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Interpretation of the association between thyroid peroxidase antibodies and thyroid function during pregnancy: An individual participant data meta-analysis

Yindi Liu [a,b], Joris A.J. Osinga [a,b], Ulla Feldt-Rasmussen [c,d], Tanja G.M. Vrijkotte [e], Peter N. Taylor [f], Ashraf Aminorroaya [g], Ghalia Ashoor [h], Sofie Bliddal [c], Liang-Miao Chen [i], Bijay Vaidya [j], Glenn E. Palomaki [k], Farkhanda Ghafoor [l], Abel López-Bermejo [m,n], Victor J.M. Pop [o], Sachiko Itoh [p], Fang-biao Tao [q,r], Lorena Mosso [s], Tuija Männistö [t,u,v], Kris G. Poppe [w], Elizabeth N. Pearce [x], Leda Chatzi [y], John P. Walsh [z,aa], Polina Popova [ab], Katrien Benhalima [ac], Scott M. Nelson [ad], Maryam Kianpour [g], Kypros H. Nicolaides [ae], Xuemian Lu [i], Andrew T. Hattersley [af], Mary E. D'Alton [ag], Amna Pirzada [ah], Judit Bassols [ai], Maarten A.C. Broeren [aj], Reiko Kishi [p], Kun Huang [q,r], Andrea Vecchiola [s], Laura Boucai [ak], Marja Vääräsmäki [al], Eila Suvanto [al], Emily Oken [am], Marina Vafeiadi [an], Suzanne J. Brown [z], Pierre Kleynen [w], Elena N. Grineva [ao], Chantal Mathieu [ac], Robin P. Peeters [a,b], Arash Derakhshan [a,b], Tim I.M. Korevaar [ap,b,*]

[a] Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands
[c] Department of Medical Endocrinology and Metabolism, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark
[d] Department of Clinical Medicine, Faculty of Health and Clinical Sciences, Copenhagen University, Copenhagen, Denmark
[e] Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Amsterdam Reproduction & Development Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[f] Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, United Kingdom
[g] Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[h] Harris Birthright Research Center for Fetal Medicine, King's College Hospital, London, United Kingdom
[i] Department of Endocrinology and Rui'an Center of the Chinese-American Research Institute for Diabetic Complications, Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[j] Department of Endocrinology, Royal Devon and Exeter Hospital NHS Foundation Trust, University of Exeter Medical School, Exeter, United Kingdom
[k] Department of Pathology and Laboratory Medicine, Women and Infants Hospital and Warren Alpert Medical School of Brown University, Providence, RI, USA
[l] Department of Research and Innovation, Shalamar Institute of Health Sciences, Lahore, Pakistan
[m] Pediatric Endocrinology Research Group, Girona Biomedical Research Institute (IDIBGI), Dr. Josep Trueta Hospital, Girona, Spain
[n] Departament de Ciències Mèdiques, Universitat de Girona, Girona, Spain
[o] Department of Medical and Clinical Psychology, Tilburg University, Tilburg, the Netherlands
[p] Center for Environmental and Health Sciences, Hokkaido University, Sapporo, Japan
[q] Department of Maternal, Child and Adolescent Health, School of Public Health, Anhui Medical University, Hefei, Anhui, China
[r] Anhui Provincial Key Laboratory of Environment and Population Health Across the Life Course, Anhui Medical University, Hefei, Anhui, China
[s] Departments of Endocrinology, Pontificia Universidad Catolica de Chile, Santiago, Chile
[t] Clinical Chemistry, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[u] Joint County Authority for ISLAB Laboratories, Kuopio, Finland
[v] Translational Medicine Research Unit, University of Oulu, Oulu, Finland
[w] Endocrine Unit, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium
[x] Section of Endocrinology, Diabetes, and Nutrition, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA
[y] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[z] Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia
[aa] Medical School, University of Western Australia, Nedlands, Western Australia, Australia
[ab] Institute of Endocrinology, Almazov National Medical Research Centre, Saint Petersburg, Russia
[ac] Department of Endocrinology, UZ Gasthuisberg, KU Leuven, Herestraat 49, 3000, Leuven, Belgium

* Corresponding author. Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Erasmus MC, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands.
E-mail address: t.korevaar@erasmusmc.nl (T.I.M. Korevaar).

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[ad] School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, United Kingdom
[ae] Department of Women and Children's Health, Faculty of Life Sciences and Medicine King's College London, London, United Kingdom
[af] Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, EX1 2LU, United Kingdom
[ag] Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, NY, USA
[ah] Shifa College of Medicine, Islamabad, Pakistan
[ai] Maternal-Fetal Metabolic Research Group, Girona Biomedical Research Institute (IDIBGI), Dr. Josep Trueta Hospital, Girona, Spain
[aj] Laboratory of Clinical Chemistry and Haematology, Máxima Medical Centre, Veldhoven, the Netherlands
[ak] Division of Endocrinology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Weill Cornell University, New York, NY, USA
[al] Department of Obstetrics and Gynecology and Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland
[am] Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
[an] Department of Social Medicine, School of Medicine, University of Crete, Heraklion, Crete, Greece
[ao] Department of Endocrinology, First Medical University, Saint Petersburg, Russia
[ap] Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Background: Thyroid peroxidase antibody (TPOAb) positivity is the most important risk factor for hypothyroidism and determines thyroid function follow-up during pregnancy. TPOAb positivity is usually defined by manufacturer cut-offs which typically derived from non-pregnant populations. However, as a state of immune tolerance, pregnancy can affect TPOAb concentrations. To improve the understanding of clinical relevance of TPOAb concentrations during pregnancy, we investigated the association of TPOAbs with maternal thyroid function.

Methods: We performed an individual participant data meta-analysis embedded in the Consortium on Thyroid and Pregnancy. Participants with multiple gestations, pre-existing thyroid disease, thyroid (interfering) medication usage, or conception by in vitro fertilization were excluded. We used mixed effects regression models to assess the association of TPOAb percentiles calculated in each cohort with maternal thyroid function.

Results: The study population comprised 62,634 pregnant women from 24 cohorts. As compared to TPOAb percentiles ≤80, there were progressively higher mean thyroid stimulating hormone (TSH) concentrations across TPOAb percentiles ≥89, with corresponding mean differences ranging from +0.11 SD (95 % confidence interval [CI] +0.04 SD, +0.19 SD) at the 89th percentile to +1.04 SD (95 % CI + 0.96 SD, 1.11 SD) at the 100th percentile. Higher TPOAb percentiles were associated with progressively lower mean free thyroxine (FT4) concentrations across TPOAb percentiles ≥91, with corresponding mean differences ranging from −0.08 SD (95 % CI -0.16 SD, −0.01 SD) at the 91st percentile to −0.48 SD (95 % CI -0.56 SD, −0.4 SD) at the 100th percentile. From the 89th TPOAb percentile upwards, there were progressively higher risks of TSH >4.0 mU/L, with absolute risks of 2.4 %, 4.0 %, and 28.1 % in cases of ≤80th, 89th, and 100th TPOAb percentiles, respectively. Higher TPOAb percentiles were also associated with lower thyroidal response to human chorionic gonadotropin stimulation and higher risks of overt and subclinical hypothyroidism. In 19 of the included cohorts, there were 0.4–6.3 % of pregnant women with TPOAb concentrations lower than the positivity cut-offs but larger than or equal to the 89th-percentile concentrations. The associations of TPOAbs with TSH and with FT4 were most apparent during early pregnancy (*P* for interaction <0.001 for both TSH and FT4).

