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Maternal thyroid hormone trajectories during pregnancy and child behavioral problems☆

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ABSTRACT

There is ample evidence demonstrating the importance of maternal thyroid hormones, assessed at single trimesters in pregnancy, for child cognition. Less is known, however, about the *course* of maternal thyroid hormone concentrations during pregnancy in relation to child behavioral development. Child sex might be an important moderator, because there are sex differences in externalizing and internalizing behavioral problems. The current study examined the associations between maternal thyroid hormone trajectories versus thyroid assessments at separate trimesters of pregnancy and child behavioral problems, as well as sex differences in these associations. In 442 pregnant mothers, serum levels of TSH and free T4 (fT4) were measured at 12, 24, and 36 weeks gestation. Both mothers and fathers reported on their children's behavioral problems, between 23 and 60 months of age. Latent growth mixture modeling was used to determine the number of different thyroid hormone trajectories. Three trajectory groups were discerned: 1) highest and non-increasing TSH with lowest fT4 that decreased least of the three trajectories; 2) increasing TSH and decreasing fT4 at intermediate levels; 3) lowest and increasing TSH with highest and decreasing fT4. Children of mothers with the most flattened thyroid hormone trajectories (trajectory 1) showed the most anxiety/depression symptoms. The following trimester-specific associations were found: 1) lower first-trimester fT4 was associated with more child anxiety/depression, 2) higher first-trimester TSH levels were related to more attention problems in boys only. A flattened course of maternal thyroid hormone concentrations during pregnancy was a better predictor of child anxiety/depression than first-trimester fT4 levels.

The importance of thyroid hormones for fetal brain development has been demonstrated in numerous studies over the past 50 years (for a review see, Henrichs et al., 2013). Many studies have demonstrated that even subtle impairments of thyroid function during pregnancy, such as maternal hypothyroxinemia (i.e., low free T4, normal TSH levels), can impede child cognitive development (Henrichs et al., 2013). Less is known about maternal thyroid function during pregnancy in relation to behavioral problems of children. Maternal thyroid dysfunction during pregnancy has been associated with cognitive developmental problems, such as language delays (Henrichs et al., 2010) and impaired executive functioning (Van Mil et al., 2012). Such cognitive problems have been found to be predictive of internalizing (i.e., depression, anxiety) and externalizing behavioral problems (i.e., aggression, attention problems, hyperactivity; Brownlie et al., 2004; Hagberg et al., 2010; Bornstein et al., 2013). Therefore, suboptimal maternal thyroid hormone functioning may also be associated with children's behavioral problems.

A series of studies within the Generation R project found evidence for this proposition. Thyroid dysfunction during pregnancy (i.e., higher maternal TSH levels, hypothyroxinemia, higher thyroid-peroxidase antibody levels) was found to be associated with more externalizing problems in infants (Ghassabian et al., 2011, 2012) and 6-year-olds (Ghassabian et al., 2014). In another study, child behavioral problems were examined in the context of iodine insufficiency during pregnancy (Vermiglio et al., 2004). In the iodine insufficient region, 50% of the mothers was hypothyroxinemic, and 88% of these hypothyroxinemic women had a child who was diagnosed with ADHD.

Moderating or mediating factors on the association between maternal thyroid hormones and child development are almost unknown (Henrichs et al., 2013). One such factor is child sex, which seems especially important in the context of child behavioral problems. Males are consistently more vulnerable to developing externalizing problems in the context of biological or environmental risk factors, whereas females are more vulnerable to developing internalizing problems (Zahn-

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Waxler et al., 2008). On the contrary, one recent study showed that higher maternal TSH levels were associated with more ADHD symptoms in girls, but not in boys, suggesting that girls might be more vulnerable to maternal thyroid deviations (Päkkilä et al., 2014). However, as this association was weak and the underlying mechanisms unclear, further study is warranted.

Little is also known about the *course* of maternal thyroid hormone concentrations during pregnancy in relation to child development, even though longitudinal thyroid assessments might be a more valid reflection of changes in thyroid hormones during pregnancy than assessments at one time point during pregnancy (Stricker et al., 2007). During normal pregnancy free thyroid hormones decrease while serum TSH levels correspondingly rise (Stricker et al., 2007). For most women, these changes are within the normal range but individual differences in the patterns of thyroid hormone changes during pregnancy (Stricker et al., 2007) may be predictive of child development (Pop et al., 2003). One small study by Pop and colleagues showed that children of mothers with low free T4 (fT4) levels early in pregnancy who showed an increase in fT4 later in pregnancy, and children of mothers with higher fT4 levels in early pregnancy that steeply decreased during pregnancy, scored within the normal range on the Bayley scales. However, mothers with low fT4 that further decreased during pregnancy had children with the lowest mental and motor development scores. The association between thyroid hormone trajectories during pregnancy and child outcomes needs to be replicated in larger studies and with more advanced statistical techniques, such as growth modeling.

The current study examined whether individual differences in thyroid hormone trajectories (fT4 and TSH levels) during pregnancy were a better predictor of child behavioral problems than maternal thyroid hormone concentrations assessed at one trimester of pregnancy. We also examined whether there were sex differences in the associations between maternal thyroid hormone trajectories or thyroid assessments at one trimester of pregnancy and child behavioral problems.

1. Methods

1.1. Sample

This study is part of a prospective research line examining the influence of prenatal maternal emotional symptoms and parental interaction styles on the self-regulation and behavioral adjustment of toddlers and preschoolers. Between July 2002 and May 2005, midwives working in seven community midwifery practices in the southern regions of the Netherlands (Kempen) invited healthy Dutch-Caucasian pregnant women on their first antenatal check-up (10–12 weeks gestation) to participate in a study on maternal thyroid hormone and delivery (Wijnen, 2005). See Fig. 1 for a flow-chart of the sample recruitment and exclusion criteria. Information was available for 1093 women. After pregnancy, the women were asked again by one of the midwives (HAAW) to participate in our research. In total, 444 mothers agreed to participate and returned questionnaires about the behavioral problems of their children (De Bruijn et al., 2009). Two families had missing thyroid data, resulting in a final sample of $N = 442$. The sample included six late preterm babies (between 34 and 36.9 weeks). As exclusion of these children did not change the results, they were retained in the current dataset. See Table 1 for sample characteristics.

