The Association of Maternal Thyroid Autoimmunity During Pregnancy with Child IQ

Arash Derakhshan[1,2], Tim I.M. Korevaar[1,2] , Peter N. Taylor[3], Deborah Levie[1,2,4], Monica Guxens[4,5,6], Vincent W.V. Jaddoe[2,7], Scott M. Nelson[8], Henning Tiemeier[9,10], Robin P. Peeters[1,2]

[1] *Academic Center for Thyroid Diseases, Erasmus MC, Dr. Molewaterplein 15, 3051 GE, Rotterdam, The Netherlands.*

[2] *The Generation R Study Group, Erasmus Medical Center, Rotterdam, The Netherlands.*

[3] *Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, United Kingdom.*

[4] *ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.*

[5] *Pompeu Fabra University, Barcelona, Spain.*

[6] *Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Spain.*

[7] *Department of Pediatrics, Erasmus MC, Rotterdam, the Netherlands.*

[8] *School of Medicine, University of Glasgow, Glasgow, United Kingdom.*

[9] *Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands.*

[10] *Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands.*

Received 05 April 2018. Accepted 12 July 2018.

Context: Thyroperoxidase antibody (TPOAb) positivity is a major risk factor for gestational thyroid dysfunction. During the first 18-20 weeks of pregnancy, high concentrations of human chorionic gonadotropin (hCG) stimulate the thyroid to ensure adequate thyroid hormone availability for the developing fetus. However, TPOAb positive women have an impaired thyroidal response to hCG stimulation.

Objective: To study the association of maternal TPOAb positivity during pregnancy with child IQ.

Design, Setting, Participants: This study was embedded in two prospective birth cohorts: Generation R (Rotterdam, the Netherlands) and the Avon Longitudinal Study of Parents and Children (ALSPAC; United Kingdom). Mother-child pairs with available early pregnancy TPOAb data (≤18 weeks of gestation) and offspring IQ were included (N=3637, Generation R and N=2396, ALSPAC).

Intervention: None.

Main Outcome Measures: Child IQ at 5 to 10 years of age.

Results: In Generation R, TPOAb positivity was associated with a 2.0 ±0.9 point lower mean child IQ (*P*=0.03). Sensitivity analyses showed negative effect estimates already from TPOAb concentrations considerably lower than currently used manufacturer cut-offs. In ALSPAC, neither TPOAb positivity nor TPOAb concentrations below manufacturer cut-offs were associated with child IQ (TPOAb positivity: 0.7 ±1.0, *P*=0.45). Adjustment for maternal TSH or FT4 concentrations or urinary iodine/creatinine ratio did not change the results.

Conclusion: TPOAb positivity during pregnancy was associated with lower child IQ in Generation R but not in ALSPAC. Further studies are needed to elucidate if differences between

the study populations, such as maternal iodine status, could be the underlying cause for these differences.

We investigated the association of early pregnancy TPO antibody positivity with child IQ and demonstrate that TPO antibody positive women have children with lower IQ in one of the two studied cohorts.

Introduction

Thyroperoxidase antibody (TPOAb) positivity occurs in about 2-17% of all pregnant women worldwide and its prevalence differs according to maternal iodine intake and ethnicity (1). TPOAb positivity reflects thyroid autoimmunity, which typically results in higher serum thyroid stimulating hormone (TSH) concentrations, lower serum free thyroxine (FT4) concentrations and ultimately hypothyroidism (2,3). Human chorionic gonadotropin (hCG) is a pregnancy-specific hormone that exerts thyrotropic activity via its affinity for the TSH receptor (4). During pregnancy, high hCG concentrations are associated with an up to 50% increase in FT4 concentrations (5). This increase in thyroid hormone availability ensures sufficient thyroxine availability for placental thyroxine transfer to the developing fetus (6). Although we recently showed that TPOAb positivity severely impairs the thyroidal response to hCG stimulation, it remains unknown whether this could affect early fetal development (7).

The fetal thyroid gland is not functionally mature until the 18th to 20th week of pregnancy; therefore, fetal thyroid hormone availability largely depends on the placental transfer of maternal thyroid hormones during early development (6,8). In humans, neurogenesis starts from approximately the 5th week of pregnancy and thyroid hormone receptors are detected in the fetal brain from the 8th week of pregnancy (8). Various critical processes of fetal brain development that reach peak activity before the 18th to 20th week of pregnancy are regulated by thyroid hormone (9). Interestingly the specific period that early fetal brain development is dependent on maternal thyroid hormones overlaps with peaking of hCG concentrations, facilitating a concomitant increase in maternal thyroid hormone concentrations (roughly 6-15 weeks of pregnancy) (5,10).