Conclusions: During pregnancy, TPOAbs were dose-dependently associated with TSH, FT4, and the risk of abnormal thyroid function. With concentrations below currently used positivity cut-offs, TPOAbs could be associated with lower maternal thyroid function, which indicates clinically relevant thyroid autoimmunity. These findings implicates that high normal TPOAb concentrations upon first assessment in pregnancy may warrant active follow-up.

1. Introduction

Thyroid peroxidase antibody (TPOAb) positivity reflects thyroid autoimmunity (TAI) and is the most important risk factor for hypothyroidism. TPOAb positivity occurs in 5.0–14 % of all pregnant women and is associated with a 24-fold higher risk of overt hypothyroidism and an 8-fold higher risk of subclinical hypothyroidism as compared to TPOAb negative women [1–5]. Overt and subclinical hypothyroidism are associated with a higher risk of various adverse pregnancy outcomes, including preterm delivery, pre-eclampsia, miscarriage, abnormal fetal growth, and suboptimal fetal neurodevelopment [6–10]. In most international guidelines, TPOAb status guides clinical decision making in the management of subclinical hypothyroidism and/or the indication for additional follow-up and frequency of thyroid function testing throughout pregnancy [11–15].

Due to alterations in thyroid physiology during pregnancy, international guidelines recommend the use of pregnancy and laboratory specific reference intervals for gestational thyroid function tests. However, there is no clinically-based recommendation for the definition of TPOAb positivity [11–15]. Instead, TPOAb positivity during pregnancy is usually defined by manufacturer provided cut-offs [16]. These cut-offs have been defined in various ways, such as population-based reference ranges, sensitivity and specificity of the method, or the risk of Hashimoto's thyroiditis. Nonetheless, these manufacturer-based cut-offs were established in non-pregnant individuals (Table S1). During pregnancy, physiology of both the thyroid and immune system change considerably, which could affect the interpretation of TPOAb concentrations [3,17]. For example, there is an increase in thyroid hormone production via thyroidal stimulation by human chorionic gonadotropin (hCG), a pregnancy-specific hormone produced by the placenta that is also a weak agonist of the thyroid stimulating hormone (TSH) receptor [18]. Another example is immune tolerance, which is necessary to ensure tolerance of the allogenic fetus but also results in a decline in autoantibody concentrations, including TPOAbs [3,19–21]. Taken together, the interpretation of TPOAb concentrations and/or positive status in pregnant women may be distinct from that in non-pregnant individuals. In a previous investigation within the Consortium on Thyroid and Pregnancy, we found that there is a dose-dependent association of TPOAb concentrations with thyroid function tests in pregnancy, and that there is a difference in thyroid function between women with antibody concentration above compared to below the manufacturer cut-offs [16]. However, in another previous study of pregnant women, we found that

besides the dose-dependency between TPOAbs and thyroid function, the clinically relevant TAI may be underestimated using the manufacturer cut-offs [22]. To date, it remains unclear if such findings can be extended and from what threshold any association would occur.

In this study, we aimed to further investigate the association of TPOAbs with maternal thyroid function to improve the understanding of clinical relevance of TPOAb concentrations during pregnancy and manifest the role of currently used TPOAb positivity cut-offs, TPOAb assays, and gestational age at blood sampling.

2. Methods

2.1. Participants

This is an individual participant data (IPD) meta-analysis conducted within the Consortium on Thyroid and Pregnancy (https://www.consortiumthyroidpregnancy.org), an international research collaboration that aims to study gestational thyroid (dys)function, physiology, determinants, and clinical risk profiles.

For this study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data guidelines and preregistered our study protocol (PROSPERO CRD42023461072). Cohorts included in the consortium were identified through a rolling systematic literature review, invitations to participate through international peer-reviewed journals and personal contacts of members [6,23,24]. Quality of the studies and risk of bias were assessed using the Newcastle-Ottawa scale [25]. Cohorts available with measurements of TPOAb, and TSH and/or free thyroxine (FT4) were eligible for this study. Participants with multiple pregnancy, conception by in vitro fertilization, history of thyroid disease, use of thyroid interfering medication, missing data on TPOAb, and missing data on both TSH and FT4 were excluded.

2.2. Exposures

Details of TPOAb measurements in each cohort are described in Table S2. Considering the differences in TPOAb assays and the range of measurements between cohorts, we standardized the data by transforming TPOAbs into cohort-specific percentiles. This was achieved by first sorting the TPOAb values within each cohort, followed by calculating their cumulative distribution using the formula: (number of values less than or equal to a given value/total number of values) * 100.

We selected TPOAb percentiles $\leq$80 as the reference group. This reference population was defined based on a preliminary model assessing the association of continuous TPOAb percentiles with TSH and FT4 using natural cubic splines, which suggested an effect threshold between the 80th and the 85th percentiles (Fig. S1).

When we initially used the percentile calculation method, identical TPOAb values would share the same rank, specifically, the highest rank within the tied group. In one cohort, the lowest calculated TPOAb percentile was initially 87.2; therefore, we adjusted this percentile to 80 for consistency with the established reference group. For statistical analysis, percentiles >80 were rounded up to the nearest whole number, ranging from 81 to 100. In individual cohorts, when missing value(s) occurred in percentiles >80, we filled these gaps by randomly reallocating observations from the subsequent percentile, distributing them evenly across both the missing percentile(s) and the subsequent one.

2.3. Outcomes

The primary outcomes were TSH and FT4. Secondary outcomes included free triiodothyronine (FT3), total triiodothyronine (TT3), total thyroxine (TT4), and the thyroidal response to hCG stimulation. Thyroidal response to hCG stimulation, including hCG-standardized TSH and FT4 concentrations, was defined cross-sectionally by the standardized residuals of the regression model with TSH or FT4 as dependent variable and hCG as the independent variables, indicating lower thyroid (hormone) secretory response to hCG stimulation in case of positive values for TSH or negative values for FT4 [22].

A TSH concentration above 4.0 mU/L and thyroid function test abnormalities defined using cohort-specific reference intervals (overt and subclinical hypothyroidism, isolated hypothyroxinemia, overt and subclinical hyperthyroidism) were also included as secondary outcomes. Cohort-specific reference intervals of TSH and FT4 were defined based on the 2.5th and 97.5th percentiles in women with TPOAb negativity [11]. Overt hypothyroidism was defined as TSH above the 97.5th percentile and FT4 below the 2.5th percentile. Subclinical hypothyroidism was defined as TSH above the 97.5th percentile and FT4 within the normal range (2.5th-97.5th percentiles). Isolated hypothyroxinemia was defined as FT4 below the 2.5th percentile and TSH within the normal range. Subclinical hyperthyroidism was defined as TSH below the 2.5th percentile and FT4 within the normal range. Overt hyperthyroidism was defined as TSH below the 2.5th percentile and FT4 above the 97.5th percentile.

Details of thyroid function tests and hCG measurements are described in Table S2. To make values comparable between cohorts and assays while retaining inter-individual differences, all thyroid function measurements were standardized to cohort-specific SD-scores.