1.2. Assessments

1.2.1. Maternal thyroid function parameters

Serum levels of TSH, fT4 and TPO-Ab were measured at 12, 24, and 36 weeks gestation. TSH was measured using a solid-phase, two-site, chemiluminescent enzyme immunometric assay (IMMULITE third generation TSH, Diagnostic Corporation, Los Angeles, CA). TSH reference range for women 20 to 40 years was 0.15–2.0 mIU/l. The inter-assay coefficients of variation were 9.8, 6.9, and 4.60–0, at concentrations of 0.02, 0.15, and 11 mIU/l, respectively. The fT4 concentration was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4). fT4 reference range for women 20 to 40 years was 8.7–19.6 pmol/l. The inter-assay coefficients of variation for this technique were 20, 5.3, and 5.20 ~ o at concentrations of 3.1, 19.8, and 55 pmol/l, respectively. TSH levels had to be square-root transformed to achieve a normal distribution on all three measurements. The IMMULITE Anti-TPO Ab kit was used for the determination of antibodies against thyroid peroxidase. The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The TPO assay was standardized in terms of the International Reference Preparation for TPO MRC 66/387. Women with TPO-Ab

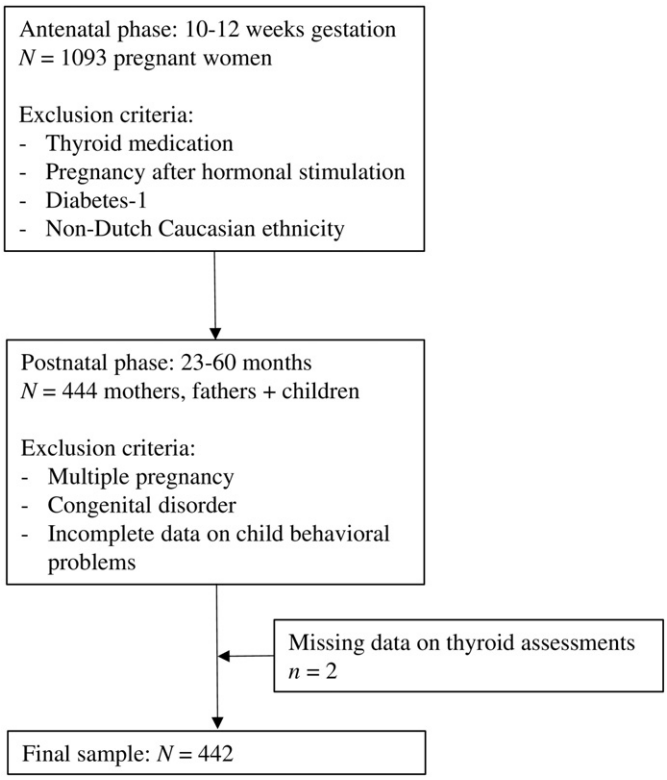

Fig. 1. Flow chart of sample recruitment.

Table 1
Sample characteristics of 442 women and their offspring.

	Overall sample
	M (*SD*)
Maternal characteristics	
Age at birth	30.69 (3.72)
Educational level (%)	
Low	11
Middle	46
High	43
Prenatal psychopathology symptoms[a]	
Depression	14.41 (3.39)
Anxiety SCL	12.38 (2.76)
Anxiety STAI	30.27 (7.27)
Child characteristics	
Male sex(%)	51
Birth weight	3538 (476)
Gestational age (weeks)	39.85 (1.33)
Age at assessment (months)	29.31 (10.38)

[a] Prenatal psychopathology symptoms were assessed with the Edinburgh Depression Scale (range: 0–30), State-Trait Anxiety Inventory (range: 20–80), Symptom Checklist anxiety scale (range: 10–50). Scores were standardized and averaged to create an overall psychopathology score.

concentrations higher than 35 kU/l at 12 weeks gestation were regarded as being antibody-positive.

In the current sample at 12 weeks gestation, a total of 9 mothers (2%) fulfilled the criteria for hypothyroxinemia, using fT4 values below the 2.5th percentile (fT4 < 11.97 pmol/l) with TSH levels within the reference range in the full sample of TPO-Ab negative mothers (Furnica et al., 2015; TSH 0.15–2.9 mIU/l). When other cut-off points for fT4 were used for values below the 5th percentile (fT4 < 12.40 pmol/l) or 10th percentile (fT4 < 13.30 pmol/l), respectively 26 (6%) and 49 (11%) of the mothers were considered hypothyroxinemic.

1.2.2. Child behavioral problems

Both mothers and fathers individually completed the Child Behavior Check List (CBCL/1.5–5; Achenbach and Rescorla, 2000) to evaluate the behavioral problems of their children between 23 and 60 months of age. This CBCL-version is specifically developed for children between 1.5 and 5 years old. The CBCL/1.5–5 is a parent-completed questionnaire that contains 100 behavioral and emotional problem items. For each item parents indicated whether a problem was seen frequently (2), sometimes (1), or not (0). The results are differentiated according to internalizing (anxiety, depression, withdrawn behavior) or externalizing (attention difficulties, aggression) problems, and summed for each subscale. To obtain a robust assessment of child behavioral problems and to avoid excluding children for which only one parent filled out the CBCL, mother ($n = 434$) and father ($n = 368$) scores were averaged. This averaging is appropriate considering the fact that mother and father scores were strongly and significantly correlated ($rs > 0.52$, $ps < 0.01$) and there were no mean level differences between mother and father scores ($ps > 0.22$). For research purposes Achenbach (1991) recommends using raw total scores, because standardized *T*-scores reduce variability especially in the low-end of the distribution. However, raw scores cannot be easily compared across sex. Therefore, standardized *T*-scores were also computed using Achenbach and Rescorla's (2000) normative sample for the CBCL/1.5–5. Norm-referenced *T*-scores above 70 are in the clinical range. *T*-scores between 65 and 70 are in the borderline/clinical range. *T*-scores below 65 are in the normal range. Analyses examining sex differences were conducted on both *T*-scores and raw scores to detect possible differences in outcomes. All other analyses were conducted on raw scores.

