European Thyroid Journal (2025) 14 e240302
https://doi.org/10.1530/ETJ-24-0302

Received 27 September 2024
Accepted 8 April 2025
Available online 8 April 2025
Version of Record published 24 April 2025

RESEARCH

Association of maternal thyroid peroxidase antibody exposure with children's emotional and behavioral problems

Penggui Wu[1,*], Mengting Yang[1,*], Yuzhu Teng[1,*], Jiajun Ouyang[1], Wenjin Cai[1], Juan Tong[1], Guopeng Gao[2], Xiaoyan Wu[1], Yan Han[3], Shuangqin Yan[2], Fangbiao Tao[1] and Kun Huang[1]

[1]Department of Maternal, Child & Adolescent Health, School of Public Health, Anhui Medical University, Key Laboratory of Population Health Across Life Cycle (Anhui Medical University), Ministry of Education of the People's Republic of China, NHC Key Laboratory of Study on Abnormal Gametes and Reproductive Tract, Anhui Provincial Key Laboratory of Population Health and Aristogenics, Hefei, Anhui, China

[2]Maternal and Child Health Center in Ma'anshan, Ma'anshan, Anhui, China

[3]School of Public Health, Xuzhou Medical University, Xuzhou, China

Correspondence should be addressed to K Huang: ahmuhuangk@163.com

*(P Wu, M Yang and Y Teng contributed equally and should be considered as joint first authors)

Abstract

Objective: Maternal thyroid peroxidase antibody (TPOAb) positivity has been associated with a variety of pregnancy complications and has potential neuropsychological developmental implications for the offspring. The aim of our study was to explore the effect of maternal TPOAb levels on emotional and behavioral problems in children.

Design: The study was designed as a cohort study.

Participants: Based on the Ma'anshan birth cohort in China, 2,464 mother-infant pairs were included in this study.

Measurements: Repeated blood samples were collected from pregnant women, and TPOAb and FT4 were measured retrospectively by electrochemiluminescence immunoassay (ECLIA). The strengths and difficulties questionnaire was used to assess the emotional and behavioral problems of 4-year-old preschoolers.

Results: After adjusting for potential confounders, maternal TPOAb positivity during the third trimester of pregnancy was found to be associated with an elevated risk of conduct problems in girls, with an odds ratio (OR) of 2.190 (95% confidence interval (CI): 1.137–4.219). Conversely, maternal TPOAb positivity in the first trimester was linked to a decreased incidence of prosocial behavior in boys, with an OR of 0.451 (95% CI: 0.237–0.861).

Conclusions: Maternal TPOAb positivity during pregnancy may be associated with emotional and behavioral problems in preschool-aged children.

Keywords: thyroid peroxidase antibody; thyroid hormone; thyroid hormone trajectories; emotional and behavioral problems; pregnancy; preschool children

Introduction

Thyroid peroxidase (TPO), a glycoprotein synthesized primarily by thyroid follicular epithelial cells in the microvilli on the luminal surface of the thyroid follicles, is a key enzyme in thyroid hormone synthesis and possesses immunogenic properties. Thyroid peroxidase autoantibodies (TPOAb) are antibodies

Published by Bioscientifica Ltd.
https://etj.bioscientifica.com

European Thyroid Journal (2025) **14** e240302
https://doi.org/10.1530/ETJ-24-0302

produced by the body against thyroid peroxidase as an antigen. TPOAb serves as a marker for autoimmune thyroid diseases. In addition, TPOAb is linked to hypothyroidism and is identified as one of the primary causes of subclinical hypothyroidism (SCH) (1).

TPOAb positivity is defined by a titer or concentration of TPOAb in the blood exceeding a specific threshold. According to the Tehran Thyroid Cohort Study (TTS), the prevalence of positive TPOAb in the general population was 19.8, 17 and 11.4% at threshold levels of 14.77, 18.38 and 40 U/L, respectively (2). Pregnancy significantly affects thyroid function in women, with studies across various countries indicating elevated rates of maternal TPOAb positivity. The Avon Longitudinal Study of Parents and Children (ALSPAC) reported a 13.1% incidence of positive TPOAb among pregnant women (3, 4). In Russia, a study documented a 13.8% prevalence of positive TPOAb in first-trimester mothers (3). The Ma'anshan birth cohort study in China revealed TPOAb positivity rates of 12.0, 6.8 and 7.0% across the first, second and third trimesters, respectively (5).

Maternal positive TPOAb has been associated with an increased risk of gestational diabetes (6, 7), hypertension (8), anemia (9), postpartum thyroiditis (10) and postpartum depression (11). Furthermore, it elevates the risk of premature birth and low birth weight (12, 13, 14). Recent research increasingly focuses on the impact of positive TPOAb during pregnancy on the neuropsychological development of offspring. Emotional and behavioral problems in offspring can impair their health, increase the risk of developing mental disorders later in life (15) and diminish both their own and their families' health-related quality of life (16, 17).

Researchers have investigated the association between maternal TPOAb exposure and the behavioral problems of offspring. Kampuri *et al.* (18) found that children of mothers with normal thyroid function but positive thyroid antibodies in the first trimester had higher inattention scores at ages 4 and 6 compared to those of mothers with negative thyroid antibodies. Ghassabian *et al.* (19), utilizing the R generation research data, discovered a correlation between maternal positive TPOAb in the first trimester and children's attention deficit hyperactivity disorder (ADHD). Brown *et al.* (20), employing a nested case-control study design, reported an increased risk of autism spectrum disorder (ASD) in children born to mothers with positive TPOAb in early pregnancy compared to those with negative TPOAb mothers. However, research on the association between maternal TPOAb exposure and the emotional development of offspring is scarce. Fetene *et al.* (21) reported that maternal TPOAb in the first trimester was not linked to depressive and anxious symptoms in children aged 7.5 and 15 years.

Recent reports indicate sex differences in the emotional and behavioral development of children following adverse early-life exposures (22). For instance, our earlier research demonstrated a correlation between the trajectory of maternal thyroid hormones and behavioral development in boys (23). Andersen *et al.* observed that low maternal free thyroxine levels during pregnancy correlated with ASD and ADHD in girls but not in boys (24). However, research on the sex-specific impacts of maternal TPOAb positivity on the emotional and behavioral outcomes of offspring remains limited.

In this study, utilizing a large birth cohort, we conducted repeated assessments of maternal TPOAb levels across the first, second and third trimesters to explore the sex-specific effects of maternal TPOAb exposure on emotional and behavioral problems in preschool-aged children.