2.4. Statistical analyses

We used linear mixed-effects regression models across all cohorts with a random intercept for each cohort to study the mean difference in TSH, FT4, FT3, TT3, TT4, and thyroidal response to hCG stimulation for each percentile of TPOAbs starting from 81. As a validation, analyses on primary outcomes were additionally performed using a two-step approach with random-effect models utilizing the DerSimonian and Laird method to pool estimates from individual cohorts [26]. The heterogeneity across cohorts was assessed using I^2 statistic, and publication bias was evaluated using funnel plots and Egger's test [27,28]. Generalized linear mixed-effects regression models with a random intercept for each cohort were used to study the association of TPOAb percentiles with the risks of TSH >4.0 mU/L and thyroid function test abnormalities.

To differentiate the assay-specific effect, we repeated analyses on primary outcomes with stratification of assay manufacturers which were employed in at least three included cohorts. We also assessed if the associations of TPOAb percentiles with maternal TSH and FT4 differed according to gestational age at blood sampling by adding a product interaction term to the linear mixed-effects regression models. A *P*-value for interaction of <0.15 was considered for subsequent stratified analyses that were used for interpreting clinical relevance of any differences [29]. We performed sensitivity analyses on the primary outcomes by excluding the cohort in which the lowest calculated TPOAb percentile was initially 87.2, and on a subset of cohorts located within mild-to-moderate iodine deficient regions. There were only four cohorts included for analyses on the thyroidal response to hCG stimulation. To assess if the results were dominantly driven by any of them, we repeated the analyses by sequentially excluding each cohort. We also performed a sensitivity analysis by excluding participants with hCG concentrations below the cohort median for analyses on the thyroidal response to hCG stimulation because low hCG concentrations are seen before and after the hCG peak, which may impact thyroid hormone concentrations [30]. In addition, we performed a sensitivity analysis by assessing TSH above the upper limit of cohort-specific reference interval as the outcome.

All models were adjusted for potential confounders, including maternal age, body mass index, smoking status, parity, maternal education level, gestational age at blood sampling, and fetal sex. These covariates were selected based on biological plausibility and acknowledgements in previous publications [16,22]. Missing data on covariates were imputed by multilevel multiple imputation, creating five imputed data sets for pooled analyses [31]. A two-sided threshold for statistical

significance of <0.05 was used. All statistical analyses were performed using R statistical software version 4.4.3 (R Development Core Team, Vienna, Austria; packages *lme4, mice, micemd, metafor, and sjPlot*) [32].

3. Results

3.1. Study population

The final study population comprised 62,634 pregnant women from 24 cohorts (Fig. 1), for whom basic characteristics are shown in Table 1. In the study population, the mean age was 29.1 years with a median gestational age of 12.4 weeks. The prevalence of TPOAb positivity was 8.3 % across all cohorts according to the manufacturer cut-offs or cut-offs previously specified by individual cohorts (e.g. Northern Finland Birth Cohort 1986, where the concentration of the 95th percentile was used as the positivity cut-off due to long-term frozen storage of the samples [33,34]). Cohort-specific iodine status, demographic characteristics, thyroid function tests, and information on missing data are provided in Tables S3–S6.

3.2. Association of TPOAbs with maternal thyroid function

Compared with TPOAb percentiles ≤80, higher TPOAb percentiles were associated with progressively higher mean TSH concentrations from the 89th percentile upwards, with corresponding mean differences ranging from +0.11 SD (95 % confidence interval [CI] +0.04 SD, +0.19 SD) at the 89th percentile to +1.04 SD (95 % CI + 0.96 SD, 1.11 SD) at the 100th percentile (Fig. 2A; Table S7). Higher TPOAb percentiles were associated with progressively lower mean FT4 concentrations from the 91st percentile upwards, with corresponding mean differences ranging from −0.08 SD (95 % CI -0.16 SD, −0.01 SD) at the 91st percentile to −0.48 SD (95 % CI -0.56 SD, −0.4 SD) at the 100th percentile (Fig. 2B; Table S7). There was no dose-dependent association of TPOAb percentiles with FT3, TT3, or TT4 concentrations (Figs. S2–S4; Tables S8–S10).

Compared with TPOAb percentiles ≤80, higher TPOAb percentiles were associated with progressively higher mean hCG-standardized TSH concentrations from the 91st percentile upwards, with corresponding mean differences ranging from +0.21 SD (95 % CI + 0.09 SD, +0.32 SD) at the 91st percentile to +0.98 SD (95 % CI + 0.86 SD, +1.1 SD) at the 100th percentile (Fig. 3A; Table S11). Higher TPOAb percentiles were associated with progressively lower mean hCG-standardized FT4 concentrations from the 93rd percentile upwards, with corresponding mean differences ranging from −0.17 SD (95 % CI -0.29 SD, −0.04 SD) at the 93rd percentile to −0.54 SD (95 % CI -0.67 SD, −0.41 SD) at the 100th percentile (Fig. 3B; Table S11).

Compared with TPOAb percentiles ≤80, higher TPOAb percentiles were associated with progressively higher risks of TSH >4.0 mU/L from the 89th percentile upwards, with corresponding ORs ranging from 1.7 (95 % CI 1.1, 2.58) at the 89th percentile to 24.6 (95 % CI 19.9, 30.4) at the 100th percentile. The absolute risks for TSH >4.0 mU/L were 2.4 %, 4.0 %, and 28.1 % in cases of ≤80th, 89th, and 100th TPOAb percentiles, respectively (Fig. 4; Table S12). Higher TPOAb percentiles were associated with progressively higher risks of overt hypothyroidism from the 90th percentile upwards, with corresponding ORs ranging from 7.4 (95 % CI 2.99, 18.4) at the 90th percentile to 136 (95 % CI 91.1, 203) at the 100th percentile. The absolute risks for overt hypothyroidism were 0.1 %, 0.8 %, and 9.1 % in cases of ≤80th, 90th, and 100th TPOAb percentiles, respectively (Fig. S5; Table S13). Higher TPOAb percentiles were associated with progressively higher risks of subclinical hypothyroidism from the 89th percentile upwards, with corresponding ORs ranging from 2.2 (95 % CI 1.51, 3.32) at the 89th percentile to 20.3 (95 % CI 16.5, 25.0) at the 100th percentile. The absolute risks for subclinical hypothyroidism were 2.1 %, 4.5 %, and 24.3 % in cases of ≤80th, 89th, and 100th TPOAb percentiles, respectively (Fig. S6; Table S14). There was no dose-dependent association of TPOAb percentiles with the risk of isolated hypothyroxinemia, subclinical hyperthyroidism, or overt hyperthyroidism (Figs. S7–S9; Tables S15–S17).

Table 1
Characteristics of the total study population.