1.2.3. Covariates

The following variables were considered potential confounders based on previous research: gestational age and weight at birth, child age at time of CBCL assessment, parity, breastfeeding, mothers' age, maternal psychopathology symptoms (prenatal and at time of CBCL assessment), smoking and alcohol use during pregnancy, and educational level (Pop et al., 1995, 2003; Kooistra et al., 2006; Cleary-Goldman et al., 2008; Ghassabian et al., 2011). We also controlled for TPO-Ab in all analyses.

Maternal psychopathology symptoms were assessed with three widely used and valid questionnaires filled out at 12, 24 and 36 weeks gestation and when the children were between 23 and 60 months of age: Edinburgh Depression Scale (EDS; Cox et al., 1987), the State version of the Dutch State-Trait Anxiety Inventory (STAI; Van der Ploeg et al., 2000), and the anxiety subscale of the Dutch version of the Symptom Check List (SCL-90; Arrindell and Ettema, 2003; Derogatis et al., 1973). The focus was specifically on anxiety and depression as these are the most common disorders during pregnancy (O'Hara and Wisner, 2014). The EDS is a 10-item self-report scale designed as a screening instrument for depression. Items were scored on four-point rating scales and total scores on the EDS ranged between 0 and 30. The State version of the STAI consists of 20 items measuring transient anxiety or anxiety at the moment of scoring. Items were scored on four-point rating scales and total scores on the State subscale ranged between 20 and 80. The anxiety scale of the SCL-90 consists of 10 items, measuring anxiety symptoms. Items were scored on five-point rating scales and total scores on the SCL-90 anxiety subscale ranged between 10 and 50. Strong correlations were found between the scores on the questionnaires at different weeks in pregnancy and between the different questionnaires (see De Bruijn et al., 2009). Therefore, the scores on the STAI, EDS and SCL were standardized and averaged to arrive at scores for mothers' prenatal as well as postnatal symptoms of psychopathology.

1.3. Analyses

1.3.1. Sex differences

Sex differences were analyzed using SPSS. Repeated measures analyses of variance, with either fT4 or TSH levels at the 3 trimesters as repeated measures and child sex as between-subject variable, were used to examine sex differences in maternal thyroid function parameters and the course of fT4 and TSH levels during pregnancy. Independent samples *t*-tests were used to examine sex differences in behavioral problems. Pearson correlations were determined to examine whether maternal thyroid function parameters in one of the three trimesters of pregnancy were associated with boys' or girls' internalizing and externalizing problems. To avoid multiple testing on the subscales of the internalizing and externalizing problem scales, further analyses on subscales were only conducted in case of an association between maternal thyroid parameters and either the internalizing or externalizing total scale (post hoc analyses). Hierarchical regression analyses were conducted to formally test whether child's sex moderated the associations between child behavioral problems and thyroid function parameters at a single trimester in pregnancy. Covariates (see Covariates section) were entered in the first step, thyroid function parameters (fT4, TSH) and child sex in the second step, and the interaction between thyroid function parameters and child sex in the third step. Inclusion of covariates was determined based on the change-in-estimate method (5% change criterion) (Rothman et al., 2008).

1.3.2. Thyroid trajectories

To model the individual thyroid hormone trajectories during pregnancy, we employed latent growth mixture modeling (GMM) in Mplus, using full information maximum likelihood estimation with parallel processes for fT4 and TSH change. With GMM it is possible to classify individuals in distinct groups based on their individual fT4 and TSH trajectories during pregnancy. The classification is made so that individuals within a group are more similar than individuals between groups. GMM is a person-centered approach that allows for different growth trajectories, instead of conventional growth modeling that assumes that a single growth trajectory can adequately describe an entire population (Jung and Wickrama, 2008). Added advantage of the parallel process GMM is that two related processes can be modeled at the same time. The number of groups was selected by fitting a series of linear parallel process GMMs that ranged from one to five trajectories. We selected the number of trajectory groups on the basis of several criteria. First, Nylund, Asparouhov, and Muthén (2007) showed that from all fit indices available in Mplus, the Bayesian Information Criterion (BIC) and Bootstrapped Likelihood Ratio Test (BLRT) are the most appropriate for selecting the final number of trajectory groups. Smaller BIC values indicate a better model fit and significant BLRT values imply that the current model has a better fit than the model with less trajectory groups. Second, a number of other criteria are also important to consider, such as class size, largest decrease in BIC, and high entropy, i.e. indicating a clear distinction between the different trajectory groups (Jung and Wickrama, 2008; Nylund et al., 2007). Individual thyroid hormone trajectories were modeled either in relation to externalizing problems or internalizing problems as they could influence class membership.

Next, class membership was exported to SPSS. Analyses of variance (ANOVA) or chi-square tests were used to compare the different thyroid trajectory groups with regard to the covariates, and internalizing and externalizing problems. In the ANOVAs on internalizing and

externalizing problems, child sex and thyroid trajectory groups were entered as between-subjects factors, to examine whether relations between maternal thyroid hormone trajectories during pregnancy and behavioral problems were different for boys and girls. Lastly, we tested whether thyroid hormone trajectories during pregnancy were better able to predict child behavioral problems than individual TSH and fT4 levels assessed at a single trimester. To this end we used hierarchical regression analyses in which relevant covariates were entered in the first step, thyroid function parameters at single trimesters in the second step, and thyroid trajectory groups in the third step. To avoid multiple testing, these analyses were only conducted in case of a trimester-specific association between TSH or fT4 and an aspect of child behavioral problems.

1.3.3. Effect sizes

Effect sizes were automatically calculated by SPSS, except for Cohen's *d* that was calculated with an online effect size calculator (http://www.uccs.edu/lbecker/index.html). Cohen's criteria (1992) were used to determine the size of the effects. Small effects are defined as: $d = 0.2$, *partial* $\eta^2 = 0.01$, $r = 0.10$, $R^2 = 0.01$. Medium effects are defined as: $d = 0.5$, *partial* $\eta^2 = 0.06$, $r = 0.30$, $R^2 = 0.09$. Large effects are defined as: $d = 0.8$, *partial* $\eta^2 = 0.14$, $r = 0.50$, $R^2 = 0.25$. Only medium or larger effect sizes are regarded as clinically relevant. As most effects are small, only medium or large effects are explicitly mentioned in the Results section.