Methods

Participants

Based on the Ma'anshan birth cohort (MABC), pregnant women who underwent the first prenatal checkup in the obstetric clinic of Ma'anshan Maternal and Child Health Center from May 2013 to September 2014 were recruited. The inclusion criteria were: i) within 14 weeks of pregnancy; ii) planning to have antenatal checkups and childbirth in the center; iii) being able to understand and fill in the questionnaire; and iv) willing to be followed up. A total of 3,474 pregnant women met these criteria and were included in the study (25).

After excluding adverse pregnancy outcomes (including embryonic arrest, spontaneous abortion, therapeutic abortion, stillbirth and ectopic pregnancy), women with multiple births, with pre-pregnancy thyroid disease and/or family history of thyroid disease, and children with missing data on emotional and behavioral assessment, a sample of 2,464 mother-child pairs were included. Subsequently, pairs with missing thyroid function data for any trimester were further excluded. The final mother-child pairs included in the analysis were 2,238 in the first trimester, 2,271 in the second trimester and 2,225 in the third trimester, respectively. The specific inclusion and exclusion process is shown in Supplementary Fig. 1 (see section on Supplementary materials given at the end of the article).

This study was approved by the biomedical ethics committee at Anhui Medical University (Number: 20131401). All participants had signed the informed consents.

Maternal thyroid function assay

Fasting venous blood samples were collected from pregnant women during the first trimester

European Thyroid Journal (2025) **14** e240302
https://doi.org/10.1530/ETJ-24-0302

(before 13 weeks of gestation), the second trimester (14–27 weeks of gestation) and the third trimester (28 weeks of gestation onward) (26). Following centrifugation, the sera were stored at −80°C. During the children's follow-up period, thyroid function indicators – namely TPOAb, thyroid-stimulating hormone (TSH) and free thyroxine (FT4) concentrations – were retrospectively measured in maternal serum from different trimesters using electrochemiluminescence immunoassay (ECLIA). ECLIA, a third-generation method for detecting thyroid function-related indicators, offers high sensitivity, high specificity, good reagent stability and an inter-batch variation coefficient of less than 10.0%. The threshold for TPOAb positivity in women was defined as TPOAb levels ≥34 IU/mL.

Evaluation of emotional and behavioral development in preschool children

The strengths and difficulties questionnaire (SDQ), completed by parents or other caregivers, was utilized to assess 4-year-old preschoolers' emotional and behavioral development. It comprised 25 items divided into five subscales: emotional symptoms, conduct problems, hyperactivity, peer relationship problems and pro-social behaviors. Each item was scored as 0, 1 or 2, corresponding to 'not true', 'somewhat true' and 'completely true', respectively. The first four subscales formed the difficulties questionnaire, reflecting negative emotions and behaviors. The pro-social behaviors subscale served as the strengths questionnaire, indicating positive emotions and behaviors (27). The following cutoffs were used to identify abnormal emotional and behavioral development: emotional symptoms (≥5), conduct problems (≥4), hyperactivity (≥8), peer problems (≥6), total difficulties (≥17) and pro-social behaviors (≤4). The questionnaire demonstrated acceptable levels of internal consistency, retest reliability and discriminant validity (28).

Confounding factors

Potential confounders were identified based on previous studies and directed acyclic graphs, including maternal age, education level, household income, lifestyle factors (smoking, alcohol consumption), pre-pregnancy body mass index (BMI), parity and history of adverse pregnancy outcomes or complications (29, 30) (as depicted in Supplementary Fig. 2). These data were collected through a questionnaire at the first antenatal visit. Adverse pregnancy outcomes included miscarriage, preterm labor, stillbirth and birth defects. Pregnancy complications identified from medical records included gestational diabetes and hypertension. For sensitivity analyses, data were collected from medical records on the child's sex, birth weight and gestational age.

Statistical analysis

EpiData 3.0 was used to establish a database and SPSS 23.0 was adopted for data analysis.

Maternal demographic and obstetric characteristics, and children's characteristics are described by *n* (%) and mean ± SD. Data on maternal thyroid indicators from the first, second and third trimesters were analyzed to model thyroid function trajectories. Using 1,882 samples with complete thyroid indicator data across all three trimesters, trajectory modeling was performed with Mplus 7.0 software using a longitudinal growth mixture model (LGMM). LGMM identifies different subgroups' growth trajectories using mixture modeling. For model selection, we evaluated common fit indices, including Akaike information criterion (AIC), Bayesian information criterion (BIC) and sample-size adjusted BIC (SSA-BIC). In addition, the Lo-Mendell-Rubin Likelihood Ratio Test (LMR-LRT) and the Bootstrap Likelihood Ratio Test (BLRT) were employed to statistically compare models with K classes to models with K-1 classes. The closer the entropy value is to 1, the more distinct the separation between classes. In addition, lower AIC, BIC and aBIC values indicate a better fitting model, and significant results of the LMRT and BLRT suggest that the model fits the data more effectively (31). The TPOAb trajectories of pregnant women were classified into high and low-level groups based on the best model fit (as shown in Supplementary Table 1) and clinical significance. The low-level group, which included the largest number of pregnant women and those with TPOAb levels closest to a specific reference range, was chosen as the reference group. We conducted descriptive comparisons of the maternal demographic and obstetric characteristics, as well as the children's characteristics, between the women included in the trajectory fitting and those not included due to missing data. In addition, descriptive comparisons were carried out by different pregnancy trimesters. Subsequently, binary logistic regression models were applied to examine the associations between maternal TPOAb trajectories and children's emotional and behavioral problems.

The impact of TPOAb exposure in individual trimesters on children's emotional and behavioral development was also analyzed using binary logistic regression models. The models were run separately in the first, second and third trimesters of pregnancy. Maternal negative TPOAb exposure in each trimester served as the control group. To satisfy the requirements of normality and chi-square, generalized estimating equations analyzed the relationship between overall TPOAb levels during pregnancy and children's emotional-behavioral development, post natural logarithmic transformation of TPOAb levels.

Sensitivity analyses were performed to refine our understanding: i) maternal TPOAb positivity was

European Thyroid Journal (2025) **14** e240302
https://doi.org/10.1530/ETJ-24-0302

associated with shorter gestational age (32) and higher risk of low birth weight (33), both of which may influence emotional/behavioral development of the offspring (34, 35). Considering gestational age and birth weight as potential mediators, we adjusted for birth weight Z-values; ii) considering the effect of TPOAb on maternal FT4 (36), which, when imbalanced, may contribute to emotional/behavioral problems in children (37), we adjusted for FT4 trajectories across trimesters in our analyses. In addition, in examining the effects of maternal TPOAb exposure during isolated gestations on children's emotional and behavioral problems, further adjustments were made for FT4 levels in the relevant trimester; iii) in addition, we reanalyzed TPOAb positivity in each trimester of pregnancy in relation to emotional and behavioral problems in children after excluding current TSH and FT4 values that were outside the specific reference range.

