho Clinical Diagnostics). The intra- and inter assay coeffi-
cients of variation were < 4.1% for TSH at a range of 3.97–22.7
mU/L and < 5.4% for FT4 at a range of 14.3–25.0 pmol/L. Ma-
ternal TPOAbs were measured using the Phadia 250 immunoassay
(Phadia AB) and were considered positive when > 60 IU/mL. Maternal
total human chorionic gonadotropin (hCG) levels (same sample as
thyroid function) were analyzed in serum using an Immulite XPi system
(Siemens Healthcare Diagnostics), details of which have been described
previously (17). Child TSH and FT4 levels for the median age of 6 years
were determined using an electrochemiluminescence immunoassay on
the Cobas e601 immunoanalyzer (Roche Diagnostics). The intra- and
inter assay coefficients of variation were 1.1–3.0% for TSH at a range of
0.4–0.04 mU/L and 1.6–5.0% for FT4 at a range of 1.6–24.1
pmol/L. Details on hCG measurements and characteristics have been
described in detail previously (17).

Statistical analyses
Nonlinearity of the association between continuous variables
and newborn/childhood TSH or FT4 levels was investigated by
ordinary least squares linear regression models with restricted
cubic splines. We used multiple linear regression models to in-
vestigate the association between other variables and newborn/
childhood TSH or FT4. Covariates were selected based on bio-
logical confounding plausibility, change in effect estimate of the
variable of interest, or the reduction of residual variance of the
model. Covariates included child sex, age, BMI, ethnicity, house-
hold income, and maternal education level. We also added hCG
to the model based on the underlying physiology and biological
effects similar to TSH, but this did not change the results. We
accounted for the high number of statistical tests (75 in total) by
controlling the false discovery rate (Benjamini and Hochberg)
using the fdrtool package (18, 19). This method allows for tai-
lored identification of the expected proportion of false positive
results among all rejected null hypotheses. We allowed for a maximum
of one expected false positive test result that corresponded with a P
value of < .009, which was thus considered as statistically significant.
All analyses were performed using R statistical software version 3.03
(package Hmisc, rms, fdrtool) or Statistical Package of Social Sciences
version 20.0 for Windows (SPSS Inc).

Results
Descriptive statistics of the study population (1) are shown
in Supplemental Table 1. The outcomes of standard mul-
tiple linear regression models investigating the association
between potential fetal programming determinants and
newborn thyroid function or childhood thyroid function
are shown in Supplemental Tables 2 and 3.

Flowchart for mother-child pairs in the final study population.

Maternal TSH or FT4 measurement available
N=6065 mother-child pairs

Excluded N=1480
No child serum available
(at birth or in childhood)

Children with TSH or FT4 measurement
N=4585 mother-child pairs

Excluded N=312
Twin pregnancies (N=128)
Pre-existing maternal thyroid disease or thyroid
(interfering) medication usage (N=89)
Children with thyroid/chronic disease or thyroid
(interfering) medication usage (N=19)

Final study population
N=4273 mother-child pairs

Children with cord blood
TSH or FT4 measurement
N=3339

Children with childhood
TSH or FT4 measurement
N=2523

Overlap N=1589

Figure 1. Flowchart for mother-child pairs showing how the final study population was selected. Differences in selected populations are
described in the Subjects and Methods section.
Maternal thyroid function as a determinant of newborn and childhood thyroid function

There was a positive association of maternal TSH with newborn and childhood TSH (Figure 2, A and B). Maternal TSH levels explained 1.5 and 4.0% of the variability in newborn and childhood TSH levels, respectively. There was a positive association of maternal FT4 with newborn and childhood FT4 (Figure 2, C and D). Maternal FT4 levels explained 1.6 and 2.9% of the variability in newborn and childhood FT4 levels, respectively.