2. Results

2.1. Cross-sectional trimester-specific relation between thyroid hormones and child behavioral problems

Descriptive statistics for maternal thyroid hormones at each trimester are shown in Table 2, separate for boys and girls. As can be seen in Table 2, TSH levels strongly increased during pregnancy, whereas fT4 levels declined significantly during pregnancy. Boys were exposed to higher levels of maternal TSH than girls, whereas boys were exposed to similar fT4 levels as girls throughout pregnancy.

Descriptive statistics for internalizing and externalizing problems are shown in Table 3, separate for boys and girls. As can be seen in Table 3, boys showed higher levels of externalizing problems than girls. However, no sex difference was found in internalizing problems.

2.1.1. Sex differences in association between thyroid function parameters and child behavioral problems

Table 4 presents correlations between maternal thyroid hormones and child problem behavior for boys and girls separately. Higher TSH in the first trimester was associated with more externalizing problems in boys only. Post-hoc analyses revealed that higher first-trimester TSH was related to higher Attention Problems scores in boys, $r(224) = 0.21$, $p < 0.01$. Boys also presented more attention problems than girls (see Table 3).

Lower fT4 in the first trimester was associated with more internalizing problems in girls only. Post-hoc analyses revealed that this association was primarily driven by anxiety/depression, $r(218) = 0.17$, $p < 0.05$, despite no overall sex difference on the Anxiety/depression subscale (see Table 3). Associations between child behavioral problems and maternal thyroid function parameters in the second and third trimester were not significant.

Table 3
Descriptive statistics for boys' and girls' problem behavior and results of *T*-tests on sex differences.

	Boys *M* (*SD*)	Girls *M* (*SD*)	*t*	*p*	*d*
Internalizing problems					
Raw scores	6.01 (4.65)	5.93 (4.46)	0.18	NS	0.02
T-scores	45.39 (8.32)	45.24 (8.62)	0.19	NS	0.02
Anxiety/depression					
Raw scores	1.18 (1.37)	1.11 (1.33)	1.16	NS	0.05
T-scores	50.99 (2.71)	50.93 (2.29)	0.28	NS	0.02
Externalizing problems					
Raw scores	12.52 (6.28)	11.16 (6.64)	2.21	<0.05	0.21
T-scores	49.73 (7.86)	47.81 (8.54)	2.46	<0.05	0.24
Attention problems					
Raw scores	2.54 (1.67)	2.07 (1.57)	3.11	<0.01	0.29
T-scores	53.93 (4.74)	52.87 (4.35)	2.46	<0.05	0.23

Note. *T*-scores represent norm referenced standardized scores in which age and sex are taken into account. NS means nonsignificant.

Hierarchical regression analyses, in which we controlled for maternal educational level, confirmed that higher first-trimester TSH was related to higher Attention Problems scores in boys only (see Fig. 2). This interaction between child sex and TSH levels was significant for both CBCL raw scores, $\beta = -0.15$, $p < 0.05$, $\Delta R^2 = 0.01$, total $R^2 = 0.07$, and CBCL *T*-scores, $\beta = -0.13$, $p < 0.05$, $\Delta R^2 = 0.01$, total $R^2 = 0.05$. The association between first-trimester fT4 and anxiety/depression was not significantly different in boys and girls. This interaction between child sex and fT4 levels was not significant for both CBCL raw scores, $\beta = 0.06$, $p = 0.38$, $\Delta R^2 < 0.01$, total $R^2 = 0.02$, and CBCL *T*-scores, $\beta = 0.03$, $p = 0.61$, $\Delta R^2 < 0.01$, total $R^2 = 0.01$. Only the main effect of fT4 on anxiety/depression was significant, $B = 0.01$, $SE = 0.005$, $\beta = 0.12$, $p < 0.05$, total $R^2 = 0.04$, in a model with maternal prenatal psychopathology symptoms as covariate, indicating that for both boys and girls lower fT4 was associated with more anxiety/depression. Too few children with anxiety/depression or attention problems had scores in the borderline/clinical range ($n = 18$ for attention problems, $n = 5$ for anxiety depression) to reliably examine differences in TSH and fT4 between children in the normal versus borderline/clinical range for behavioral problems.

2.2. Thyroid hormone trajectories during pregnancy and child behavioral problems

GMM models for which within-class variation on the growth factors was estimated, did not lead to models that fit the data. Therefore, we fixed growth factor variation to zero within each class. See Table 5 for class solutions of one to five classes, separate for internalizing and externalizing problems. The best fit was a solution with three thyroid trajectory groups, as evidenced by largest decrease in BIC, highest entropy, significant BLRT, and sufficient mothers in each group. In this 3-trajectory solution, slopes were uncorrelated with intercepts, thus change in fT4

Table 2
Descriptive statistics for maternal TSH and fT4 and results of repeated-measures ANOVAs on thyroid hormone change across pregnancy and sex differences.

	T1 *M* (*SD*)	T2 *M* (*SD*)	T3 *M* (*SD*)	*F* (df)	*p*	*Partial* η^2	Significant contrasts
TSH	1.28 (0.82)	1.40 (0.77)	1.53 (0.79)	52.19 (1.93, 810.78)	<0.01	0.11	T1 < T2 < T3
Boys	1.35 (0.86)	1.48 (0.88)	1.63 (0.87)	5.40 (1, 421)	<0.05	0.01	Boys > girls
Girls	1.21 (0.76)	1.32 (0.64)	1.44 (0.68)				
fT4	16.14 (2.48)	13.83 (1.96)	13.18 (1.96)	354.32 (1.91, 799.31)	<0.01	0.46	T1 > T2 > T3
Boys	16.02 (2.51)	13.90 (1.89)	13.24 (2.02)	0.34 (1, 421)	NS		–
Girls	16.27 (2.45)	13.75 (2.02)	13.12 (1.90)				

Note. Abbreviations are; trimester 1 (T1), trimester 2 (T2), trimester 3 (T3), nonsignificant (NS). Means and *SDs* represent nontransformed variables.