We employed the Benjamini–Hochberg procedure to conduct multiple testing on the results and adjust the false discovery rate (FDR) (38).

Results

Participants' basic characteristics

Table 1 displays the basic characteristics of the participants. The majority of participants were nulliparous women from urban areas with pre-pregnancy BMIs within the normal range. A minority of the women reported smoking, alcohol consumption and experienced pregnancy complications. Supplementary Table 1 shows that compared with the population not included in the trajectories group, the population included in the trajectories group had a relatively slightly higher educational level, a slightly higher proportion of urban residents, a higher proportion of primiparas and a slightly lower incidence of pregnancy complications. The basic characteristics classified according to the pregnancy trimesters are shown in Supplementary Table 2. Analysis of maternal FT4 concentration trajectories during pregnancy revealed two distinct trajectories: a high maternal FT4 concentration group (40.9%, 769 women) and a low concentration group (58.8%, 1,106 women), illustrated in Supplementary Fig. 3.

Maternal TSH concentrations in the first, second and third trimesters were 2.0 ± 2.6, 2.7 ± 1.5 and 2.5 ± 1.4 μIU/mL, respectively. Maternal FT_4 concentrations in the first, second and third trimesters were 17.1 ± 3.2, 12.0 ± 1.7 and 13.4 ± 2.4 pmol/L, respectively. Maternal TPOAb concentrations in the first, second and third trimesters were 35.0 ± 68.9, 20.7 ± 45.5 and21.0 ± 33.0 IU/mL, respectively.

Table 1 Basic characteristics of the participants.

Characteristics	Values, *n* (%)
Demographic characteristics	
Maternal age (years)	
≤24	799 (32.4)
25–29	1,256 (51.0)
≥30	409 (16.6)
Maternal educational level	
Junior high school and below	494 (20.0)
High school to college	1,321 (53.6)
Bachelor degree or above	649 (26.3)
Husband's educational level	
Junior high school and below	362 (14.7)
High school to college	1,375 (55.8)
Bachelor degree or above	727 (29.5)
Household monthly income per capita (yuan)	
<2,500	692 (28.1)
2,500–4,000	1,039 (42.2)
>4,000	733 (29.7)
Residence	
Urban areas	1,904 (77.3)
Rural areas	560 (22.7)
Obstetric characteristics	
Parity	
Nulliparous	2,234 (90.7)
Multiparous	230 (9.3)
Previous adverse pregnancy outcomes	
No	1,461 (59.3)
Yes	1,003 (40.7)
Pre-pregnancy BMI (kg/m2)*	
18.5–23.9	1,599 (64.9)
<18.5	555 (22.5)
≥24	271 (11.0)
Smoking during pregnancy	
No	2,359 (95.7)
Yes	105 (4.3)
Drinking during pregnancy	
No	2,274 (92.3)
Yes	190 (7.7)
Pregnancy complications	
No	2,036 (82.6)
Yes	428 (17.4)
Maternal FT4 trajectory*	
Low level	1,106 (58.8)
High level	769 (40.9)
Children's sex	
Boys	1,269 (51.5)
Girls	1,195 (48.5)
Birth weight Z-values (mean ± SD)	2,463 (−0.02 ± 0.98)

*There are missing values.

Maternal TPOAb trajectories fitting

Based on optimal model fit indicators and clinical relevance, two distinct trajectories of maternal thyroid peroxidase antibodies (TPOAb) were identified: a higher-level trajectory, encompassing 3.7% of the cohort (68 women), and a lower-level trajectory, comprising 96.3% of the cohort (1,814 women), as depicted in Fig. 1. Throughout the course of pregnancy, there was

European Thyroid Journal (2025) **14** e240302
https://doi.org/10.1530/ETJ-24-0302

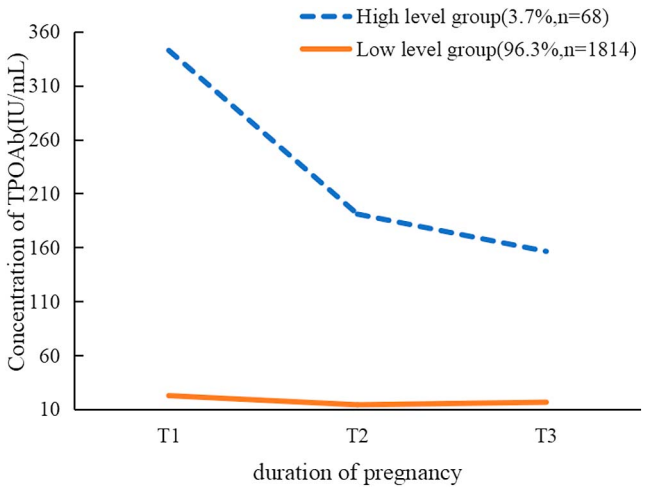

Figure 1

Maternal TPOAb trajectories during pregnancy.

a notable decrease in maternal TPOAb concentrations. We presented the trajectory fitting information in Supplementary Table 3.

Association between maternal TPOAb levels and children's emotional and behavioral problems

In Table 2, after controlling for potential confounders, it was observed that daughters of mothers with higher thyroid peroxidase antibodies (TPOAb) trajectories exhibited an increased risk for conduct problems compared to those from mothers with lower TPOAb trajectories, evidenced by an odds ratio (OR) of 2.670 with a 95% confidence interval (CI) of 1.040–6.852. In Table 3, maternal thyroid peroxidase antibodies (TPOAb) positivity in the third trimester was linked to a higher incidence of conduct problems in girls, with OR of 2.190 (95% CI: 1.137, 4.219), after adjusting for potential confounders. Maternal TPOAb positivity during the first trimester of pregnancy was associated with a lower incidence of prosocial behavior in boys with an OR of 0.451 (95% CI: 0.237, 0.861). Table 4 shows that overall pregnancy TPOAb levels were associated with a higher risk of behavioral problems in the total cohort with an OR of 1.178 (95% CI: 1.023, 1.357). After adjusting the *P*-values for multiple testing corrections, we still observed that positive TPOAb in the third trimester of pregnancy was associated with an increased risk of conduct problems in girls ($P\text{-}_{FDR}$ = 0.038) and positive TPOAb in the first trimester of pregnancy was associated with a decreased risk of prosocial behavior problems in boys ($P\text{-}_{FDR}$ = 0.032) (as shown in Table 3). Sensitivity analyses, as detailed in Supplementary Tables (Supplementary Tables 4, 5, 6, 7), all of which did not alter the results of the primary analysis, corroborated the robustness of these primary outcomes.