The current guidelines of the American Thyroid Association (ATA) state that for TPOAb positive women, levothyroxine treatment can be considered when TSH concentrations are above 2.5 mU/l (1). This recommendation is predominantly based on studies showing that TPOAb positivity is associated with a higher risk of miscarriage and premature delivery (1,11-14). Mild maternal thyroid dysfunction, particularly hypothyroxinemia has been associated with suboptimal child neurodevelopmental outcomes, such as attention-deficit/hyperactivity disorder symptoms, lower IQ, autism and schizophrenia (15-18); however, studies on the association of maternal TPOAb positivity with child neurodevelopment remain sparse. While some studies have shown that maternal TPOAb positivity is associated with lower child IQ or other adverse neurodevelopmental outcomes (19-22), the majority of these studies were either retrospective, had a small sample size, were unable to adjust for potential confounders and/or did not specifically investigate the combination of TPOAb positivity and an elevated TSH concentration.

Considering that an attenuated thyroidal response to hCG stimulation in TPOAb positive women likely leads to a relative form of thyroid hormone shortage during early pregnancy, during which fetal brain development depends on maternal thyroid hormone, we hypothesized that TPOAb positivity is associated with lower child IQ. To address this, we examined the association of maternal TPOAb positivity during pregnancy with child IQ in two large, prospective, population-based cohorts.

Methods

This study was embedded in two prospective birth cohorts: Generation R (Rotterdam, the Netherlands) and the Avon Longitudinal Study of Parents and Children (ALSPAC, United Kingdom).

Study design and participants

In Generation R, 7,069 women with a delivery date between April 2002 and January 2006 were enrolled during early pregnancy (≤18 weeks) in hospitals and midwife practices in Rotterdam (23). Blood samples were drawn in 6,398 of these women and 5,793 had enough material for measurement of TPOAbs. When the children reached 5 years of age, all enrolled mothers and children were invited to visit the research center at the Erasmus MC Sophia Children's Hospital in Rotterdam, where 3,753 (64%) children underwent IQ assessments. The general study design, all research aims, and the specific measurements in the Generation R Study have been approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, Netherlands. Written informed consent was obtained from all participants and/or the children's parents or guardians.

In ALSPAC, eligible women were those living in the former Avon area in southwest England, United Kingdom, with an expected delivery date between April, 1991, and December, 1992. In total, blood samples were available in 7,501 pregnant women, of which 4,947 were enrolled during early pregnancy (≤18 weeks) (24) with 4,916 women having TPOAb measurements. Subsequently, all participants were invited to attend a research clinic where trained psychologists measured the IQ of 2,552 children. The study website contains details of all the data that are available through a fully searchable database www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

The exclusion criteria for both cohorts were twin pregnancies, women with pre-existing thyroid disease or fertility treatment and outliers of child IQ (defined as ±2.5*median absolute deviation).

Laboratory Measurements

In Generation R, maternal blood samples were stored at -80° C. TPOAbs were measured using the Phadia 250 immunoassay (Phadia AB, Uppsala, Sweden) and considered positive when the serum concentrations were >60 IU/ml. FT4 and TSH were measured using chemiluminescence assays (Vitros ECI Immunodiagnostic System Ortho Clinical Diagnostics, Rochester, NY). The intra- and interassay coefficients of variation were <4.1% for TSH at a range of 3.97–22.7 mU/L and <5.4% for FT4 at a range of 14.3–25.0 pmol/L. Details of the urinary iodine and creatinine measurement are reported elsewhere (25).

In ALSPAC, TPOAb, FT4 and TSH were measured in stored serum samples using an Abbott Architect i2000. Inter- and intra-assay coefficients of variation were less than 5% for all analytes. TPOAbs were considered positive when the serum concentrations were ≥6 IU/ml. Details on urinary iodine and creatinine measurements on a very limited subset are reported elsewhere (26).

Outcomes

In Generation R, non-verbal child IQ was evaluated using two subtests of a Dutch non-verbal intelligence test, the Snijders-Oomen Niet-Verbale Intelligentie Test when the children were 5 to 8 years of age. The test generally evaluates a range of intelligence functions without relying on language skills and is therefore suitable for assessing the cognitive abilities of ethnic minorities'

children and children with verbal communication problems (27). The two subtests were mosaics (evaluating spatial visualization abilities) and categories (evaluating abstract reasoning abilities) and the correlation between subtests with complete test were: r=0.86. Raw test scores were converted into non-verbal IQ scores using normal values tailored to exact age. Research staff who did the IQ tests were unaware of any other mother-child measurements and outcomes.

In ALSPAC, child IQ was measured in a research clinic using a well-validated age-adjusted shortened form of the Wechsler Intelligence Scale for Children (WISC) which provides a well-standardized assessment of performance and verbal intelligence when children were 7 to 10 years of age (26,28). WISC assessments were administered by trained psychologists. To compare analyses to Generation R, the performance component of child IQ was used as the primary outcome, supplementary analyses were also performed for the verbal component.