Table 4
Correlations between maternal thyroid hormones and internalizing and externalizing problems, separate for boys and girls.

	1.	2.	3.	4.	5.	6.	7.	8.
1. T1 TSH		0.72**	0.74**	−0.29**	−0.12	−0.12	−0.01	−0.04
2. T2 TSH	0.66**		0.77**	−0.17*	−0.08	−0.13	−0.01	−0.02
3. T3 TSH	0.64**	0.74**		−0.15*	−0.12	−0.15*	−0.04	−0.07
4. T1 fT4	−0.28**	−0.31**	−0.26**		0.32**	0.29**	−0.15*	−0.07
5. T2 fT4	−0.11	−0.15*	−0.14*	0.48**		0.42**	−0.07	0.06
6. T3 fT4	−0.07	−0.18**	−0.15*	0.39**	0.47**		−0.13	−0.03
7. Internalizing problems	0.07	0.01	0.00	−0.11	−0.13	−0.10		0.60**
8. Externalizing problems	0.14*	0.06	0.02	−0.05	−0.01	0.01	0.58**	

Note. Abbreviations are; trimester 1 (T1), trimester 2 (T2), trimester 3 (T3). Correlations below the diagonal represent correlations for boys, correlations above the diagonal represent correlations for girls. $N = 429$ for analyses with T2 TSH and T2 free T4, $N = 439$ for analyses with T3 TSH, $N = 437$ for analyses with T3 free T4.

or TSH during pregnancy was independent from first-trimester fT4 and TSH levels. As can be seen in Fig. 3, 21% ($n = 93$) of the pregnant mothers (class 1) are characterized by high TSH levels at baseline with no further increase throughout gestation and low fT4 levels at baseline that decrease least of the three groups. Compared to mothers in class 1, mothers in class 2 (64%, $n = 283$) and 3 (15%, $n = 66$) are characterized by a more steep increase in TSH levels and a more steep decrease in fT4 levels. Mothers in class 3 have higher fT4 and lower TSH levels than mothers in class 2. A chi-square test showed that class solutions from the GMM for internalizing problems were highly similar to class solutions from the GMM for externalizing problems, χ^2 (4) = 793.76, $p <$ 0.01. Only 12 mothers (3%) were classified differently in the two models.

2.2.1. Characterization of the mothers in each trajectory group

In class 1, 13% of the mothers were TPO-Ab positive (TPO-Ab >35), whereas in class 2 and 3 7% and 6% of mothers respectively were TPO-Ab positive, a difference that was significant at 90% level, χ^2 (2) = 3.63, $p = 0.06$. The results were similar when a cut-off of >19 was used for TPO-Ab positivity (Korevaar et al., 2017). The percentage of hypothyroxinemic mothers was not significantly different between the trajectories (*ps* > 0.16). Mothers in class 1 reported more prenatal emotional symptoms than mothers in class 3 (class 1: $M = 0.16$, $SD =$ 0.93; class 3: $M = -0.20$, $SD = 0.64$; $F(2, 436) = 4.19$, $p < 0.05$, *partial* $\eta^2 = 0.02$). The other covariates (see Covariates section) did not differ between the trajectories (*ps* > 0.35).

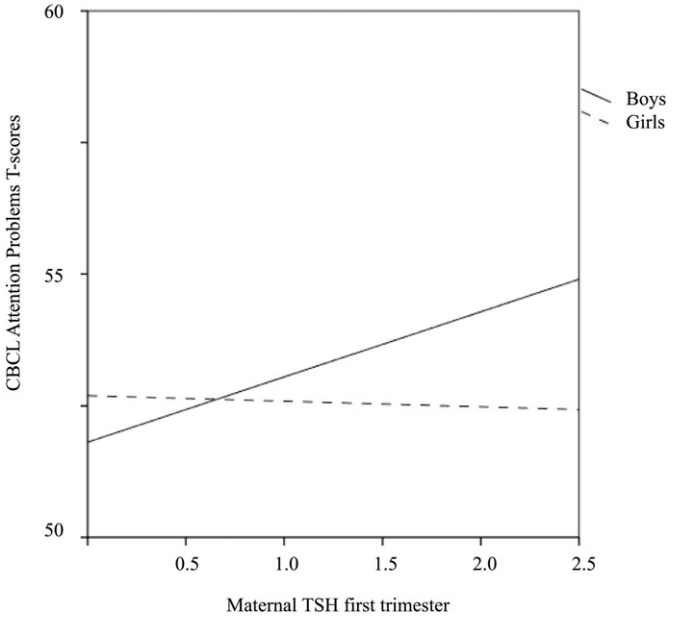

Fig. 2. The association between TSH and attention problems separately for boys and girls.

2.2.2. Associations between trajectory groups and child behavioral problems

The logistic regression in the GMM examining differences in externalizing problems between the thyroid trajectory groups did not reveal significant differences (class 3 vs class 1: $\beta = -0.05$, $SE = 0.03$, $p =$ 0.12, class 2 vs class 1: $\beta = 0.01$, $SE = 0.02$, $p = 0.60$). The logistic regression analysis for internalizing problems revealed that children of mothers in class 3 (lowest and increasing TSH with highest and decreasing fT4), displayed significantly less internalizing problems than children of mothers in class 1 (highest and non-increasing TSH with lowest fT4 that decreased least of the three trajectories) ($\beta = -0.11$, $SE = 0.05$, $p < 0.05$, $e^{\beta} = 0.97$). Class 2 did not differ from class 1 in internalizing problems ($\beta = -0.03$, $SE = 0.03$, $p = 0.26$).

Analyses of variance, with thyroid trajectory groups and child sex as between subject variables revealed an effect of trajectory on anxiety/depression, $F(2, 433) = 4.60$, $p < 0.01$, *partial* $\eta^2 = 0.02$. Specifically, children born to mothers in class 1 showed more anxiety/depression symptoms than did children born to mothers in class 3 (see Fig. 4). There was no interaction between the thyroid trajectory groups and child sex, $F(2, 436) = 0.84$, $p = 0.43$.