Discussion

Drawing from the prospective cohort study, our research indicates a possible connection between TPOAb exposure during the third trimester and conduct problems in girls.

Table 2 Logistic regression analyses on the effect of TPOAb trajectories on children's emotional and behavioral problems (OR (95% CI)).

SDQ dimensions/model*	Total (*n* = 1,882)	Boys (*n* = 974)	Girls (*n* = 908)
Emotional symptoms			
1	1.619 (0.759, 3.455)	0.871 (0.204, 3.722)	2.256 (0.909, 5.603)
2	1.662 (0.768, 3.598)	0.966 (0.218, 4.282)	2.029 (0.789, 5.215)
Conduct problems			
1	1.700 (0.853, 3.389)	1.230 (0.423, 3.581)	2.328 (0.937, 5.784)
2	1.801 (0.891, 3.639)	1.326 (0.441, 3.987)	2.670 (1.040, 6.852)†
Hyperactivity problems			
1	1.249 (0.588, 2.654)	1.430 (0.539, 3.792)	1.092 (0.326, 3.655)
2	1.277 (0.592, 2.759)	1.767 (0.639, 4.886)	1.069 (0.311, 3.678)
Peer problems			
1	0.527 (0.072, 3.869)	-	1.529 (0.197, 11.854)
2	0.570 (0.077, 4.230)	-	1.373 (0.160, 11.806)
Prosocial behavior			
1	0.441 (0.159, 1.224)	0.372 (0.088, 1.576)	0.567 (0.134, 2.402)
2	0.466 (0.167, 1.299)	0.400 (0.093, 1.719)	0.615 (0.142, 2.658)
Total difficulties			
1	0.969 (0.437, 2.150)	0.988 (0.341, 2.866)	0.995 (0.298, 3.323)
2	1.038 (0.463, 2.328)	1.226 (0.406, 3.699)	0.957 (0.281, 3.262)

- indicates insufficient sample size for analysis. The normal concentration group of maternal TPOAb was used as the control; SDQ, strengths and difficulties questionnaire.

*Model 1, unadjusted model; Model 2, adjusted for maternal age, parental educational level, household monthly income per capita, residence, parity, previous adverse pregnancy outcomes, pre-pregnancy BMI, maternal smoking and drinking and pregnancy complications. †$P < 0.05$.

European Thyroid Journal (2025) **14** e240302
https://doi.org/10.1530/ETJ-24-0302

Table 3 Logistic regression analysis on the effect of maternal TPOAb positivity during pregnancy on children's emotion and behavior problems (OR (95% CI)).

SDQ/model*/sex	First trimester (*n* = 2,238)	Second trimester (*n* = 2,271)	Third trimester (*n* = 2,225)
Emotional symptoms			
1			
Total	1.022 (0.647, 1.613)	1.427 (0.842, 2.418)	1.484 (0.897, 2.455)
Boys	1.003 (0.505, 1.994)	1.337 (0.594, 3.009)	1.432 (0.665, 3.081)
Girls	1.038 (0.563, 1.914)	1.477 (0.736, 2.964)	1.624 (0.830, 3.181)
2			
Total	1.073 (0.674, 1.710)	1.519 (0.889, 2.598)	1.579 (0.944, 2.642)
Boys	1.131 (0.560, 2.283)	1.599 (0.692, 3.695)	1.702 (0.772, 3.749)
Girls	1.021 (0.542, 1.924)	1.414 (0.694, 2.882)	1.629 (0.813, 3.264)
Conduct problems			
1			
Total	1.183 (0.791, 1.769)	0.970 (0.559, 1.683)	1.520 (0.956, 2.418)
Boys	1.155 (0.670, 1.993)	0.852 (0.382, 1.899)	1.157 (0.581, 2.306)
Girls	1.217 (0.670, 2.212)	1.135 (0.530, 2.431)	2.026 (1.076, 3.815)†,‡
2			
Total	1.247 (0.827, 1.881)	1.015 (0.579, 1.777)	1.587 (0.987, 2.552)
Boys	1.207 (0.691, 2.110)	0.963 (0.425, 2.184)	1.223 (0.603, 2.483)
Girls	1.274 (0.690, 2.353)	1.187 (0.542, 2.602)	2.190 (1.137, 4.219)†,‡
Hyperactivity problems			
1			
Total	1.211 (0.805, 1.823)	1.292 (0.773, 2.157)	1.236 (0.749, 2.037)
Boys	1.158 (0.681, 1.972)	1.219 (0.610, 2.435)	1.073 (0.539, 2.136)
Girls	1.295 (0.681, 2.462)	1.506 (0.697, 3.253)	1.533 (0.737, 3.187)
2			
Total	1.352 (0.889, 2.055)	1.374 (0.812, 2.323)	1.336 (0.799, 2.232)
Boys	1.327 (0.766, 2.299)	1.384 (0.673, 2.845)	1.194 (0.581, 2.455)
Girls	1.501 (0.776, 2.905)	1.649 (0.746, 3.644)	1.736 (0.815, 3.699)
Peer problems			
1			
Total	1.343 (0.675, 2.671)	0.950 (0.340, 2.654)	1.546 (0.694, 3.446)
Boys	1.289 (0.530, 3.132)	1.269 (0.381, 4.223)	1.449 (0.503, 4.171)
Girls	1.429 (0.481, 4.246)	0.576 (0.077, 4.337)	1.774 (0.516, 6.096)
2			
Total	1.397 (0.693, 2.814)	1.050 (0.372, 2.969)	1.700 (0.753, 3.840)
Boys	1.384 (0.558, 3.435)	1.481 (0.434, 5.054)	1.573 (0.533, 4.644)
Girls	1.483 (0.482, 4.567)	0.593 (0.076, 4.646)	1.882 (0.532, 6.656)
Prosocial behavior			
1			
Total	0.716 (0.468, 1.095)	0.812 (0.476, 1.384)	0.796 (0.474, 1.338)
Boys	0.490 (0.265, 0.907)†,‡	0.776 (0.379, 1.590)	0.867 (0.449, 1.673)
Girls	1.127 (0.622, 2.043)	0.922 (0.413, 2.059)	0.724 (0.307, 1.705)
2			
Total	0.705 (0.455, 1.092)	0.841 (0.490, 1.441)	0.773 (0.451, 1.325)
Boys	0.451 (0.237, 0.861)†,‡	0.809 (0.390, 1.678)	0.839 (0.419, 1.681)
Girls	1.220 (0.658, 2.261)	0.928 (0.409, 2.108)	0.728 (0.303, 1.746)
Total difficulties			
1			
Total	1.035 (0.694, 1.543)	0.937 (0.549, 1.599)	1.277 (0.798, 2.043)
Boys	1.013 (0.597, 1.718)	1.091 (0.547, 2.175)	1.069 (0.552, 2.069)
Girls	1.064 (0.577, 1.964)	0.799 (0.339, 1.886)	1.624 (0.830, 3.181)
2			
Total	1.087 (0.723, 1.636)	0.995 (0.577, 1.715)	1.377 (0.852, 2.226)
Boys	1.080 (0.628, 1.859)	1.323 (0.649, 2.697)	1.231 (0.624, 2.426)
Girls	1.075 (0.571, 2.025)	0.769 (0.320, 1.846)	1.629 (0.813, 3.264)