Statistical analysis

We used multivariable linear regression analyses to investigate the association of maternal TPOAb positivity with child IQ. We have recently shown that thyroid function and the response to hCG stimulation is already lower from concentrations below currently used TPOAb positivity cut-offs as provided by assay manufacturers (29). Therefore, we also performed sensitivity analyses to evaluate the effects of cut-offs below the currently used manufacturer-based cut-offs. TPOAbs were categorized at 20, 30, 40, 50 and 60 IU/ml in Generation R (corresponding to population-based percentiles: 90.6, 92.2, 93, 93.6 and 94.1, respectively). Considering that the manufacturer's cut-off of TPOAb in the ALSPAC population (6 IU/ml) already stood at the 87.2 percentile, to enable comparison between cohorts, population-based cut-offs equivalent to the cut-offs in Generation R were defined in ALSPAC (14.2, 29.6, 41.4, 54.8 and 63.1 IU/ml, respectively). The effect estimates for these cut-offs were compared with TPOAb <10 IU/ml (population-based percentile of 83) in Generation R and the corresponding percentile (<4.16 IU/ml) in ALSPAC. The severely skewed distribution of (log-transformed) TPOAb concentrations did not allow for reliable analyses using TPOAb concentrations as a continuous exposure.

Based on the current ATA guidelines (1), we additionally investigated the group of TPOAb positive women with a TSH concentration >2.5 mU/L (N=118 (3.4 %) and N=52 (2.46 %), in Generation R and ALSPAC, respectively. Because maternal iodine status is a well-known determinant of both thyroid autoimmunity and child IQ (26,30), in a subset of mothers with available early pregnancy iodine data (N=1330 in Generation R and N=1065 in ALSPAC) we investigated the possible effects of maternal iodine status on the association of TPOAbs with child IQ by: 1) studying the association of TPOAbs with maternal urinary iodine/creatinine ratio (UICr) using a linear regression model; 2) additionally adjusting all analyses for maternal UICr; and 3) stratified analyses in both cohorts according to a UICr below and above 150 µg/g. Furthermore, we also investigated if the association of maternal TPOAbs with child IQ would be (partially) mediated via changes in maternal thyroid function by additionally adjusting all models for maternal FT4 and TSH.

All analyses were adjusted for maternal age, body mass index and gestational age at the time of blood sampling, parity, smoking status, education level, ethnicity, child sex and birth weight. We used multiple imputation by chained equations to deal with missing data of covariates (31). The maximum percentage of missing data was 10.3% in Generation R and 3.7% for ALSPAC. The number of imputations were based on the percentage of missing data using at least 1 imputation per percent of incomplete cases . All statistical analyses were performed using SPSS

version 21.0 for Windows or R statistical software version 3.3.2 (packages *mice* and *rms*; https://www.r-project.org/).

Results

After exclusions, the final study population included 6,033 mother-child pairs (Generation R: N=3,564; ALSPAC: N=2,362, Figure 1). Mother-child characteristics of the study population are shown in Table 1. In Generation R, the prevalence of TPOAb positivity was 5.9%, mean gestational age at blood sampling was 13.4 (SD 1.9) weeks and the study population was mainly of Dutch ethnicity (57.3%). In ALSPAC, the prevalence of TPOAb positivity was 12.8%, mean gestational age at blood sampling was 10.9 (SD 3.1) weeks and the study population was mainly of Caucasian ethnicity (98.5%). In both cohorts, there was no difference in maternal TPOAb positivity or thyroid function between mother-child pairs with or without IQ data available (Supplemental Tables 1 and 2).

In Generation R, maternal TPOAb positivity was associated with lower mean child IQ (-2.0 ±0.9 points, *P*=0.03; Table 2). Subsequent sensitivity analyses showed that mean child IQ was already lower at TPOAb cut-offs below the currently used manufacturer-based cut-off for TPOAb positivity (Table 2). In ALSPAC, using cut-offs equivalent to Generation R, neither TPOAb positivity nor TPOAb cut-offs below the manufacturer-based cut-off were associated with child IQ (TPOAb positivity: 0.7 ±0.9 points; *P*=0.45; Table 2). The combination of TPOAb positivity with a TSH above 2.5 mU/l was not associated with child IQ in Generation R (*P* for interaction=0.52) while this combination was associated with a higher mean child IQ in ALSPAC (*P* for interaction=0.09; Supplemental Table 3). All results remained essentially unchanged after adjusting for maternal FT4 concentrations (Table 2), UICr (Supplemental Table 4), maternal TSH concentrations (data not shown) or hCG concentrations (Generation R only; data not shown). In Generation R, the association of TPOAbs with child IQ did not differ according to maternal ethnicity.

The median maternal UICr differed considerably between Generation R and ALSPAC (median (IQR): 295 (199-425) vs. 117 (80-190), *P*<0.001). In ALSPAC, but not in Generation R, higher TPOAb concentrations or TPOAb positivity were associated with higher maternal UICr, although these analyses did not reach statistical significance in the smaller subgroups (Supplemental Table 5). Sensitivity analyses suggested that the association of maternal TPOAb positivity with child IQ may differ according to maternal iodine status, although we lacked adequate statistical power for this analysis (Supplemental Table 6). There was no association of UICr with thyroid function in the two cohorts (Data not shown).