2.2.3. Thyroid hormone trajectories as better predictor of child behavioral problems than thyroid function assessments in a single trimester

Thyroid hormone trajectory groups were added to a hierarchical regression analyses in which child attention problems and child anxiety/depression were predicted by respectively TSH and fT4 during the first trimester. The addition of thyroid hormone trajectories led to a significant improvement to the prediction of anxiety/depression ($\Delta R^2 =$ 0.01, $p < 0.05$, total $R^2 = 0.05$, $B = 0.05$, $SE = 0.02$, $\beta = 0.10$, $p < 0.05$) and fT4 levels in the first trimester were no longer a significant predictor of anxiety/depression ($B = 0.01$, $SE = 0.01$, $\beta = 0.09$, $p = 0.06$). Thyroid hormone trajectories did not improve the prediction of child attention problems ($\Delta R^2 < 0.01$, $p = 0.27$, total $R^2 = 0.05$, $B = 0.23$, $SE = 0.21$, $\beta = 0.09$, $p = 0.27$).

3. Discussion

This study examined for the first time whether child behavioral problems could be predicted from trimester-specific maternal thyroid hormones or maternal thyroid hormone trajectories during pregnancy, as well as sex differences in these associations. The following trimester-specific associations were found: higher first-trimester TSH levels were related to more attention problems in boys only, and lower first-trimester fT4 was associated with more child anxiety/depression in both boys and girls. Three thyroid hormone trajectory groups were discerned: 1) highest and non-increasing TSH with lowest fT4 that decreased least of the three groups; 2) increasing TSH and decreasing fT4 at intermediate levels; 3) lowest and increasing TSH with highest and decreasing fT4. Children of mothers with the most flattened thyroid hormone trajectories (trajectory 1) showed the most anxiety/depression symptoms.

Table 5
Class solutions of parallel process GMM models for thyroid hormone level changes (TSH and fT4) during pregnancy in relation to internalizing or externalizing problems of the offspring.

	Number of classes				
	1	2	3	4	5
Internalizing					
BIC	6461.23	6095.19	5941.05	5913.44	5882.67
BLRT	N/A	< 0.01	< 0.01	< 0.01	< 0.01
Entropy	1.0	0.76	0.84	0.75	0.78
Externalizing					
BIC	6472.57	6104.57	5954.67	5917.91	5891.97
BLRT	N/A	< 0.01	< 0.01	< 0.01	< 0.01
Entropy	1.0	0.80	0.83	0.82	0.76

Note. Shaded areas represent best fitting models, based on largest decrease in BIC and largest entropy. Models include following covariates: child sex, mothers' educational level, and internalizing or externalizing problems assessed when the children were between 23 and 60 months of age.

Mothers' thyroid hormone trajectory during pregnancy was a better predictor of child anxiety/depression than first-trimester fT4 levels.

We only found associations between first-trimester thyroid hormones (i.e., fT4, TSH) and child problem behavior (i.e., attention problems, anxiety/depression), and not between later-trimester thyroid hormones and child problem behavior. This finding is consistent with previous studies specifically demonstrating associations between maternal thyroid hormone levels in the first trimester and child cognitive functioning (Pop et al., 1999; Pop et al., 2003). It appears that maternal thyroid hormones in the first trimester of pregnancy are more important for children's behavioral problems than thyroid levels in later trimesters.

The trimester-specific association between higher TSH levels in the first trimester and more attention problems in boys only, is difficult to explain. The association between TSH and attention problems has been demonstrated previously, but in a sample of boys and girls together (Ghassabian et al., 2011). Based on these findings it was suggested that maternal TSH, although not the biologically active hormone in the fetal brain, might be a more sensitive indicator of maternal thyroid functioning, because of the thyroid stimulating effects of hCG in the first trimester of pregnancy (Glinoer et al., 1993). It appears that mild increases in TSH, as a signal of low levels of maternal thyroid hormones, may lead to impaired fetal brain development and subsequent attention problems, specifically in boys. An explanation for this finding in boys might be found in the high levels of testosterone male fetuses start producing from about 8–24 weeks of gestation (Hines, 2011). Testosterone is converted in the brain to estrogens by the enzyme aromatase, while high levels of estrogen are related to neural and behavioral masculinization (Hines, 2011). This period of heightened sex-steroids in the male fetus largely overlaps with the first 20 weeks of pregnancy when the fetus relies completely on the mother for its supply of thyroid hormones (see Williams, 2008). Interestingly, sex steroids have been linked to deiodinase type 3 (D3) activity (Wasco et al., 2003), the major enzyme that converts maternal thyroid hormones to inactive metabolites in