- indicates insufficient sample size for analysis. Maternal TPOAb negative was used as the control; SDQ, strengths and difficulties questionnaire.
*Model 1, unadjusted model; Model 2, adjusted for maternal age, parental educational level, household monthly income per capita, residence, parity, previous adverse pregnancy outcomes, pre-pregnancy BMI, maternal smoking and drinking and pregnancy complications. †$P < 0.05$. ‡$P\text{-}_{FDR} < 0.05$.

European Thyroid Journal (2025) **14** e240302
https://doi.org/10.1530/ETJ-24-0302

Table 4 Generalized estimating equations for the effect of overall levels of TPOAb during pregnancy on children's emotional and behavioral problems (OR (95% CI)).

SDQ dimensions/model*	Total (*n* = 1,882)	Boys (*n* = 974)	Girls (*n* = 908)
Emotional symptoms			
1	1.150 (0.986, 1.343)	1.093 (0.881, 1.355)	1.195 (0.964, 1.480)
2	1.151 (0.981, 1.351)	1.134 (0.896, 1.434)	1.154 (0.923, 1.442)
Conduct problems			
1	1.168 (1.020, 1.338)†	1.148 (0.971, 1.358)	1.196 (0.960, 1.490)
2	1.178 (1.023, 1.357)†	1.174 (0.982, 1.403)	1.195 (0.945, 1.509)
Hyperactivity problems			
1	1.072 (0.928, 1.239)	1.116 (0.931, 1.338)	1.013 (0.792, 1.296)
2	1.079 (0.929, 1.252)	1.139 (0.939, 1.382)	1.035 (0.809, 1.325)
Peer problems			
1	1.172 (0.945, 1.453)	1.123 (0.853, 1.478)	1.256 (0.892, 1.770)
2	1.202 (0.964, 1.497)	1.170 (0.875, 1.565)	1.266 (0.894, 1.792)
Prosocial behavior			
1	0.962 (0.851, 1.087)	0.915 (0.776, 1.080)	1.037 (0.865, 1.243)
2	0.959 (0.845, 1.088)	0.916 (0.771, 1.088)	1.032 (0.853, 1.249)
Total difficulties			
1	1.039 (0.910, 1.186)	1.034 (0.865, 1.236)	1.050 (0.860, 1.281)
2	1.041 (0.908, 1.194)	1.065 (0.885, 1.282)	1.008 (0.821, 1.239)

*Model 1, unadjusted model; Model 2, adjusted for maternal age, parental educational level, household monthly income per capita, residence, parity, previous adverse pregnancy outcomes, pre-pregnancy BMI, maternal smoking and drinking and pregnancy complications. †$P < 0.05$.
SDQ, strengths and difficulties questionnaire.

Meanwhile, we also observed an association between maternal TPOAb positivity in the first trimester of pregnancy and a relatively lower incidence of prosocial behavior in boys. In addition, there seemed to be a weak yet significant correlation between high-level maternal TPOAb trajectories and an increased risk of behavioral problems in girls as well as between overall TPOAb levels and the increase of childhood behavioral problems. However, it is important to note that these correlations became non-significant after multiple testing corrections.

This study suggests that there may be an association between positive TPOAb in the third trimester of pregnancy and behavioral problems in girls. In addition, no association was found between positive TPOAb in the second and third trimesters of pregnancy and problems in children's emotional and behavioral development. While prior investigations have delved into the impacts of maternal TPOAb exposure on children's behavior, they predominantly focused on TPOAb levels during specific pregnancy trimesters. For example, two research studies had demonstrated a relationship between elevated TPOAb titers in the first trimester and children's behavioral problems (19, 20). Yet, Päkkilä *et al.* (39) contended that first-trimester maternal TPOAb positivity bore no relation to behavioral issues in 8-year-old children. Similarly, utilizing ALSPAC data, Fetene *et al.* found no association between first-trimester maternal TPOAb positivity and offspring's emotional and behavioral problem trajectories (40). Our research contributes novel insights into the dynamic influence of TPOAb levels throughout pregnancy on neural development in children, especially in girls. Inconsistencies in study results could be attributed to methodology, sample size (41), the definition of antibody positivity (42), and the instruments used to assess children's neuropsychological development (43).

The causal mechanisms linking high maternal thyroid peroxidase antibodies (TPOAb) levels to children's emotional and behavioral issues remain unclear. Wilson *et al.* (44) observed that infants born to mothers with normal thyroid function but positive for TPOAb had reduced head circumference, brain weight and brain-body ratios, suggesting a potential direct impact of IgG-type TPOAb on fetal development via transplacental transfer (45, 46). Moreover, Zhou *et al.*'s work with a TPOAb-positive pregnant mouse model indicated that TPOAb positivity might alter biochemical markers in the dam's brain tissue, notably decreasing levels of brain-derived neurotrophic factor and serotonin (5-HT) in the prefrontal cortex (47). In addition, TPOAb positivity could disrupt the normal stimulating effect of human chorionic gonadotropin (hCG) on the thyroid, attenuating hCG's ability to reduce TSH levels and increase FT4 levels (13, 48). Given the critical role of maternal thyroid hormones in the developmental programming of offspring's emotional and behavioral traits (37), TPOAb might indirectly influence child development by modulating the hCG-mediated effects on thyroid hormones during pregnancy.