Discussion

In this study, we investigated the association of TPOAb positivity during early pregnancy with child IQ in two large prospective population-based cohorts. We show that TPOAb positivity as defined by currently used manufacturer-based cut-offs was associated with lower mean child IQ in the Netherlands (Generation R) but not in the United Kingdom (ALSPAC). Furthermore, the association of TPOAbs with lower child IQ in the Netherlands was already present from TPOAb cut-offs below the currently used manufacturer-based cut-offs. Additional adjustment for maternal FT4 or TSH or UICr did not change the results.

There is an overlap in the time period of fetal brain development's peak activity, fetal dependency on placental transfer of maternal thyroid hormones and hCG mediated increase in maternal FT4 concentrations (4,8,9). However, TPOAb positive women have an impaired

response to the thyroidal stimulation by hCG and low maternal thyroid hormone availability is associated with lower child IQ in some but not all studies (32-35). In the current study, TPOAb positivity was associated with lower child IQ in Generation R, which might have been due to a lack of hCG mediated increase in FT4 concentrations during early pregnancy (29). Alternatively, TPOAb positivity could be associated with lower child IQ because TPOAb positivity reflects a higher general susceptibility to autoimmunity. Maternal autoimmunity or a familial history of autoimmune disorders has been associated with a higher risk of child autism (36,37). A third potential explanation would be a direct effect of TPOAbs on the brain. TPOAbs can cross the placenta and have been detected in the cerebrospinal fluid of patients with Hashimoto's encephalitis (38,39). In addition, since newborn and childhood TSH or FT4 do not differ between TPOAb-positive and TPOAb-negative mothers (40) and newborn thyroid function is not associated with neurocognitive outcomes (41,42) a pathway via changes in child thyroid function is highly unlikely.

However, although TPOAb positivity was associated with a lower child IQ in Generation R, there was no association in ALSPAC, with point estimates even suggesting a positive association of TPOAb positivity with child IQ. There might be several reasons for the discrepancy between the two cohorts. First, there is a large difference in iodine status of pregnant women between the Netherlands (more than sufficient) and United Kingdom (mildly deficient), as was also reflected by the UICr analyses in the current study. Both low and high iodine intake are risk factors for low maternal thyroid hormone availability and both are associated with an increased risk of thyroid autoimmunity (30,43). Previous studies have shown that in the iodine sufficient population of Generation R, a single low maternal UICr measurement is not associated with child IQ, whereas a low UICr measurement in the iodine deficient ALSPAC cohort is associated with lower child IQ (26,44). Stratified analysis suggested that in Generation R, the association of TPOAb positivity with lower child IQ was driven predominantly by women with a UICr $\geq$150 µg/g. This would indicate that in Generation R, low iodine status is not the underlying mechanism. In ALSPAC, there was a suggestive association of higher TPOAb concentrations or TPOAb positivity with a higher maternal UICr, although the small size of the subset with available data did not provide adequate statistical power. Similarly, a higher iodine availability could underlie the higher mean IQ in the small subset of TPOAb positive women with a TSH above 2.5 mU/L. However, neither in Generation R nor in ALSPAC we could adequately asses iodine status in this small subset due to a lack of data availability (data not shown) and in addition, we were only powered to detect a roughly 3.6 point IQ difference in the subset of TPOAb positive women with a TSH above 2.5 mU/L in Generation R. Taken together, this might suggest that the difference between Generation R and ALSPAC could be due to the differences in iodine status between the two cohorts. Unfortunately, data on UICr were only available in a small subset for both studies, precluding adequate analyses to investigate the role of UICr as an underlying cause for the differences between the two cohorts. In line with our hypothesis, TPOAb positivity has been associated with impaired child cognition, autism and behavioral problems in other studies from iodine sufficient populations (21,22,45) whereas a Scottish study with 40% of women being iodine deficient did not find an association with neurodevelopmental outcomes (20).

Second, while serum samples in Generation R were collected between 2002 and 2005, and TPOAbs were measured in 2006, ALSPAC samples were collected between 1991 and 1992 and measured in 2016. A study from Finland shows that in stored serum samples, there is a strong positive association of storage time with TPOAb concentrations, with storage time explaining

19.7% of the total variation in TPOAb concentrations (46). This indicates that TPOAb concentrations in ALSPAC are much more likely to be subject to measurement error than those in Generation R. Although it is unknown whether the extent of the increase in TPOAb concentration by storage time is differential on factors that may affect IQ, the difference in storage time may hamper the comparisons between Generation R and ALSPAC in the current study.

The current ATA guidelines recommend that treatment can be considered in TPOAb positive women if the TSH concentration is >2.5 mU/l (1). In the current study, the association of TPOAb positivity with lower child IQ in Generation R did not differ according to a TSH below or above 2.5 mU/l. Given that the guideline recommendations are predominantly based on studies focusing on adverse obstetric outcomes, the lack of effects in the current study cannot be considered as an argument against current recommendations. Nonetheless, further studies are required to investigate from which TSH threshold the risk of adverse outcomes in TPOAb positive women starts to increase.