There was a negative association between maternal FT4 and newborn TSH (Figure 3), and this association remained unchanged after additional adjustment of newborn FT4 (data not shown). Maternal TSH was not associated with newborn or childhood FT4, and maternal FT4 was not associated with childhood TSH (Supplemental Tables 2 and 3; similar when nonlinear associations were analyzed). There was no difference in newborn and childhood TSH or FT4 between TPOAb-positive and TPOAb-negative mothers (Supplemental Tables 2 and 3). All results remained unchanged after addition of a GRS for TSH and FT4 to the model, and maternal urinary iodine/creatinine ratio was not associated with newborn or childhood thyroid function (data not shown). There was no effect modification by child gender (data not shown).

Common genetic variants as determinants of newborn and childhood thyroid function

A GRS for TSH was associated with newborn TSH, explaining between 0.8 and 1.0% of the variability in newborn TSH (Figure 4A). A GRS for FT4 was associated with newborn FT4, explaining between 0.2 and 0.3% of the variability in newborn FT4 (Figure 4D). A GRS for TSH was associated with childhood TSH, explaining 5.3 to 5.5% of the variability of childhood TSH (Figure 4B). A GRS for FT4 was associated with childhood FT4 and explained between 1.9 and 3.6% of the variability of childhood FT4 (Figure 4C).

The combined effect of SNPs on newborn TSH was 60% less as compared to the effects of the same SNPs on childhood TSH (Table 1). The combined effect of SNPs on newborn FT4 was 62% less as compared to the effects of the same SNPs on childhood FT4 (Table 1).

To investigate the extent to which the effects of the GRS and maternal thyroid function overlapped, we investigated the explained variability of different models for newborn or childhood thyroid function (Table 2). These analyses showed that the overlap of the explained variability between maternal TSH and a GRS for TSH was 7.8% and 5.5% for newborn and childhood TSH, respectively. The overlap of explained variability between maternal FT4 and a GRS for FT4 was 5.1% for both newborn and childhood FT4.

GWAS data of the mothers was not available, but because mother-child pairs are expected to share about half of their genetics, we investigated whether the GRS scores based on thyroid related SNPs in the offspring would be associated with maternal thyroid function. We found

Figure 2. The association of maternal TSH and FT4 during pregnancy with thyroid function of the offspring. Plots show the association between maternal TSH or FT4 levels during pregnancy and child TSH or FT4 at birth or during childhood as predicted mean with 95% confidence interval.
that the offspring GRS for TSH was associated with maternal TSH levels and the offspring GRS for FT4 was associated with maternal FT4 levels (Supplemental Figure 1).

Discussion

In this large population-based prospective cohort study among healthy mother-child pairs, we investigated which perinatal maternal and birth characteristics were associated with thyroid function of the offspring at birth and during later childhood. We demonstrated that maternal TSH and FT4 levels are the strongest predictors for both newborn and childhood TSH and FT4 levels, respectively. Maternal FT4 was also associated with newborn TSH levels. Various stress-related factors were associated with newborn TSH and FT4, but these associations did not persist into childhood. We also show evidence that offspring thyroid function may differ according to the inherited SNPs that have been associated with thyroid function.

Intrauterine fetal adaptation to the outside environment is an important mechanism via which the fetus increases its chance to thrive after birth. Animal studies and case reports suggest that offspring exposed to very high maternal TH levels have central hypothyroidism, decreased TSH and/or greater resistance to TH at the level of the pituitary (4–8). Our findings among a healthy population demonstrate a strong positive association of maternal TSH and FT4 during pregnancy with offspring TSH and FT4, respectively, suggesting that maternal thyroid function is the strongest determinant of the offspring HPT-axis development in normal physiology. Interestingly, in this study the association of maternal thyroid function during pregnancy with offspring thyroid function attenuated as maternal TSH or FT4 levels increased, suggesting a ceiling effect protecting the offspring from a too extreme HPT-axis set point. Although this is purely speculative, it may also be plausible that the true association between maternal thyroid function during pregnancy and offspring thyroid function has a U-shape (TSH) or inverted U-shape (FT4) because very high levels of FT4 have been shown to cause central congenital hypothyroidism and loss of integrity of thyroid morphology (3, 5, 6).