Variables	N = 62,634[a]
Maternal characteristics	
Age (years)	29.1 (5.2) [N = 61,924]
Gestational age (weeks)	12.4 (7–39.3) [N = 62,267]
BMI (kg/m^2)	24.2 (4.6) [N = 46,966]
Parity, N (%)	
0	31,435 (53.2)
1	17,539 (29.7)
2	6,293 (10.6)
≥3	3,840 (6.5)
Active smoking, N (%)	
Non/past smoker	53,567 (91.6)
Current smoker	4,928 (8.4)
Fetal sex, N (%)	
Male	22,135 (50.8)
Female	21,435 (49.2)
Maternal Education, N (%)	
Primary	11,600 (25.6)
Secondary	19,476 (43.1)
Higher	14,152 (31.3)
Maternal test results	
TPOAb positivity, N (%)[b]	5,215 (8.3)
TSH (mU/L)	1.3 (0.1–4.5) [N = 62,272]
FT4 (pmol/L)	13.9 (7.5–21.9) [N = 62,422]
FT3 (pmol/L)	4.5 (2.8–6.4) [N = 26,824]
TT3 (nmol/L)	1.6 (1–21.2) [N = 13,927]
TT4 (nmol/L)	115.3 (64–206.1) [N = 20,134]
hCG (IU/L)	57,712 (17,071–147,049) [N = 16,616]
TSH >4.0 mU/L, N (%)	2,233 (3.6)

Abbreviations: BMI, body mass index; TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; TT3, total triiodothyronine; TT4, total thyroxine; hCG, human chorionic gonadotropin.

[a] Descriptive statistics of all included women, denoted as the mean (SD), median (95 % range), or count (percentage), as appropriate. Descriptive characteristics per cohort and detailed descriptions of missing data are shown in the Supplementary Data.

[b] TPOAb positivity was defined based on the manufacturer or previously cohort-specified cut-offs.

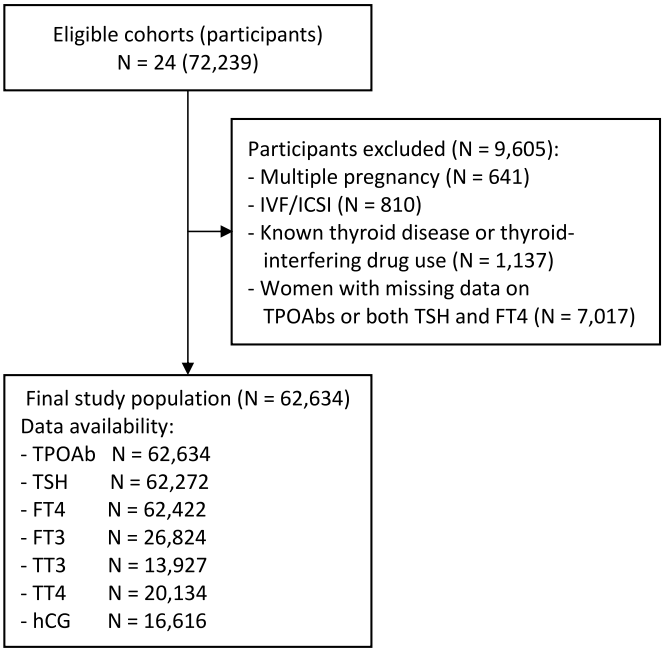

Fig. 1. Study flowchart.

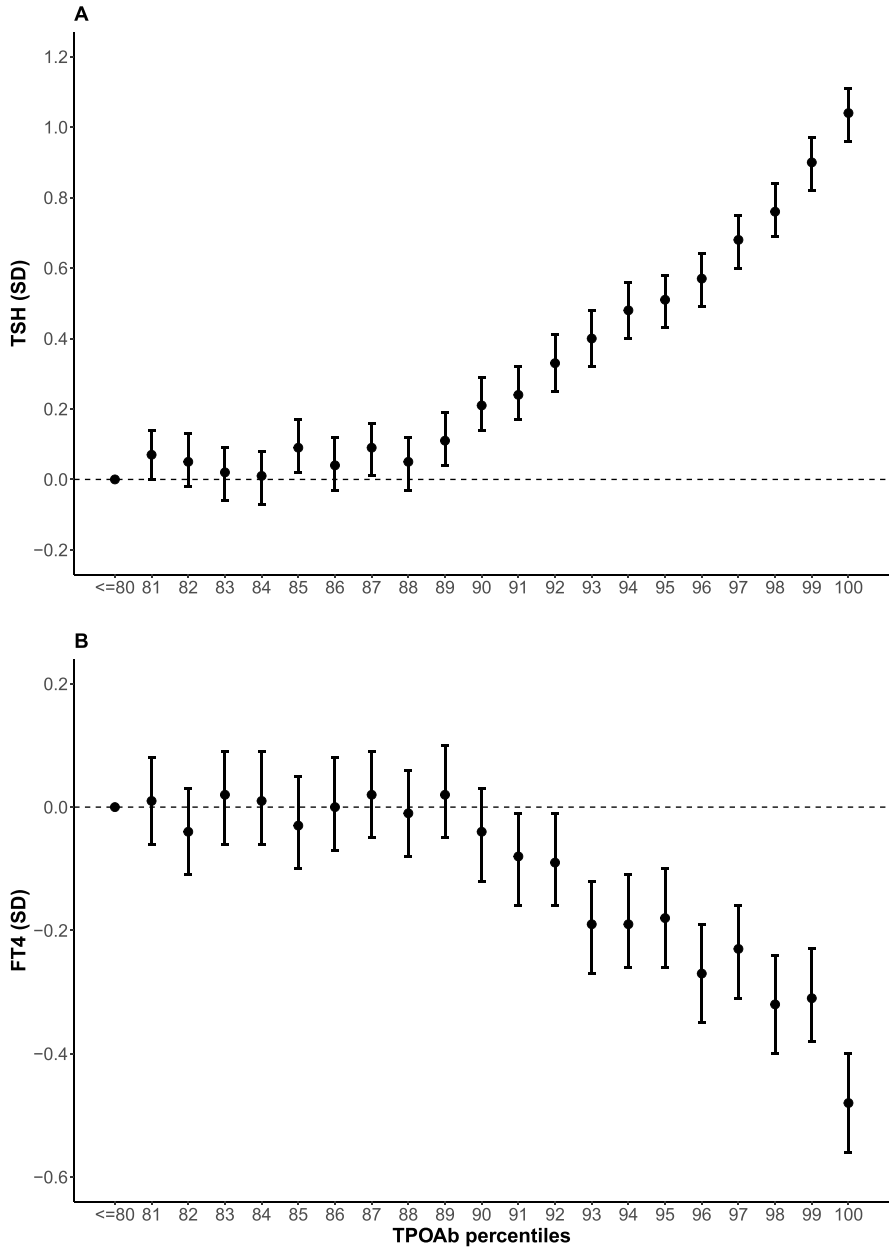

Fig. 2. Association of TPOAb percentiles with maternal TSH and FT4 concentrations. Figures display the mean differences in the SD scores of TSH (A) and FT4 (B) and related 95 % confidence intervals for each population-based TPOAb percentile as compared to the reference group (≤80th percentiles). All analyses were adjusted for maternal age, gestational age at blood sampling, parity, smoking status, BMI, maternal education, and fetal sex.

The absolute TPOAb concentration that corresponded to the 89th percentile was lower than the manufacturer or previously cohort-specified TPOAb positivity cut-off in 19 out of the 24 included cohorts (Table 2). There were 0.4–6.3 % of pregnant women with TPOAb concentrations lower than the currently used positivity cut-offs but larger than or equal to the 89th-percentile concentrations (Table 2), among whom the prevalence of TSH >4.0 mU/L, overt hypothyroidism, and subclinical hypothyroidism varied up to 25.0 %, 7.7 %, and 15.4 %, respectively (Table S18).