In the current study, we also showed that TPOAb cut-offs below the currently used manufacturer-based cut-offs for TPOAb positivity were associated with a lower child IQ. This is in line with a previous study from our group, showing that TPOAb concentrations already below currently used manufacturer cut-offs are associated with a higher TSH and a higher risk of premature delivery (29). Taken together, this suggests that the clinically relevant cut-off for TPOAb positivity may differ from the currently used manufacturer-based cut-offs and that future studies should focus on identifying the optimal threshold for TPOAb positivity for different pregnancy and offspring outcomes.

To the best of our knowledge, this is the first study to assess the association of early pregnancy TPOAb positivity with child IQ in two large prospective, population-based cohorts. We were able to study this association in two study populations with a different population iodine status with detailed data that allowed us to adjust the models for important confounders and run additional sensitivity analyses.

A potential limitation of this study is that data on maternal iodine excretion were not available for all mothers which left us with inadequate statistical power for sensitivity analysis investigating the potential role of iodine intake. Further studies are therefore needed to investigate the role of maternal thyroid autoimmunity in relation to iodine status with regard to child cognitive development. In addition, the number of TPOAb positive women with a TSH >2.5 mU/l was small, hampering an adequately powered analysis for this subgroup. Finally, the comparisons of the two cohorts was limited mainly because of differences in tests used to assess IQ. In ALSPAC, a verbal IQ test was performed which differs from non-verbal IQ as tested in Generation R, the latter of which can overcome potential interference by language development delays. Nonetheless, in a recent study comparing three cohorts using three different IQ test, similar results were obtained for the effects of low thyroid function (47).

In conclusion, we demonstrate that TPOAb positivity during early pregnancy is associated with lower child IQ in a Dutch, iodine sufficient population, but not in a mildly iodine deficient population from the United Kingdom. In addition, TPOAb cut-offs below the current manufacturer-based cut-offs were associated with lower mean child IQ in the Netherlands. Further studies are needed to investigate the association of TPOAbs with child neurodevelopment outcomes in different populations, and evaluate whether factors that affect thyroid autoimmunity, such as iodine status, might possibly modify this association.

Acknowledgements
The Generation R study is conducted by the Erasmus Medical Center (Rotterdam) in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam; the Municipal Health Service Rotterdam area, Rotterdam; the Rotterdam Homecare Foundation, Rotterdam; and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond, Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. The general design of the Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam; the Erasmus University Rotterdam; The Netherlands Organization for Health Research and Development; The Netherlands Organisation for Scientific Research; the Ministry of Health, Welfare, and Sport; and the Ministry of Youth and Families.

We are extremely grateful to all the families who took part in ALSPAC, the midwives for help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The UK Medical Research Council and Wellcome (Grant 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. Data collection is funded from a wide range of sources, which are detailed on the ALSPAC website: http://www.bristol.ac.uk/alspac/about/. Thyroid function tests in ALSPAC were performed using grants from the Bupa Research Foundation, British Thyroid Association, and the Above and Beyond Foundation.

Funding: This work was supported by a clinical fellowship from ZonMw, project number 90 700 412 (to R.P.P.)

ZonMw, 90 700 412, Robin P. Peeters

Corresponding author and contact information: Tim I.M. Korevaar, MD, PhD., Na 2913, Postbus 2040, 3000 CA Rotterdam, the Netherlands, E-mail: t.korevaar@erasmusmc.nl

Disclosure:
The authors have nothing to disclose.

References:

1. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017; 27:315-389

2. Glinoer D, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. The Journal of Clinical Endocrinology & Metabolism 1994; 79:197-204

3. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Human reproduction update 2003; 9:149-161

4. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nature Reviews Endocrinology 2017; 13:610

5. Korevaar TI, de Rijke YB, Chaker L, Medici M, Jaddoe VW, Steegers EA, Visser TJ, Peeters RP. Stimulation of Thyroid Function by Human Chorionic Gonadotropin During