For maternal thyroid function, we found that TSH was associated with childhood TSH and maternal FT4 with childhood FT4. There was no association between maternal TSH and childhood FT4 or vice versa. This suggests that there is an important genetic component in the specific establishment of the TSH or FT4 set point. Alternatively, this may suggest that the set point development for TSH and FT4 is not as intertwined as would be expected but is separately determined.

Figure 3. Plots show the association between maternal FT4 levels during pregnancy and child TSH at birth as predicted mean with 95% confidence interval.

Figure 4. The association between GRS and newborn or child TSH and FT4. Plots show the association between a GRS for TSH or FT4 and, respectively, TSH or FT4 at birth or during childhood as predicted mean with 95% confidence interval.
by factors such as genes and maternal TSH and FT4, respectively. Interestingly, we did find that maternal FT4, which is known to cross the placenta, was associated with TSH in newborns. Although a maximum of 30–50% of newborn T4 levels can be reached via transplacental transportation of maternal T4, this number is likely lower in healthy newborns (20, 21). The association of maternal FT4 with newborn TSH remained similar after adjustment for newborn FT4 and a GRS for FT4. Although we cannot exclude the effects of binding proteins, undiscovered genetic variants, or other residual confounding, our data confirm that T4 that passes the placenta during late pregnancy influences the newborn HPT axis.

Many research efforts focus on the association of maternal thyroid (dys)function during early pregnancy and child development. It is possible that part of the adverse health outcomes associated with maternal thyroid dysfunction (ie, cognitive development) is mediated by prolonged exposure to slightly higher or lower TH levels. We previously showed that the association of maternal thyroid function during pregnancy with child IQ and magnetic resonance imaging outcomes does not change after additional correction for childhood TSH and FT4 (22). However, future research is needed to elucidate to what extent the strong association between gestational thyroid function of the mother and offspring thyroid function can confound the association of maternal thyroid function during pregnancy and other child outcomes.

Cord blood measurements of TH have been deemed more unreliable as compared to other serum thyroid function measurements because newborn thyroid function is subdue to stress-related factors. The associations of stress-related markers including maternal parity, fetal distress, gestational age at birth, birth weight, and mode of delivery with cord blood TSH and/or FT4 in this study confirm the effects of stress on newborn thyroid function. We also show that the effect of thyroid SNPs for newborn TSH and FT4 was 60 and 62% lower, respectively, compared to childhood TSH and FT4 levels. Together with a much lower explained variability of the GRS for cord blood TSH and FT4, these findings re-emphasize the role of stress as a determinant of thyroid function in newborns. However, because we were able to study thyroid function at two time points, we demonstrated that the stress-related changes in newborn TSH and FT4 are transient and do not persist into early childhood.

We showed that previously identified SNPs associated with thyroid function in adults explain 5.3–5.5% and 1.9–3.6% of the variability in childhood TSH and FT4, respectively. In a similar approach, a recent study by Taylor et al. (23) among a mixed population of children and adults from the United Kingdom found that a GRS based on 67 known thyroid function-related SNPs explained 7.1% of the variability in TSH but only 1.9% of the variability in FT4 levels. Most likely, the differences between explained variability reported in both studies are due to a difference in GRS methodology because based on a similar direction of the association with TSH or FT4 as in the populations they were identified in and excluded SNPs in high linkage disequilibrium. This overcomes collinearity and overestimation of allelic effects. In addition, we used adult betas from another population as opposed to betas from our own population. Alternatively, differences between the Dutch and UK populations can also be caused by differences in population characteristics such as iodine status. Interestingly, the study by

### Table 1. Combined Effect of Genes Associated With TSH or FT4 and Association With Newborn or Childhood Thyroid Function