3.3. Sensitivity analyses

There were four assay manufacturers (Abbott ARCHITECT, Roche Cobas, Siemens ADVIA Centaur, and Siemens IMMULITE), each used for TPOAb measurements in three or more included cohorts (Table 2). Despite to some extent different patterns, the association of TPOAb percentiles with maternal TSH and/or FT4 was dose-dependent across these assay manufacturers (Figs. S10 and S11). For assay manufacturers, including Abbott ARCHITECT, Roche Cobas, and Siemens IMMULITE, higher TSH concentrations were seen at TPOAb percentile(s) lower than the percentiles corresponding to the manufacturer cut-offs (Fig. S10).

The associations of TPOAb percentiles with TSH and with FT4 differed according to gestational age at blood sampling (*P* for interaction <0.001 for both TSH and FT4). In subsequent stratified analyses, there was a more prominent pattern of the positive association of TPOAb percentiles with TSH in early pregnancy as compare to later pregnancy (Fig. 5A). Similarly, the negative association of TPOAb percentiles with FT4 was most apparent in early pregnancy (Fig. 5B).

Consistent with one-step meta-analyses, TPOAb percentiles were associated with progressively higher TSH concentrations and

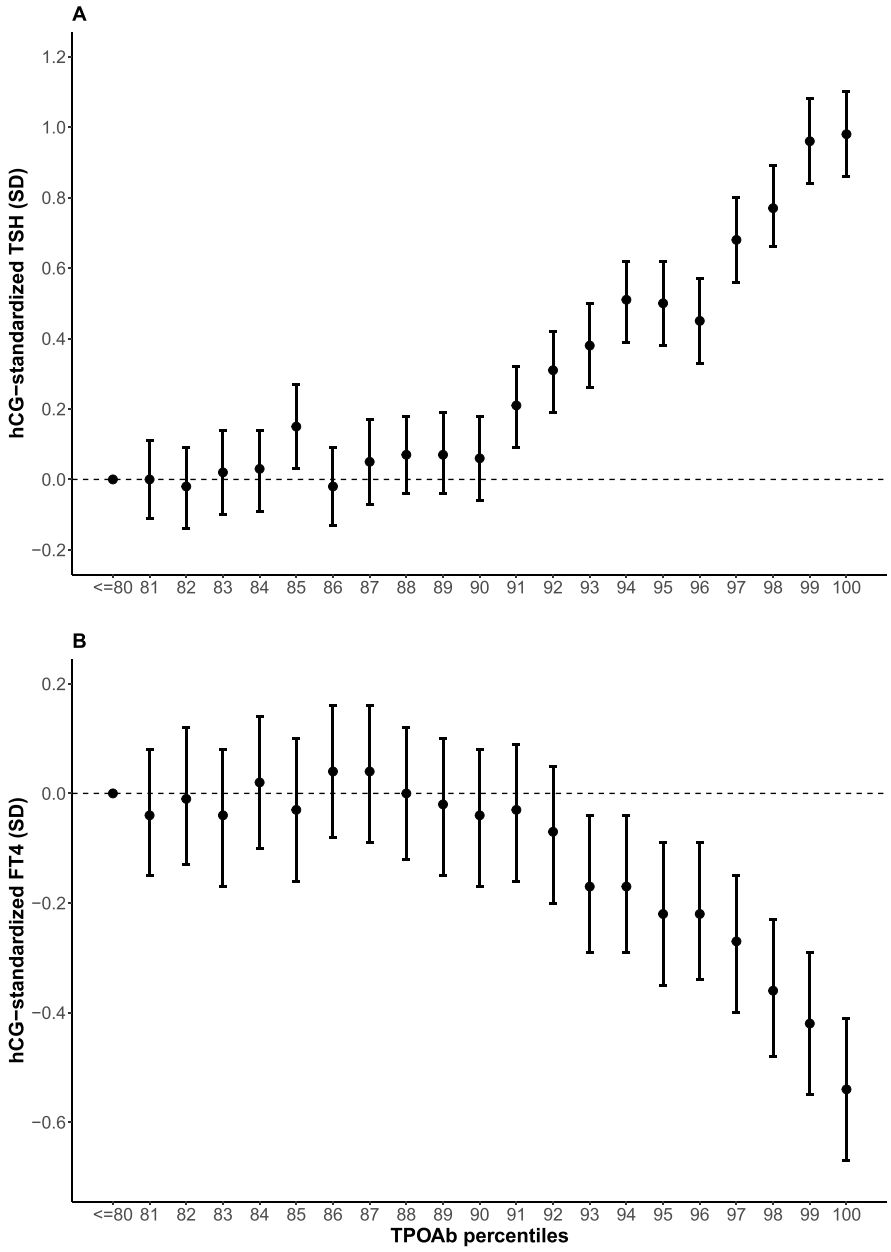

Fig. 3. Association of TPOAb percentiles with maternal thyroidal response to hCG stimulation. Figures display the mean differences in the SD scores of hCG-standardized TSH (A) and FT4 (B) and related 95 % confidence intervals for each population-based TPOAb percentile as compared to the reference group (≤80th percentiles). All analyses were adjusted for maternal age, gestational age at blood sampling, parity, smoking status, BMI, maternal education, and fetal sex.

progressively lower FT4 concentrations from the 89th and 91st percentiles upwards using the two-step approach, respectively (Figs. S12 and S13). In analyses on TSH, I^2 values ranged from 0 % to 80 %, and no relevant publication bias was identified by funnel plots or Egger's tests except at the 99th TPOAb percentile (Figs. S12 and S14). In analyses on FT4, I^2 values ranged from 0 % to 62 %, and no relevant publication bias was identified by funnel plots or Egger's tests except at the 90th, 96th, and 99th TPOAb percentiles (Figs. S13 and S15).

The association of TPOAb percentiles with TSH and FT4 was robust after excluding the cohort in which the lowest calculated TPOAb percentile was initially 87.2 (Figs. S16 and S17). Within cohorts in mild-to-moderate iodine deficient regions, TPOAb percentiles were associated with progressively higher TSH concentrations and progressively lower FT4 concentrations from 91st and 93rd percentiles upwards, respectively (Figs. S18 and S19). Sequential exclusion of cohorts with hCG measurements did not alter the association of TPOAb percentiles with the thyroidal response to hCG stimulation (Figs. S20 and S21). After excluding women with hCG concentrations lower than the cohort median, the association of TPOAb percentiles with the thyroidal response to hCG stimulation remained similar with slightly larger effect estimates (Figs. S22 and S23). Compared with TPOAb percentiles ≤80, elevated TPOAbs were associated with progressively higher risks of TSH above the upper limit of cohort-specific reference interval from the 89th percentile upwards (Fig. S24).