Pregnancy: A Risk Factor for Thyroid Disease and a Mechanism for Known Risk Factors. Thyroid 2017; 27:440-450
6. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. New England Journal of Medicine 1991; 324:532-536
7. Korevaar TIM, Steegers EAP, Pop VJ, Broeren MA, Chaker L, de Rijke YB, Jaddoe VWV, Medici M, Visser TJ, Tiemeier H, Peeters RP. Thyroid Autoimmunity Impairs the Thyroidal Response to Human Chorionic Gonadotropin: Two Population-Based Prospective Cohort Studies. The Journal of Clinical Endocrinology & Metabolism 2017; 102:69-77
8. Bernal J. Thyroid hormone regulated genes in cerebral cortex development. Journal of Endocrinology 2017; 232:R83-R97
9. Rovet JF. The role of thyroid hormones for brain development and cognitive function. Endocrine development 2014; 26:26-43
10. Laurberg P, Andersen SL, Hindersson P, Nohr EA, Olsen J. Dynamics and Predictors of Serum TSH and fT4 Reference Limits in Early Pregnancy: A Study Within the Danish National Birth Cohort. J Clin Endocrinol Metab 2016; 101:2484-2492
11. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. Bmj 2011; 342:d2616
12. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Ross HA, Hooijkaas H, Tiemeier H, Bongers-Schokking JJ, Jaddoe VW, Visser TJ, Steegers EA, Medici M, Peeters RP. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. The Journal of clinical endocrinology and metabolism 2013; 98:4382-4390
13. Liu H, Shan Z, Li C, Mao J, Xie X, Wang W, Fan C, Wang H, Zhang H, Han C, Wang X, Liu X, Fan Y, Bao S, Teng W. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid 2014; 24:1642-1649
14. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol 2017; 176:253-265
15. Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A. Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. JAMA pediatrics 2015; 169:838-845
16. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clinical endocrinology 2010; 72:825-829
17. Gyllenberg D, Sourander A, Surcel H-M, Hinkka-Yli-Salomäki S, McKeague IW, Brown AS. Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort. Biological Psychiatry 2016; 79:962-970
18. Roman GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Verhulst FC, Tiemeier H. Association of gestational maternal hypothyroxinemia and increased autism risk. Annals of neurology 2013; 74:733-742
19. Wasserman EE, Pillion JP, Duggan A, Nelson K, Rohde C, Seaberg EC, Talor MV, Yolken RH, Rose NR. Childhood IQ, hearing loss, and maternal thyroid autoimmunity in the Baltimore Collaborative Perinatal Project. Pediatric research 2012; 72:525-530

20. Williams FLR, Watson J, Ogston SA, Visser TJ, Hume R, Willatts P. Maternal and umbilical cord levels of T4, FT4, TSH, TPOAb, and TgAb in term infants and neurodevelopmental outcome at 5.5 years. The Journal of Clinical Endocrinology & Metabolism 2013; 98:829-838
21. Brown AS, Surcel H-M, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Bao Y, Sourander A. Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2015; 57:86-92
22. Ghassabian A, Bongers-Schokking JJ, De Rijke YB, Van Mil N, Jaddoe VW, de Muinck Keizer-Schrama SM, Hooijkaas H, Hofman A, Visser W, Roman GC. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. Thyroid 2012; 22:178-186
23. Jaddoe VWV, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, van der Lugt A, Mackenbach JP, Moll HA, Raat H. The Generation R Study: design and cohort update 2012. European journal of epidemiology 2012; 27:739-756
24. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Smith GD, Henderson J, Macleod J, Molloy L, Ness A. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International journal of epidemiology 2013; 42:97-110
25. Medici M, Ghassabian A, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Visser WE, Hooijkaas H, Hofman A, Steegers EA, Bongers-Schokking JJ, Ross HA, Tiemeier H, Visser TJ, de Rijke YB, Peeters RP. Women with high early pregnancy urinary iodine levels have an increased risk of hyperthyroid newborns: the population-based Generation R Study. Clin Endocrinol (Oxf) 2014; 80:598-606
26. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). The Lancet 2013; 382:331-337
27. Tellegen PJ, Winkel M, Wijnberg-Williams BJ, Laros JA. Snijders-Oomen Niet-Verbale intelligentietest SON-R 2 ½-7. Handleiding en verantwoording.[Snijders-Oomen Non-verbal Intelligence test SON-R 2 ½-7. Manual]. Lisse, NL: Swets & Zeitlinger 1998;
28. Wechsler D, Golombok S, Rust J. WISC-III UK Wechsler intelligence scale for children: UK manual. Sidcup, UK: The Psychological Corporation 1992;
29. Korevaar TIM, Steegers EAP, Chaker L, Medici M, Jaddoe VWV, Visser TJ, de Rijke YB, Peeters RP. Thyroid Function and Premature Delivery in TPO Antibody-Negative Women: The Added Value of hCG. The Journal of clinical endocrinology and metabolism 2017; 102:3360-3367
30. Shi X, Han C, Li C, Mao J, Wang W, Xie X, Li C, Xu B, Meng T, Du J. Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China. The Journal of Clinical Endocrinology & Metabolism 2015; 100:1630-1638
31. Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. Journal of statistical software 2011; 45
32. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol Oxf Feb 1999; 50:149-155
33. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, N., J. Maternal Thyroid Deficiency during Pregnancy and Subsequent Neuropsychological Development of the Child. Aug 19 1999; 341:549-555

34. Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiol Camb Mass Jan 2013; 24:150-157
35. Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. The Lancet Diabetes & Endocrinology 2016; 4:35-43
36. Chen S-w, Zhong X-s, Jiang L-n, Zheng X-y, Xiong Y-q, Ma S-j, Qiu M, Huo S-t, Ge J, Chen Q. Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: a systematic review and meta-analysis. Behavioural brain research 2016; 296:61-69
37. Wu S, Ding Y, Wu F, Li R, Xie G, Hou J, Mao P. Family history of autoimmune diseases is associated with an increased risk of autism in children: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 2015; 55:322-332
38. Leyhe T, Müssig K. Cognitive and affective dysfunctions in autoimmune thyroiditis. Brain, behavior, and immunity 2014; 41:261-266
39. Seror J, Amand G, Guibourdenche J, Ceccaldi P-F, Luton D. Anti-TPO antibodies diffusion through the placental barrier during pregnancy. PloS one 2014; 9:e84647
40. Korevaar TIM, Chaker L, Jaddoe VWV, Visser TJ, Medici M, Peeters RP. Maternal and birth characteristics are determinants of offspring thyroid function. The Journal of Clinical Endocrinology 2016; 101:206-213
41. Oken E, Braverman LE, Platek D, Mitchell ML, Lee SL, Pearce EN. Neonatal thyroxine, maternal thyroid function, and child cognition. The Journal of Clinical Endocrinology & Metabolism 2009; 94:497-503
42. Trumpff C, De Schepper J, Vanderfaeillie J, Vercruysse N, Van Oyen H, Moreno-Reyes R, Tafforeau J, Vanderpas J, Vandevijvere S. Thyroid-stimulating hormone (TSH) concentration at birth in belgian neonates and cognitive development at preschool age. Nutrients 2015; 7:9018-9032
43. Bliddal S, Boas M, Hilsted L, Friis-Hansen L, Juul A, Larsen T, Tabor A, Faber J, Precht DH, Feldt-Rasmussen U. Increase in thyroglobulin antibody and thyroid peroxidase antibody levels, but not preterm birth-rate, in pregnant Danish women upon iodine fortification. European Journal of Endocrinology 2017; 176:603-612
44. Ghassabian A, Steenweg-de Graaff J, Peeters RP, Ross HA, Jaddoe VW, Hofman A, Verhulst FC, White T, Tiemeier H. Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area. BMJ open 2014; 4:e005520
45. Pop VJ, de Vries E, van Baar AL, Waelkens J, De Rooy H, Horsten M, Donkers M, Komproe I, Van Son M, Vader H. Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? The Journal of Clinical Endocrinology & Metabolism 1995; 80:3561-3566
46. Mannisto T, Surcel HM, Bloigu A, Ruokonen A, Hartikainen AL, Jarvelin MR, Pouta A, Vaarasmaki M, Suvanto-Luukkonen E. The effect of freezing, thawing, and short- and long-term storage on serum thyrotropin, thyroid hormones, and thyroid autoantibodies: implications for analyzing samples stored in serum banks. Clin Chem 2007; 53:1986-1987
47. Levie D, Korevaar TIM, Bath SC, Dalmau-Bueno A, Murcia M, Espada M, Dineva M, Ibarluzea JM, Sunyer J, Tiemeier H, Rebagliato M, Rayman MP, Peeters RP, Guxens M. Thyroid Function in Early Pregnancy, Child IQ, and Autistic Traits: a Meta-analysis of

Individual-participant Data. The Journal of Clinical Endocrinology & Metabolism 2018:jc.2018-00224-jc.02018-00224

Figure 1. Flowchart of the study population.

Table 1. Characteristics of mother–child pairs from the Generation R Study and Avon Longitudinal Study of Parents And Children (ALSPAC).

	Generation R	ALSPAC
Maternal characteristics	N=3564	N=2362
Thyroid peroxidase antibodies (IU/mL)	3.2 (0.0-7.1)	1.9 (1.3-3.1)
Thyroid peroxidase antibodies positivity, n(%)	214 (5.9)	286 (12.8)
Free thyroxine (pmol/L)	15.2 (3.6)	16.5 (2.5)
Thyroid-stimulating hormone (mU/L)	1.37 (0.85-2.05)	0.99 (0.64-1.44)
Gestational age (weeks)	13.4 (1.8)	10.9 (3.1)
Age	30.3 (4.8)	28.2 (4.5)
BMI	24.4 (4.2)	22.8 (3.5)
Education level, %		
None or primary only	8.4	13.1
Secondary phase 1 (3–4 years)	12.5	9.0
Secondary phase 2 (4–5 years)	31.6	35.6
Higher phase 1 (6–8 years)	22.3	26.6
Higher phase 2 (>8 years)	25.2	15.7
Parity, %		
0	59.0	47.2
1	29.1	34.2
≥2	11.7	18.6
Smoking, %		
Non-smokers	73.4	81.0
Previous smokers	9.65	4.8
Current smokers	16.9	14.2
Ethnic origin, %		
Dutch	57.3	-
Moroccan	5.14	-
Turkish	7.34	-
Surinamese	7.80	-
Cape Verdian	4.09	-
Asian	4.26	-
Other European, North American, or Australian	8.71	-
Other ethnicities	5.30	-
Caucasian	-	98.5
Other ethnicities	-	1.5
Child characteristics		
Child IQ	101.41 (15.1)	99.5 (16.9)
Birthweight (g)	3434 (548)	3460 (523)
Sex (female), %	50.8	49.8