Our research appears to suggest a notable finding: positive TPOAb during pregnancy seems to be associated with an increase in conduct problems among girls. This could potentially be regarded as a new line of inquiry into the sex-specific impacts that

maternal TPOAb exposure might have on the emotional and behavioral development of offspring. The current literature highlights the link between maternal thyroid dysfunction and increased risk of ASD and ADHD in girls (24, 39). Notably, hCG secretion varies by fetal sex, with higher maternal hCG levels associated with female fetuses (49). This sex-specific secretion pattern of hCG, when influenced by positive maternal TPOAb, may predispose girls to greater adverse effects due to TPOAb's impact on the thyroid-stimulating capacity of hCG (13, 48).

Our findings also revealed that first-trimester TPOAb positivity was associated with prosocial behavior in boys, which was inconsistent with the findings reported by Fetene *et al.* (21). The specific developmental periods during which maternal TPOAb most significantly affects the brain remain uncertain. Previous research has linked early pregnancy elevated TPOAb levels with externalizing behavior problems in 3-year-old children (19), while late-pregnancy TPOAb levels might affect children's intelligence quotient and developmental delay risk (50). Considering the reduction of TPOAb levels in approximately 50% of pregnant women from early to late pregnancy (51), persistent thyroid autoimmunity during pregnancy may be more critical for neurodevelopmental outcomes. Future research is needed to unravel the molecular mechanisms of maternal TPOAb and its distinct impacts during critical developmental periods.

Our study found that there may be an association between relatively high maternal TPOAb trajectories and behavioral problems in girls. In addition, there may be a connection between the overall level of TPOAb during pregnancy and behavioral problems in the general population. However, this association disappeared after multiple testing corrections. This could be due to the weak long-term impact of this exposure during pregnancy on children's health or it may require a study with a larger sample size for support. Although the results are negative, they are still valuable as there is currently a lack of research exploring the association between TPOAb levels throughout all trimesters of pregnancy (the first, second and third trimesters) and long-term child health development. In the future, large sample cohort studies are still needed for further exploration.

Notably, the comprehensive sensitivity analyses we conducted showed that whether thyroid hormone levels were adjusted based on Model 2 or the analysis was re-performed within the normal ranges of FT4 and TSH, the results did not change significantly. This implies that the association between TPOAb and the emotional and behavioral development of children may not be achieved through alterations in thyroid hormone levels (30). Instead, it may act directly or indirectly through some other pathways. In addition, there is a possibility that TPOAb positivity reflects a higher susceptibility to autoimmunity and maternal autoimmunity or a family history of autoimmune diseases may be associated with an increased risk of neuropsychological development problems in children (52, 53). Further animal experiments are needed to explore this.

This study leverages a large prospective birth cohort where maternal thyroid function was comprehensively measured across all three trimesters, a rarity in contemporary cohort studies. The study uniquely employs the trajectory model of maternal TPOAb throughout pregnancy, delving into the dynamic influence of maternal TPOAb levels on children's neurodevelopment. For the first time, it presents the seemingly possible association between TPOAb trajectories and children's behavioral problems. The longitudinal design with prospectively collected data on exposure, outcomes and confounders mitigates recall bias and enhances data accuracy. Moreover, we meticulously adjusted for potential precision variables to refine our findings' precision.

Despite its strengths, this study faces limitations. Due to sample size constraints, it was not feasible to exclude TPOAb positive samples from other trimesters when identifying critical periods for maternal TPOAb exposure's impact on emotional and behavioral development. In addition, child emotional and behavioral assessments were conducted by primary caregivers during routine healthcare visits, limiting the inclusion of teacher assessments or professional evaluations. Caregiver health and emotional status, which could influence assessments, were not comprehensively evaluated. Finally, the study did not account for background iodine status, which influences thyroid function. However, it is noted that Ma'anshan City is not considered iodine-deficient, potentially mitigating this concern (54).

Conclusion

Maternal TPOAb positivity during pregnancy may be associated with emotional and behavioral problems in preschool-aged children.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/10.1530/ETJ-24-0302.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

Funding

This study was funded by the National Natural Science Foundation of China (82273639), the National Key Research and Development Program of China (2022YFC2702901), the Scientific Research Promotion Project of Anhui Medical University (2023xkjT005), the Research Fund of Anhui Institute of translational medicine (ZHYX2020A001), the Scientific Research Platform Base Construction

Foundation of Anhui Medical University (2023xkjT053) and the 'Early Scientific Exposure' Training Program of Anhui Medical University (2022-ZQKY-82).

Author contribution statement

P Wu and M Yang participated in cohort follow-up, analyzed data and contributed to writing and revising the articles. Y Teng and J Ouyang participated in cohort follow-up and data analysis. W Cai, J Tong and X Wu participated in cohort follow-up. Y Han was responsible for testing maternal indicators of thyroid function. G Gao and S Yan provided a platform for conducting the cohort and actively promoted its implementation. F Tao served as the overall leader, implementer and controller of the cohort implementation and follow-up. K Huang was responsible for the on-site work of the cohort, provided writing methods and ideas and contributed to revising and refining the articles.

Data availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Acknowledgements

The authors are grateful to the mothers and children in the study for their active cooperation and also would like to thank all the investigators in Ma'anshan Maternal and Child Health Hospital for their assistance and support in the study.

References

1 Shimizu Y, Kawashiri SY, Noguchi Y, *et al.* Anti-thyroid peroxidase antibody and subclinical hypothyroidism in relation to hypertension and thyroid cysts. *PLoS One* 2020 **15** e0240198. (https://doi.org/10.1371/journal.pone.0240198)

2 Keyhanian M, Sarvghadi F, Mehran L, *et al.* Long-term variations of antithyroperoxidase antibodies and its clinical significance. *Horm Metab Res* 2019 **51** 347–352. (https://doi.org/10.1055/a-0887-6213)

3 Quinn FA, Gridasov GN, Vdovenko SA, *et al.* Prevalence of abnormal thyroid stimulating hormone and thyroid peroxidase antibody-positive results in a population of pregnant women in the Samara region of the Russian Federation. *Clin Chem Lab Med* 2005 **43** 1223–1226. (https://doi.org/10.1515/cclm.2005.212)

4 Fetene DM, Betts KS & Alati R. Maternal prenatal thyroid function and offspring ADHD: findings from the ALSPAC cohort. *J Nerv Ment Dis* 2018 **206** 859–864. (https://doi.org/10.1097/nmd.0000000000000891)

5 Yan H. *A Birth Cohort Study of the Association of Maternal Tpoab Positivity During Pregnancy with Adverse Pregnancy Outcomes and Offspring Growth Retardation*. Anhui Medical University, 2020.