4. Discussion

In this IPD meta-analysis, we studied the association of TPOAb percentiles with maternal thyroid function in pregnancy. We showed that higher TPOAb percentiles were dose-dependently associated with higher

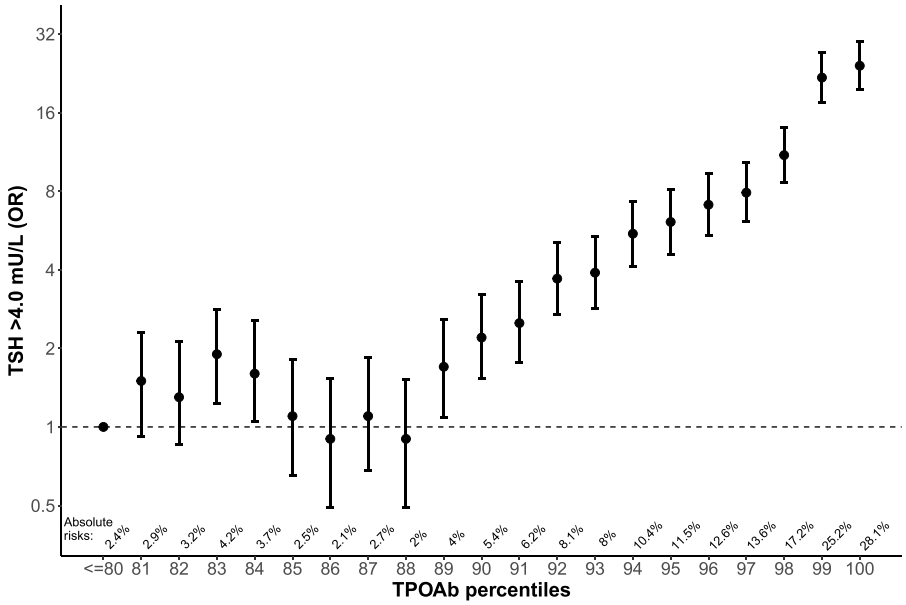

Fig. 4. Association of TPOAb percentiles with the risk of TSH concentrations >4.0 mU/L. Figures display the odds ratios for the risk of TSH concentrations >4.0 mU/L and related 95 % confidence intervals for each population-based TPOAb percentile as compared to the reference group (≤80th percentiles). All analyses were adjusted for maternal age, gestational age at blood sampling, parity, smoking status, BMI, maternal education, and fetal sex. Absolute risks are also provided as percentages for each percentile.

Table 2
Prevalence difference between manufacturer or previously cohort-specified TPOAb positivity cut-off and clinically relevant TPOAb concentration.

Cohort (Country)	Assay Manufacturer	Positivity Cut-off[a]	P89 TPOAb Concentration[b]	In-between Prevalence, N (%)[c]
ALSPAC (United Kingdom)	Abbott ARCHITECT	6	7	△ 70 (1.4)
GIRONA 1&2 (Spain)[d]	Abbott ARCHITECT	5.61	4	▽ 5 (0.7)
NFBC1986 (Finland)	Abbott ARCHITECT	167.7	22	▽ 361 (6.3)
Western Australia	Abbott ARCHITECT	5.61	4	▽ 13 (0.5)
Mosso et al. (Chile)	Abbott AxSYM	12	11	▽ 4 (0.5)
Chen et al. (China)	Beckman Coulter Access	50	30	▽ 497 (5.8)
ABCD (Netherlands)	ELISA ELIZEN TGAb	80	15	▽ 213 (5.2)
Ghafoor et al. (Pakistan)	ELISA, in-house	100	86	▽ 37 (2)
Project Viva (United States)	Nichols Advantage	2	20	△ 20 (2.7)
BEDIP-N (Belgium)	Roche Cobas	34	15	▽ 27 (5.3)
EFSOCH (United Kingdom)	Roche Cobas	34	19	▽ 38 (4)
HAPPY (Netherlands)	Roche Cobas	35	22	▽ 64 (3)
Hokkaido Study (Japan)	Roche Cobas	16	15	▽ 10 (1.5)
Ma'anshan Birth Cohort Study (China)	Roche Cobas	34	40	△ 57 (1.8)
Popova et al. (Russia)	Roche Cobas	34	30	▽ 2 (0.4)
Aminorroaya et al. (Iran)	Siemens ADVIA Centaur	60	108	△ 18 (4.8)
Ashoor et al. (United Kingdom)	Siemens ADVIA Centaur	60	42	▽ 71 (1.5)
Poppe et al. (Belgium)	Siemens ADVIA Centaur	60	48	▽ 74 (4.9)
FASTER (USA)	Siemens IMMULITE	35	27	▽ 156 (1.7)
Rhea (Greece)	Siemens IMMULITE	35	23	▽ 18 (2)
Wijnen & Pop (Netherlands)	Siemens IMMULITE	35	22	▽ 34 (2.2)
Bliddal et al. (Denmark)	Thermo Fisher Scientific BRAHMS	60	76	△ 18 (1.6)
Generation R (Netherlands)	Thermo Fisher Scientific Phadia	60	15	▽ 283 (5.3)

Abbreviations: TPOAb, thyroid peroxidase antibody.

[a] Positivity cut-offs for TPOAbs provided by assay manufacturers or previously specified in individual cohorts: manufacturer cut-offs can be referred to Table S1; for Northern Finland Birth Cohort 1986 (NFBC1986), previously cohort-specified cut-off based on the 95th percentile was used due to long-term frozen storage of the samples. Values are expressed in units specific to respective cohorts: IU/mL, mU/L, mIU/L, IU/L, kIU/L, and kU/L, as appropriate.

[b] TPOAb concentration corresponding to the 89th percentile in the current study population of each cohort. Values are expressed in units specific to respective cohorts: IU/mL, mU/L, ^{mIU}/L, IU/L, kIU/L, and kU/L, as appropriate.

[c] In-between prevalence indicates the number (and percentage) of individuals with TPOAb concentrations between the positivity cut-off (A) and the 89th-percentile TPOAb concentration (B). ▽, ^{subgroup} where B < A; △, subgroup where B > A.

[d] Cohorts GIRONA 1 and GIRONA 2 were combined due to the same population background.

TSH, lower FT4, and lower thyroidal response to hCG stimulation. With higher TPOAb percentiles, there were progressively higher risks of abnormal TSH as well as overt and subclinical hypothyroidism. In addition, we showed that there could be lower maternal thyroid function at TPOAb concentrations below the currently used positivity cut-offs, which typically applied to three assay manufacturers (Abbott ARCHITECT, Roche Cobas, and Siemens IMMULITE). Moreover, we showed a gestational age dependent pattern of the association between