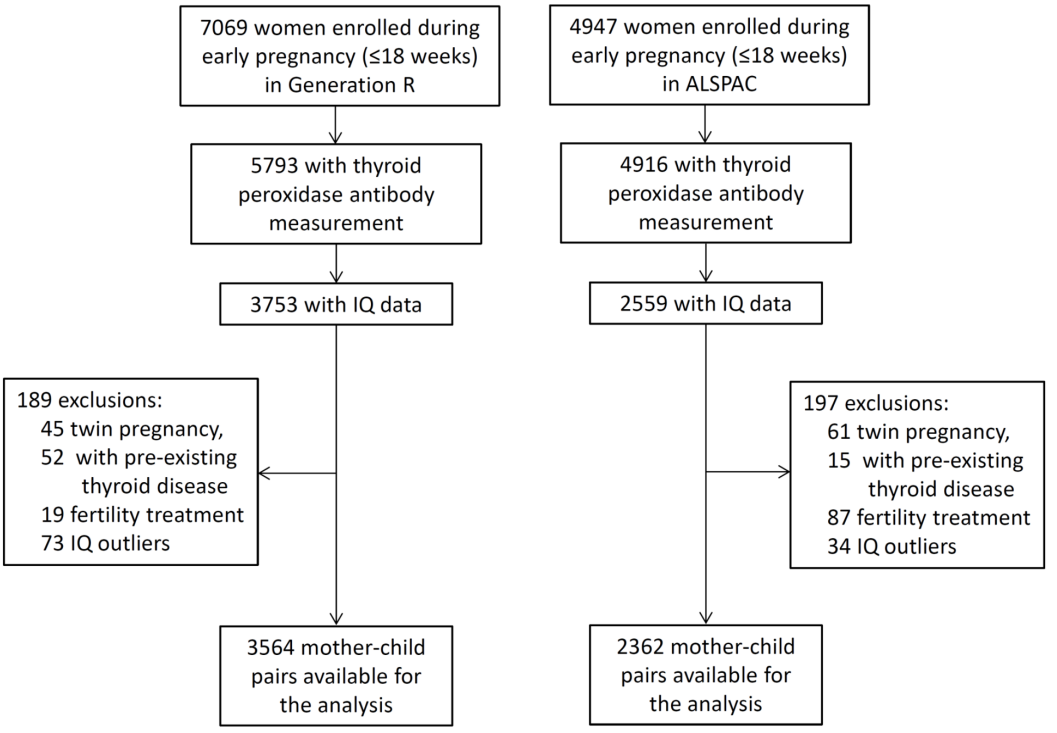
Data are median (inter-quartile range), mean (SD) or percentage.

Table 2. Differences in mean child IQ scores according to thyroid peroxidase antibodies in Generation R and ALSPAC.

Generation R				
TPOAb (IU/mL)	β±SE	P value	β±SE (+FT4)[a]	P value
Positivity [b]	-2.10±0.92	0.02	-2.00±0.92	0.03
vs. <10 [c]				
>20	-1.30±0.75	0.08	-1.14±0.75	0.13
>30	-1.72±0.81	0.03	-1.55±0.82	0.05
>40	-1.80±0.85	0.03	-1.69±0.85	0.04
>50	-2.17±0.89	0.01	-2.06±0.89	0.02
ALSPAC				
TPOAb (IU/mL)	β±SE	P value	β±SE (+FT4)[a]	P value

Positivity [b]	0.74±0.97	0.43	0.72±0.97	0.45
vs. <4.16 [c]				
>14.2	1.73±1.12	0.12	1.68±1.12	0.13
>29.6	1.79±1.21	0.13	1.73±1.21	0.15
>41.4	1.80±1.27	0.15	1.74±1.28	0.17
>54.8	2.29±1.32	0.08	2.22±1.33	0.09
>63.1	2.11±1.38	0.12	2.03±1.38	0.14

TPOAb, Thyroid Peroxidase Antibodies; SE, standard error; FT4, maternal free thyroxine.
Beta±SE are calculated using a linear regression model, adjusted for gestational age at the time of sampling, maternal age, maternal body mass index, education, ethnicity, smoking status, parity, birth weight and child sex.
[a] Additionally adjusted with FT4.
[b] Defined as TPOAb>60 (IU/mL) or TPOAb>6 (IU/mL) in Generation R and ALSPAC, respectively.
[c] Those with TPOAbs values between 10 IU/mL or 4.16 IU/mL and each cut-off were excluded from the analysis.


7069 women enrolled during early pregnancy (≤18 weeks) in Generation R
4947 women enrolled during early pregnancy (≤18 weeks) in ALSPAC
5793 with thyroid peroxidase antibody measurement
4916 with thyroid peroxidase antibody measurement
3753 with IQ data
2559 with IQ data
189 exclusions:
45 twin pregnancy,
52 with pre-existing thyroid disease
19 fertility treatment
73 IQ outliers
197 exclusions:
61 twin pregnancy,
15 with pre-existing thyroid disease
87 fertility treatment
34 IQ outliers
3564 mother-child pairs available for the analysis
2362 mother-child pairs available for the analysis