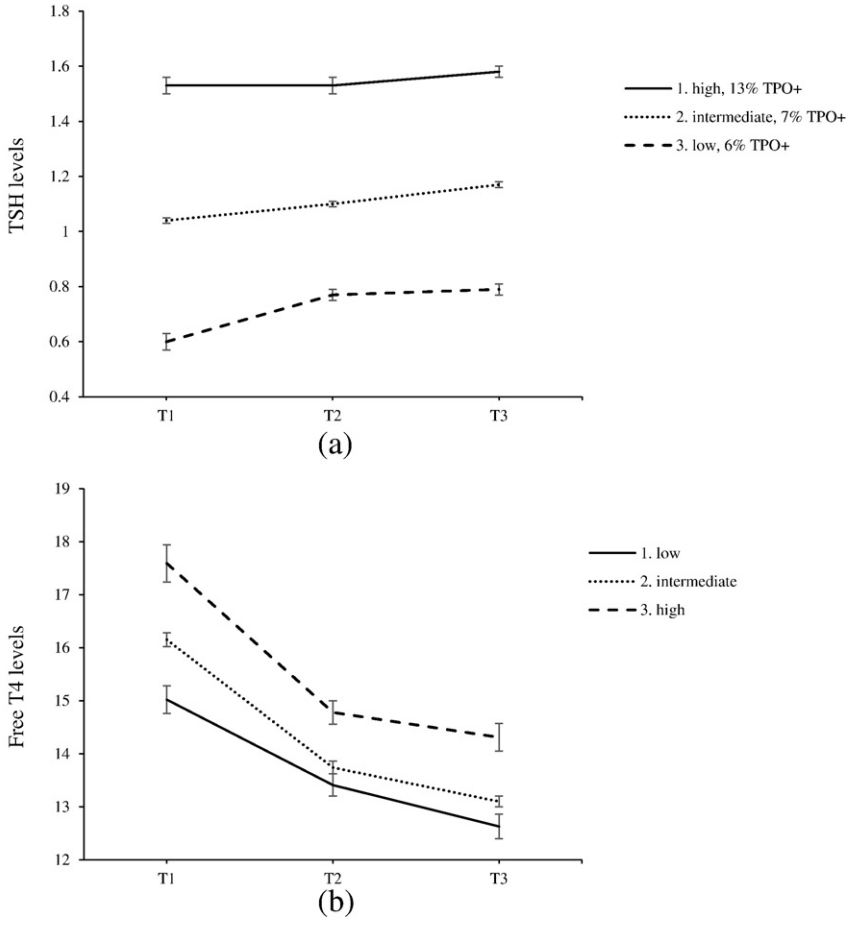

Fig. 3. Three trajectories of TSH (a) and fT4 (b) Change From First to Third Trimester of Pregnancy. *Note*. Thryoid hormone levels on the Y-axis represent nontransformed variables. Mothers in trajectory 1 are characterized by highest initial TSH levels that did not increase during pregnancy and lowest initial fT4 levels that decreased the least of the three groups. Mothers in trajectory 2 are characterized by intermediate initial TSH levels that subsequently increased during pregnancy and intermediate initial fT4 levels that subsequently decreased. Mothers in trajectory 3 are characterized by lowest initial TSH levels that subsequently increased during pregnancy and highest initial fT4 levels that subsequently decreased. TPO + represents percentage of TPO-Ab positive (TPO-Ab >35) mothers in each group.

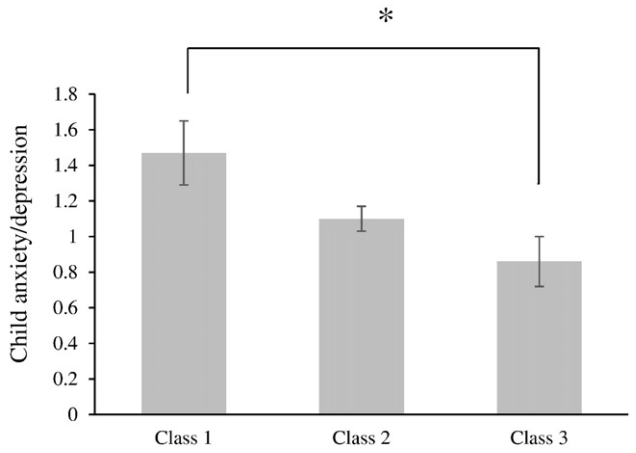

Fig. 4. Child anxiety/depression for different prenatal thyroid hormone trajectories *Note*. Raw scores are presented for child anxiety/depression (range = 0–26). Class 1 represents high and stable TSH levels during the three trimesters and low fT4 levels that decrease least of the three groups. Mothers in class 2 and 3 are characterized by a more steep increase in TSH levels and a more steep decrease in fT4 levels, than mother in class 1. Mothers in class 3 have higher fT4 and lower TSH levels than mothers in class 2. * $p < 0.05$.

utero (Germain et al., 2005). Therefore, it could be suggested that male fetuses have a more active metabolism of maternal thyroid hormones that enter the fetal system via the placenta than female fetuses. This increased thyroid hormone metabolism via D3 may make boys more vulnerable to maternal thyroid status. More research is necessary in this regard, especially in humans. What we do know already from research with rats, is the importance of D3 as a determinant of behavior, especially of hyperactivity and anxiety/depression symptoms (Stohn et al., 2016). In addition, in the newborn rat brain, D3 activity is located predominantly in areas related to sexual differentiation of the brain (Escámez et al., 1999).

It should also be mentioned that our finding is totally opposite to a previous Finnish study showing that girls were more vulnerable to develop attention problems in response to heightened maternal TSH levels (Päkkilä et al., 2014). Possible explanations for the differences between the studies are that in the Finnish study the children were older (8 years old) than those in the current study and a different analytic approach was employed (i.e., TSH levels predicting presence or non-presence of clinical levels of ADHD symptoms).

The current study also demonstrated that lower fT4 levels in the first trimester were related to more depression and anxiety symptoms in both boys and girls. This finding suggests that boys are likely to developing both attention problems and internalizing problems in response to deviations in the maternal thyroid system (i.e., higher TSH, lower fT4) during pregnancy, whereas girls only develop internalizing problems in response to maternal fT4 levels. An explanation for these findings can be found in the high comorbidity between externalizing problems (including attention problems) and internalizing problems (Lilienfeld, 2003). Externalizing and internalizing problems have been found to be more strongly linked in boys than in girls (Marmorstein, 2007). Thus, girls might be less likely to developing comorbid behavioral problems in response to biological or environmental risk factors. It is possible that anxious boys may feel pressure to hide their anxiety and may do so by engaging in acting-out behavior, while girls may not feel a similar pressure and therefore be less likely to act-out as a consequence of anxiety (Marmorstein, 2007). Similarly, anxiety, which is more common in girls, has been found to be a protective factor in the development of externalizing problems, whereas externalizing problems have been found to be a risk factor of internalizing problems instead (for a review, Lilienfeld, 2003). It is important to mention that in the current study, sex differences in externalizing problems were mainly based on attention problems and not on aggression. However, the literature is inconsistent as to whether attention problems are considered as externalizing problems. For example in the preschool CBCL, attention problems are part of externalizing problems (Achenbach and Rescorla, 2000) but are not in the older-age versions of the CBCL (Achenbach and Rescorla, 2001).