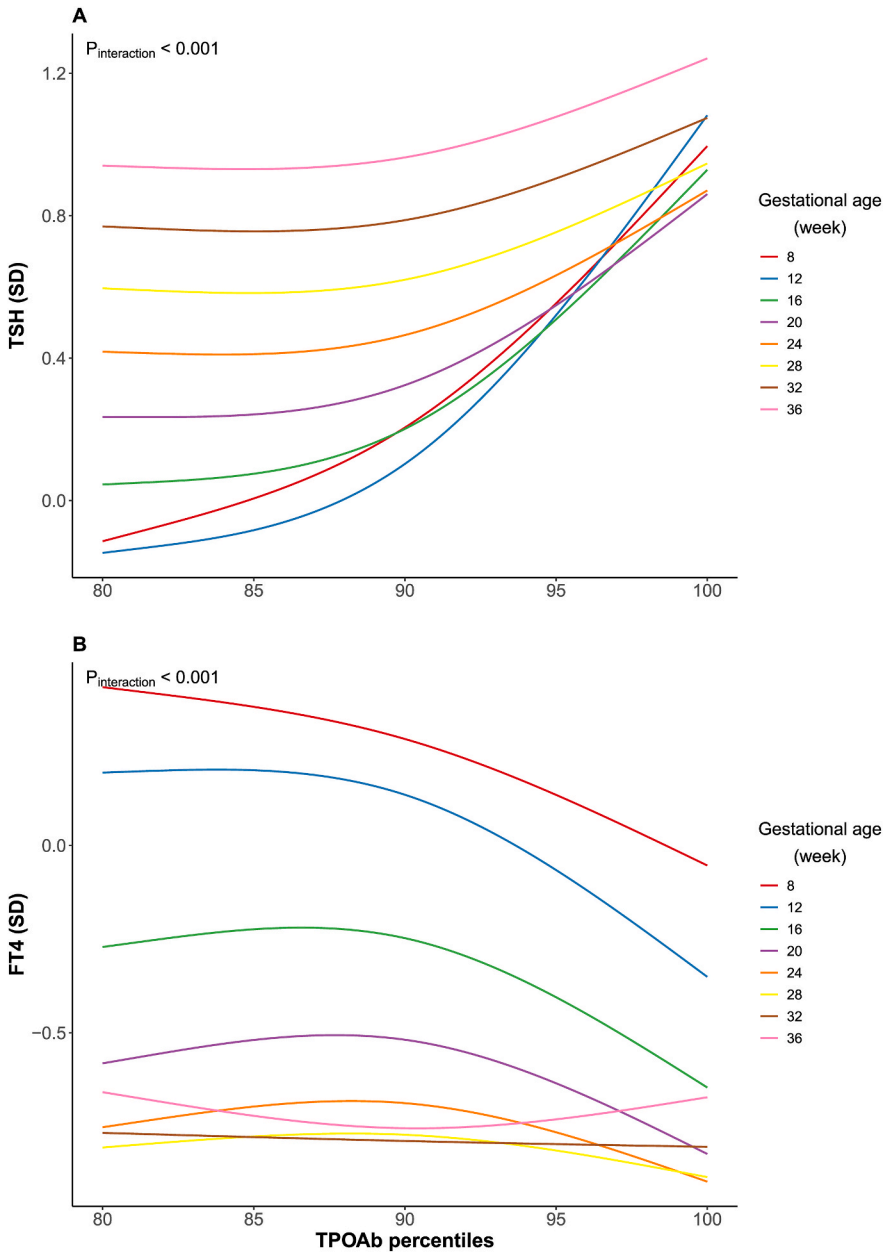

Fig. 5. Association of TPOAb percentiles with maternal TSH and FT4 concentrations stratified by gestational age at blood sampling. All analyses were adjusted for maternal age, parity, smoking status, BMI, maternal education, and fetal sex.

TPOAb percentiles and maternal thyroid function.

In the current study, TPOAbs were positively associated with maternal TSH concentrations across TPOAb percentiles ≥89, and negatively associated with maternal FT4 concentrations across TPOAb percentiles ≥91. We also found TPOAbs were positively associated with a higher risk of TSH >4.0 mU/L from the 89th percentile upwards. In 19 out of the 24 included cohorts, up to 6.3 % of the pregnant women with high normal TPOAb concentrations could have a higher TSH concentration. This suggests that currently used cut-offs for TPOAb positivity may underdiagnose clinically relevant TAI during pregnancy. According to international guidelines, TPOAb positivity not only guides decision making on levothyroxine treatment during pregnancy, but also is an indication for TSH testing and follow-up monitoring [11–15]. Therefore, our results implicate three potentially clinically relevant consequences for women found to have a high normal TPOAb concentration during pregnancy that need further investigation in future studies. First, they could benefit from active TSH monitoring through gestation since TPOAb positivity (defined by the manufacturer or previously cohort-specified cut-off) is the main risk factor for hypothyroidism [5]. Second, pregnant women with a high normal TPOAb concentration may benefit from active counseling for the signs and symptoms of postpartum thyroiditis (PPT), because TPOAbs are the most important risk factor for PPT [11,35,36]. Third, they could be considered for thyroid function testing upon planning a future fertility treatment [37–39], or during a subsequent pregnancy [11]. Follow-up studies are required to quantify if high-normal gestational TPOAb concentrations are associated with the adverse pregnancy outcomes that have previously been associated with TPOAb positivity. Although there were still five of the included cohorts indicating that currently used positivity cut-offs could overdiagnose clinically relevant TAI during pregnancy, the presence of the inconsistent results actually reflect the inter-cohort variability using real-world data and also underscore the need for a more comprehensive population-based and assay-specific approach of defining TPOAb positivity in pregnancy. Before an improved definition is established, the

majority of the included cohorts in this study provides a relatively robust implication of taking into account high normal TPOAb concentrations when currently used positivity cut-offs are used. On the other hand, considering the heterogeneity in methods of establishing pregnancy-specific TPOAb cut-offs [34,40–45], future studies are warranted to further investigate and develop the definition of TPOAb positivity during pregnancy.

The TPOAb percentiles from which there was an association with TSH differed from those for FT4 (89th and 91st percentiles, respectively). The maximum mean difference in TSH was up to +1.04 SD, considerably larger in absolute value than the −0.49 SD observed for FT4. This discrepancy is explained by the fact that minor fluctuations in FT4 can trigger relatively larger variations in TSH because of their log-linear relationship, which is in line with the general concept that TSH is the most sensitive marker for detecting changes in thyroid function [46,47].

We did not find a dose-dependent association of TPOAb percentiles with FT3, TT3, or TT4, although there seemed to be a trend of lower FT3 and a trend of initially higher but then lower TT3 as well as TT4 in cases of higher TPOAb percentiles. These results are in line with previous studies [16,48,49]. The insignificant associations can possibly be explained by limited data availability of FT3, TT3, and TT4 for each percentile. In addition, considering the relative contributions of serum T3 from thyroid secretion versus peripheral deiodination (approximately 20 % and 80 %, respectively) [50,51], although TAI can decrease the thyroid functional capacity, the T3 that is produced by peripheral deiodination presumably is able to maintain T3 concentrations within the normal range even if the circulating FT4 is mildly reduced [52,53]. In our previous IPD meta-analysis within the Consortium on Thyroid in Pregnancy, there was a lower TT4 concentration with a higher TPOAb concentration, while this association disappeared after adjusting for thyroglobulin antibodies [16]. This may indicate TT4 concentrations during pregnancy are primarily influenced by increased thyroxine binding globulin rather than reductions in thyroid hormone availability due to TAI.

We identified an impaired thyroidal response to hCG stimulation when there was a higher level of TPOAbs, which is consistent with the findings in a previous study where hCG was not associated with either FT4 or TSH in TPOAb-positive pregnant women (in contrast to TPOAb-negative women) [54]. In addition, although we identified significant associations of TPOAbs with both TSH and FT4 up until approximately 24–28 weeks, the effects were considerably larger in earlier pregnancy. This phenomenon was compatible with the trajectory of hCG production, where hCG concentrations rise rapidly from pregnancy implantation and peak at around 10 weeks of gestation before they slowly decline [55]. An alternative explanation for the gestational age specific differences could be that the effect of immune tolerance on thyroid antibodies becomes more prominent as pregnancy progresses [56]. Most TPOAb measurements during pregnancy are performed during early pregnancy, upon first presentation to a healthcare provider.