6 Ying H, Tang YP, Bao YR, *et al.* Maternal TSH level and TPOAb status in early pregnancy and their relationship to the risk of gestational diabetes mellitus. *Endocrine* 2016 **54** 742–750. (https://doi.org/10.1007/s12020-016-1022-6)

7 Huang K, Xu Y, Yan S, *et al.* Isolated effect of maternal thyroid-stimulating hormone, free thyroxine and antithyroid peroxidase antibodies in early pregnancy on gestational diabetes mellitus: a birth cohort study in China. *Endocr J* 2019 **66** 223–231. (https://doi.org/10.1507/endocrj.ej18-0340)

8 Han Y, Mao LJ, Ge X, *et al.* Thyroid autoantibodies in pregnancy are associated with hypertensive disorders of pregnancy: Ma'anshan birth cohort study. *Clin Endocrinol* 2018 **88** 928–935. (https://doi.org/10.1111/cen.13590)

9 Yang Y, Hou Y, Wang H, *et al.* Maternal thyroid dysfunction and gestational anemia risk: meta-analysis and new data. *Front Endocrinol* 2020 **11** 201. (https://doi.org/10.3389/fendo.2020.00201)

10 Chen X, Jin B, Xia J, *et al.* Effects of thyroid peroxidase antibody on maternal and neonatal outcomes in pregnant women in an iodine-sufficient area in China. *Int J Endocrinol* 2016 **2016** 6461380. (https://doi.org/10.1155/2016/6461380)

11 Minaldi E, D'Andrea S, Castellini C, *et al.* Thyroid autoimmunity and risk of post-partum depression: a systematic review and meta-analysis of longitudinal studies. *J Endocrinol Investig* 2020 **43** 271–277. (https://doi.org/10.1007/s40618-019-01120-8)

12 Chen LM, Zhang Q, Si GX, *et al.* Associations between thyroid autoantibody status and abnormal pregnancy outcomes in euthyroid women. *Endocrine* 2015 **48** 924–928. (https://doi.org/10.1007/s12020-014-0420-x)

13 Korevaar TI, Steegers EA, Pop VJ, *et al.* Thyroid autoimmunity impairs the thyroidal response to human chorionic gonadotropin: two population-based prospective cohort studies. *J Clin Endocrinol Metab* 2017 **102** 69–77. (https://doi.org/10.1210/jc.2016-2942)

14 Yuan N, Sun J, Li Z, *et al.* Relationship between anti-thyroid peroxidase antibody positivity and pregnancy-related and fetal outcomes in euthyroid women: a single-center cohort study. *BMC Pregnancy Childbirth* 2020 **20** 491. (https://doi.org/10.1186/s12884-020-03176-4)

15 Lerner JA, Inui TS, Trupin EW, *et al.* Preschool behavior can predict future psychiatric disorders. *J Am Acad Child Psychiatry* 1985 **24** 42–48. (https://doi.org/10.1016/s0002-7138(09)60408-8)

16 Sawyer MG, Whaites L, Rey JM, *et al.* Health-related quality of life of children and adolescents with mental disorders. *J Am Acad Child Adolesc Psychiatry* 2002 **41** 530–537. (https://doi.org/10.1097/00004583-200205000-00010)

17 Herring S, Gray K, Taffe J, *et al.* Behaviour and emotional problems in toddlers with pervasive developmental disorders and developmental delay: associations with parental mental health and family functioning. *J Intellect Disabil Res* 2006 **50** 874–882. (https://doi.org/10.1111/j.1365-2788.2006.00904.x)

18 Kampouri M, Margetaki K, Koutra K, *et al.* Maternal mild thyroid dysfunction and child behavioral and emotional difficulties at 4 and 6 years of age: the rhea mother-child cohort study, Crete, Greece. *Horm Behav* 2019 **116** 104585. (https://doi.org/10.1016/j.yhbeh.2019.104585)

19 Ghassabian A, Bongers-Schokking JJ, de Rijke YB, *et al.* Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the generation R study. *Thyroid* 2012 **22** 178–186. (https://doi.org/10.1089/thy.2011.0318)

20 Brown AS, Surcel HM, Hinkka-Yli-Salomäki S, *et al.* Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. *Prog Neuropsychopharmacol Biol Psychiatry* 2015 **57** 86–92. (https://doi.org/10.1016/j.pnpbp.2014.10.010)

21 Fetene DM, Betts KS & Alati R. The role of maternal prenatal thyroid function on offspring depression: findings from the ALSPAC cohort. *Dev Psychopathol* 2020 **32** 189–196. (https://doi.org/10.1017/s0954579418001657)

22 Eurenius E, Richter Sundberg L, Vaezghasemi M, *et al.* Social-emotional problems among three-year-olds differ based on the child's gender and custody arrangement. *Acta Paediatr* 2019 **108** 1087–1095. (https://doi.org/10.1111/apa.14668)

23 Li P, Teng Y, Ru X, *et al.* Sex-specific effect of maternal thyroid hormone trajectories on preschoolers' behavioral development: a birth cohort study. *J Clin Endocrinol Metab* 2022 **107** e2037–e2046. (https://doi.org/10.1210/clinem/dgab887)

24 Andersen SL, Andersen S, Vestergaard P, *et al.* Maternal thyroid function in early pregnancy and child neurodevelopmental disorders: a Danish nationwide case-cohort study. *Thyroid* 2018 **28** 537–546. (https://doi.org/10.1089/thy.2017.0425)

25 Huang K, Tong J, Tao S, *et al.* Cohort profile: the Ma'anshan birth cohort (MABC) study. *Int J Epidemiol* 2024 **53** dyae142. (https://doi.org/10.1093/ije/dyae142)

26 Reese JA, Peck JD, Deschamps DR, *et al.* Platelet counts during pregnancy. *N Engl J Med* 2018 **379** 32–43. (https://doi.org/10.1056/nejmoa1802897)

27 Goodman R. The strengths and difficulties questionnaire: a research note. *J Child Psychol Psychiatry* 1997 **38** 581–586. (https://doi.org/10.1111/j.1469-7610.1997.tb01545.x)

28 Du Y, Kou J & Coghill D. The validity, reliability and normative scores of the parent, teacher and self report versions of the strengths and difficulties questionnaire in China. *Child Adolesc Psychiatry Ment Health* 2008 **2** 8. (https://doi.org/10.1186/1753-2000-2-8)

29 Yang M, Zhang S, Teng Y, *et al.* Association of maternal TSH, FT4 with children's BMI trajectories, and obesity: a birth cohort study. *J Clin Endocrinol Metab* 2023 **109** e190–e199. (https://doi.org/10.1210/clinem/dgad441)