This study extends previous work by showing that there are individual differences in the *course* of maternal thyroid hormone concentrations during pregnancy. Most mothers (79%) showed expected increases in TSH and decreases in fT4. However, 21% of the mothers did not show increases in TSH and had low fT4 in the first trimester. This pattern deviated from normal thyroid hormone changes during pregnancy. Serum TSH is normally lowered (and fT4 is higher) during the first trimester due to the thyroid stimulating effects of human chorionic gonadotropin (hCG) that return back to normal after the first trimester (Glinoer et al., 1993). It is possible that the higher percentage of TPO-Ab positive women in this group can explain the flattened TSH and fT4 trajectories. Recent studies demonstrated that TPO-Ab positivity impairs thyroid stimulation by hCG (Korevaar et al., 2017), dampens fT4 response to hCG administration (Poppe et al., 2004), and mitigates the classical TSH dip in early pregnancy (Glinoer et al., 1994). The percentage of TPO-Ab positive women was two times higher in the group of women with the highest TSH trajectories, although not significantly higher. The failure to detect significant group differences between the thyroid trajectories in TPO-Ab status is probably related to power issues (low sample size) and also because we modeled the TSH and fT4 trajectories together. It is well known that TPO-Ab positivity is predominantly associated with increased TSH levels rather than decreased fT4 levels (Glinoer et al., 1994). Future studies with larger samples should examine whether TSH and fT4 trajectories during pregnancy are different in TPO-Ab positive and negative mothers and what the underlying mechanisms are.

More importantly, thyroid hormone trajectories were found to be a better predictor of anxiety/depression than maternal fT4 hormones as assessed in one trimester of pregnancy. In the current study, children of mothers with the lowest fT4 levels that decreased least in combination with the highest and non-increasing TSH levels during pregnancy showed the most anxiety and depression symptoms. These findings could not be attributed completely to the fact that the mothers with the most flattened thyroid hormone trajectories also had the highest TSH levels and lowest fT4 levels to begin with in the first trimester. The change during pregnancy (slope) was not related with the starting levels (intercept). Thus, the change in thyroid levels in itself was predictive of child outcomes. In other hormonal systems than the thyroid system, such as the testosterone and cortisol systems, flat diurnal or annual hormonal rhythms have been associated with negative behavioral and psychosocial outcomes in both children and adults (e.g., Burke et al., 2005; Marceau et al., 2015), however the mechanisms remain unclear.

The association we found between thyroid hormone trajectories and child anxiety/depression concurs with an earlier study by our group showing similar associations between thyroid hormone trajectories and child psychomotor and mental development (Pop et al., 2003). However, in that study another small group of mothers was identified with low fT4 levels early in pregnancy, who showed an increase in fT4 later in pregnancy. These mothers had children with normal psychomotor and mental development. The presence of this subgroup indicated that screening for fT4 at 12 weeks gestation could expose a subgroup of hypothyroxinemic women whose children would possibly benefit from an increase of maternal fT4 (e.g. thyroxin treatment) after the first trimester (Pop et al., 2003). A group of mothers with low, increasing fT4 levels was not found in the current study. This difference in findings between the current study and the study by Pop et al. might be due to the larger sample size, the lower number of hypothyroxinemic women, or the more advanced statistical modeling used in the current study.

The results of the current study need to be viewed in light of its limitations. First, the age-range of the children examined in this study was

quite broad and may have affected our results. However, controlling for child age did not change our findings. Second, possible relevant confounders like iodine intake and iron intake were not assessed. Therefore, it was not possible to evaluate an independent effect of thyroid parameters on children's behavioral problems, while controlling for iodine and iron levels. Iodine and iron levels are known to be related to both TSH and fT4 levels (Bastian et al., 2010; Zimmermann et al., 2007; Zimmermann, 2009). In addition, there is evidence that even mild maternal iodine deficiency is related to reduced cognitive outcomes in children (Bath et al., 2013). Low maternal iodine levels might be even more important for children's cognitive outcomes than maternal thyroid levels (Moleti et al., 2016). However, the area where the study was conducted is iodine sufficient as shown in 2001 (Wiersinga et al., 2001). Also, the results of congenital heel screening in 886 neonates of the sample from which the current sample was selected, resulted in the detection of 13 (1.5%) newborns with a TSH > 5 mIU/l, a figure that is below 3%, a generally accepted cut-off showing sufficient iodine intake at a population level (Kuppens et al., 2011; Zimmermann, 2009). However, adequate iodine intake in the general population does not necessarily guarantee adequate intake of iodine during pregnancy (Pearce et al., 2013). In this regard, data on iodine intake in large samples of pregnant women are certainly warranted. Third, some of the associations between maternal thyroid hormones assessed at one time point and child behavioral problems were found specifically for mothers' fT4 levels, while other associations were only significant for mothers' TSH levels. This is a common problem in research on thyroid hormones during pregnancy, as hCG distorts the association between fT4 and TSH. In the current study, this problem was overcome with growth mixture modeling with parallel processes for fT4 and TSH change. Finally, the generalizability of the results to samples with maternal clinical thyroid dysfunction or child problems in the clinical range is limited, because in our community-sample, there were very few hypothyroxinemic mothers and few children with behavioral problems in the borderline/clinical range. Relatedly, our sample was homogeneous with regard to ethnicity. This ethnic homogeneity limits the generalizability of our findings to the Dutch multi-ethnic and multi-racial population, especially since there are ethnic differences in maternal thyroid parameters during pregnancy (Korevaar et al., 2013).

To conclude, we demonstrated in a sample of women without thyroid disease or hypothyroidism that even subtle individual differences in maternal thyroid hormone levels during pregnancy may have an impact on children's behavioral problems. Boys appear to be more vulnerable than girls to deviations in the maternal thyroid system (i.e., higher TSH, lower fT4) during pregnancy. Furthermore, thyroid hormone trajectories during pregnancy better predict children's anxious and depressed symptoms than do maternal thyroid hormone levels assessed at a single time point only (e.g., during the first trimester). Future studies with T4 replacement therapy should take into account different thyroid hormone trajectories when discriminating who to supply and who not.

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