<table>
<thead>
<tr>
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<th>Newborn</th>
<th>Childhood</th>
<th>Difference Between Newborn and Childhood Levels, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta \pm SE$</td>
<td>$P$</td>
<td>Standardized $\beta$</td>
</tr>
<tr>
<td>TSH</td>
<td>0.218 ± 0.43</td>
<td>&lt;.0001</td>
<td>0.091</td>
</tr>
<tr>
<td>FT4</td>
<td>0.055 ± 0.019</td>
<td>.005</td>
<td>0.051</td>
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Analyses show $\beta$ coefficients with standard error and standardized $\beta$ coefficients (for comparison between effect estimates for different outcomes) for the association between a GRS for TSH or FT4 and newborn or childhood TSH or FT4, respectively.
Taylor et al (23) also demonstrated that the total genetically explained variability in their mixed childhood/adult population (based on all independent SNPs) is about 24% for TSH and 20% for FT4. The results by Taylor et al (23) and the quite low explained variabilities reported in this study suggest that most genetic determinants for thyroid function remain to be identified. Potentially, such undiscovered genetic determinants may underlie the association between maternal and offspring thyroid function and/or the low overlap in explained variability of the maternal thyroid function and GRSs of 5.1–7.8%. Future studies are needed to identify more genetic determinants of thyroid function and to investigate to what extent genetic thyroid function determinants overlap between children and adults.

Maternal TPOAb positivity, particularly during pregnancy, has been associated with TPOAb levels in cord blood and an increased risk of TPOAb positivity of the offspring (10, 24, 25). In a study by Päkkilä et al (10) among 16-year-old offspring, a difference in TPOAb levels and particularly TPOAb positivity between children from TPOAb-positive versus TPOAb-negative mothers (9.0 vs 3.7% for boys, and 22.7 vs 7.5% for girls; both, $P < .001$) was shown, but this difference did not result in differences for TSH or FT4 levels (10). This is in line with our study, in which we also did not find any differences in TSH or FT4 levels in children from TPOAb-positive mothers compared to TPOAb-negative mothers (10). Combined with the fact that TPOAbs are in themselves biologically inactive, it is likely that maternal TPOAbs have no clinically relevant effects on the thyroid function of the child. Taken together, these data suggest that the clear genetic link of TPOAb positivity does not lead to thyroid function changes before adulthood.

This is the first study to investigate the effects of fetal programming on newborn and childhood thyroid function. We were able to study a large number of mother-child pairs that had extensive pregnancy, phenotype, and thyroid function data available, which allowed us to test for many potential fetal programming factors. We retained a proper multiple testing correction and used flexible modeling techniques that allowed us to better capture physiological thresholds in the association between maternal thyroid function and offspring thyroid function as compared to other studies. Although the explained variability in child thyroid function by maternal thyroid function was only 1.5–4%, it is important to note that the variation and measurement error of both maternal and childhood thyroid function lead to suboptimal models and underestimation of the effect size. Nonetheless, these numbers may also suggest that many determinants remain to be identified. Although there were no relevant differences between the groups of data availability (mother, newborn, child overlap), we were limited by the fact that thyroid function data during pregnancy, birth, and childhood did not fully overlap. Another potential limitation is the fact that we did not have any data on whether women received thyroid medication after inclusion in the study. Given that all measurements were performed after pregnancy and there is no screening program for thyroid dysfunction during pregnancy, it is very unlikely that this would affect our results. We were also limited by the fact that data on child TPOAb levels were unavailable. Nevertheless, in the study by Päkkilä et al (10), TPOAb positivity did not influence child TSH or FT4 levels at age 16, and it is therefore unlikely that in our younger sample this would have influenced our results. Finally, there were no genetic data available from the mothers. This made it impossible to study to what extent overlap between maternal and child genetics influences the association between maternal and offspring thyroid function.

In conclusion, this study demonstrates that there is a consistent association between maternal thyroid function during pregnancy and thyroid function of offspring at birth and during childhood. Stress-related factors are an important determinant of newborn thyroid function, but these effects do not persist into childhood. More classical markers of fetal programming such as birth weight and maternal smoking were not associated with offspring thyroid function. Future research is needed to investigate whether the strong association between maternal thyroid function during pregnancy and childhood thyroid function could potentially confound or mediate the association of maternal thyroid function during pregnancy and adverse child outcomes.

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