The strengths of this study include a large sample size, a diverse geographic and ethnic construction of study population, and a homogenized statistical methodology to study the association of interest, including assay-specific and gestational age dependent sub-analyses. Nevertheless, the current study also has some limitations. On the one hand, because of the observational nature of the included studies, causal inferences cannot be made. On the other hand, although our analyses were adjusted for key confounding factors based on previous identification and biological plausibility, we could not entirely rule out residual or unmeasured confounding with the limited covariates available in the included cohorts. In addition, it should be noted that across different assay manufacturers, there were slightly different patterns of the association between TPOAbs and maternal thyroid function, which fits with the known substantial inter-method variability between TPOAb assays (correlation coefficients: 0.65–0.87) [57]. However, as the assay information were derived from different populations, the assay-specific differences that we identified should optimally be confirmed by future studies with different assay measurements of the same gestational serum samples.

5. Conclusions

In this study, we show that during pregnancy, TPOAbs were dose-dependently associated with TSH, FT4, and the risk of thyroid function test abnormalities. TPOAb concentrations below the currently used positivity cut-offs could be associated with lower maternal thyroid function. This suggests that high normal TPOAb concentrations could be indicative of clinically relevant TAI in pregnant women, for whom follow-up TSH testing throughout pregnancy, postpartum thyroiditis counseling, and thyroid function testing prior to or during a future pregnancy may be valuable. In addition, future studies are needed to explore and substantiate the viability of population-based and assay-specific definition of TPOAb positivity in pregnancy.

CRediT authorship contribution statement

Yindi Liu: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Joris A.J. Osinga:** Writing – review & editing, Validation, Methodology, Data curation. **Ulla Feldt-Rasmussen:** Writing – review & editing, Validation, Data curation. **Tanja G.M. Vrijkotte:** Writing – review & editing, Validation, Data curation. **Peter N. Taylor:** Writing – review & editing, Validation, Data curation. **Ashraf Aminorroaya:** Writing – review & editing, Validation, Data curation. **Ghalia Ashoor:** Writing – review & editing, Validation, Data curation. **Sofie Bliddal:** Writing – review & editing, Validation, Data curation. **Liang-Miao Chen:** Writing – review & editing, Validation, Data curation. **Bijay Vaidya:** Writing – review & editing, Validation, Data curation. **Glenn E. Palomaki:** Writing – review & editing, Validation, Data curation. **Farkhanda Ghafoor:** Writing – review & editing, Validation, Data curation. **Abel López-Bermejo:** Writing – review & editing, Validation, Data curation. **Victor J.M. Pop:** Writing – review & editing, Validation, Data curation. **Sachiko Itoh:** Writing – review & editing, Validation, Data curation. **Fang-biao Tao:** Writing – review & editing, Validation, Data curation. **Lorena Mosso:** Writing – review & editing, Validation, Data curation. **Tuija Männistö:** Writing – review & editing, Validation, Data curation. **Kris G. Poppe:** Writing – review & editing, Validation, Data curation. **Elizabeth N. Pearce:** Writing – review & editing, Validation, Data curation. **Leda Chatzi:** Writing – review & editing, Validation, Data curation. **John P. Walsh:** Writing – review & editing, Validation, Data curation. **Polina Popova:** Writing – review & editing, Validation, Data curation. **Katrien Benhalima:** Writing – review & editing, Validation, Data curation. **Scott M. Nelson:** Writing – review & editing, Validation, Data curation. **Maryam Kianpour:** Writing – review & editing, Validation, Data curation. **Kypros H. Nicolaides:** Writing – review & editing, Validation, Data curation. **Xuemian Lu:** Writing – review & editing, Validation, Data curation. **Andrew T. Hattersley:** Writing – review & editing, Validation, Data curation. **Mary E. D'Alton:** Writing – review & editing, Validation, Data curation. **Amna Pirzada:** Writing – review & editing, Validation, Data curation. **Judit Bassols:** Writing – review & editing, Validation, Data curation. **Maarten A.C. Broeren:** Writing – review & editing, Validation, Data curation. **Reiko Kishi:** Writing – review & editing, Validation, Data curation. **Kun Huang:** Writing – review & editing, Validation, Data curation. **Andrea Vecchiola:** Writing – review & editing, Validation, Data curation. **Laura Boucai:** Writing – review & editing, Validation, Data curation. **Marja Vääräsmäki:** Writing – review & editing, Validation, Data curation. **Eila Suvanto:** Writing – review & editing, Validation, Data curation. **Emily Oken:** Writing – review & editing, Validation, Data curation. **Marina Vafeiadi:** Writing – review & editing, Validation, Data curation. **Suzanne J. Brown:** Writing – review & editing, Validation, Data curation. **Pierre Kleynen:** Writing – review

& editing, Validation, Data curation. **Elena N. Grineva:** Writing – review & editing, Validation, Data curation. **Chantal Mathieu:** Writing – review & editing, Validation, Data curation. **Robin P. Peeters:** Writing – review & editing, Validation, Supervision, Funding acquisition, Data curation. **Arash Derakhshan:** Writing – review & editing, Validation, Supervision, Methodology, Data curation. **Tim I.M. Korevaar:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter N. Taylor declares personal consulting fees from Immunovant and leadership roles in the Society for Endocrinology and British Thyroid Association. Emily Oken reports grants from the National Institutes of Health. Elena N. Grineva received speaker's fees and payment for expert testimony from Merck and consulting fees from Brunel Rus. Tanja G. M. Vrijkotte reports grants from the Netherlands Organization for Health Research and Development. Scott M. Nelson has received consultancy, speakers' fees, or travel support from Access Fertility, Beckman Coulter, Ferring Pharmaceuticals, Merck, Modern Fertility, Roche Diagnostics, and The Fertility Partnership. Scott M. Nelson also reports payments for medical–legal work and investment in The Fertility Partnership. Tim I. M. Korevaar reports lectureship fees from Berlin-Chemie, Goodlife Healthcare, Institut Biochimique SA, Merck, and Quidel. Ulla Feldt-Rasmussen's research salary was sponsored by an unrestricted grant from Kirsten and Freddy Johansen's Fund and reports lecture fee from Merck, Darmstadt. Sofie Bliddal's research salary was sponsored by the Capital Region of Denmark's Research Foundation and the Novo Nordisk Foundation (ID 0077221). Sofie Bliddal received a lecture fee from Merck and Novo Nordisk. Kris G. Poppe received lecture fees from the Berlin-Chemie AG and Merck company. Laura Boucai is supported in part by an MSK Core grant (P30 CA008748). Elizabeth N. Pearce reports honoraria for speaking at Merck China Symposium and for speaking on behalf of the National Dairy Council. Elizabeth N. Pearce is Management Council Member for the Iodine Global Network. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2025.103491.

Data availability

The authors do not have permission to share data.

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