30 Teng Y, Zhou J, Zhu L, *et al.* Sex-specific associations between maternal thyroid peroxidase antibodies and cognitive development in preschool children: a prospective cohort study. *Thyroid* 2024 **34** 899–911. (https://doi.org/10.1089/thy.2023.0612)

31 Herle M, Micali N, Abdulkadir M, *et al.* Identifying typical trajectories in longitudinal data: modelling strategies and interpretations. *Eur J Epidemiol* 2020 **35** 205–222. (https://doi.org/10.1007/s10654-020-00615-6)

32 Medici M, de Rijke YB, Peeters RP, *et al.* Maternal early pregnancy and newborn thyroid hormone parameters: the generation R study. *J Clin Endocrinol Metab* 2012 **97** 646–652. (https://doi.org/10.1210/jc.2011-2398)

33 Männistö T, Vääräsmäki M, Pouta A, *et al.* Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab* 2009 **94** 772–779. (https://doi.org/10.1210/jc.2008-1520)

34 Hornman J, de Winter AF, Kerstjens JM, *et al.* Emotional and behavioral problems of preterm and full-term children at school entry. *Pediatrics* 2016 **137** e20152255. (https://doi.org/10.1542/peds.2015-2255)

35 Saha UR, Bijwaard GE, Muhajarine N, *et al.* Disadvantaged neighborhoods, birth weight, and problem behavior in five- and six-year-old pre-school children: evidence from a cohort born in Amsterdam. *Soc Sci Med* 2020 **265** 113400. (https://doi.org/10.1016/j.socscimed.2020.113400)

36 Derakhshan A, Korevaar TIM, Taylor PN, *et al.* The association of maternal thyroid autoimmunity during pregnancy with child IQ. *J Clin Endocrinol Metab* 2018 **103** 3729–3736. (https://doi.org/10.1210/jc.2018-00743)

37 Endendijk JJ, Wijnen HAA, Pop VJM, *et al.* Maternal thyroid hormone trajectories during pregnancy and child behavioral problems. *Horm Behav* 2017 **94** 84–92. (https://doi.org/10.1016/j.yhbeh.2017.06.007)

38 Pike N. Using false discovery rates for multiple comparisons in ecology and evolution. *Methods Ecol Evol* 2011 **2** 278–282. (https://doi.org/10.1111/j.2041-210x.2010.00061.x)

39 Päkkilä F, Männistö T, Pouta A, *et al.* The impact of gestational thyroid hormone concentrations on ADHD symptoms of the child. *J Clin Endocrinol Metab* 2014 **99** E1–E8. (https://doi.org/10.1210/jc.2013-2943)

40 Fetene DM, Betts KS, Scott JG, *et al.* Maternal prenatal thyroid function and trajectories of offspring emotional and behavioural problems: findings from the ALSPAC cohort. *Eur Child Adolesc Psychiatry* 2020 **29** 871–879. (https://doi.org/10.1007/s00787-019-01404-7)

41 Noordzij M, Tripepi G, Dekker FW, *et al.* Sample size calculations: basic principles and common pitfalls. *Nephrol Dial Transplant* 2010 **25** 1388–1393. (https://doi.org/10.1093/ndt/gfq563)

42 D'Aurizio F, Tozzoli R, Villalta D, *et al.* Immunoassay of thyroid peroxidase autoantibodies: diagnostic performance in automated third generation methods. A multicentre evaluation. *Clin Chem Lab Med* 2015 **53** 415–421. (https://doi.org/10.1515/cclm-2014-0545)

43 Kettler RJ, Feeney-Kettler KA & Dembitzer L. Social, emotional, and behavioral screening: a comparison of two measures and two methods across informants. *J Sch Psychol* 2017 **64** 93–108. (https://doi.org/10.1016/j.jsp.2017.05.002)

44 Wilson RE, Salihu HM, Groer MW, *et al.* Impact of maternal thyroperoxidase status on fetal body and brain size. *J Thyroid Res* 2014 **2014** 872410. (https://doi.org/10.1155/2014/872410)

45 Kohno Y, Kijima M, Yamaguchi F, *et al.* Comparison of the IgG subclass distribution of anti-thyroid peroxidase antibodies in healthy subjects with that in patients with chronic thyroiditis. *Endocr J* 1993 **40** 317–321. (https://doi.org/10.1507/endocrj.40.317)

46 Palmeira P, Quinello C, Silveira-Lessa AL, *et al.* IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol* 2012 **2012** 985646. (https://doi.org/10.1155/2012/985646)

47 Zhou Y, Wang X, Zhao Y, *et al.* Elevated thyroid peroxidase antibody increases risk of post-partum depression by decreasing prefrontal cortex BDNF and 5-HT levels in mice. *Front Cell Neurosci* 2016 **10** 307. (https://doi.org/10.3389/fncel.2016.00307)

48 Glinoer D, de Nayer P, Bourdoux P, *et al.* Regulation of maternal thyroid during pregnancy. *J Clin Endocrinol Metab* 1990 **71** 276–287. (https://doi.org/10.1210/jcem-71-2-276)

49 Yaron Y, Lehavi O, Orr-Urtreger A, *et al.* Maternal serum HCG is higher in the presence of a female fetus as early as week 3 post-fertilization. *Hum Reprod* 2002 **17** 485–489. (https://doi.org/10.1093/humrep/17.2.485)

50 Wasserman EE, Pillion JP, Duggan A, *et al.* Childhood IQ, hearing loss, and maternal thyroid autoimmunity in the Baltimore collaborative perinatal project. *Pediatr Res* 2012 **72** 525–530. (https://doi.org/10.1038/pr.2012.117)

51 Smyth PP, Wijeyaratne CN, Kaluarachi WN, *et al.* Sequential studies on thyroid antibodies during pregnancy. *Thyroid* 2005 **15** 474–477. (https://doi.org/10.1089/thy.2005.15.474)

52 Wu S, Ding Y, Wu F, *et al.* Family history of autoimmune diseases is associated with an increased risk of autism in children: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2015 **55** 322–332. (https://doi.org/10.1016/j.neubiorev.2015.05.004)

53 Chen SW, Zhong XS, Jiang LN, *et al.* Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: a systematic review and meta-analysis. *Behav Brain Res* 2016 **296** 61–69. (https://doi.org/10.1016/j.bbr.2015.08.035)

54 T Z, Gh F, K Y, *et al.* Analysis of iodine deficiency disease monitoring results in Ma'anshan City. *Anhui J Prev Med* 2008 **01** 50–57.