Association of maternal thyroid function with gestational hypertension and preeclampsia: a systematic review and individual participant data meta-analysis

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SUMMARY

Background

Adequate maternal thyroid function during pregnancy is important for an uncomplicated pregnancy. Although multiple observational studies have evaluated the association of thyroid dysfunction with hypertensive disorders of pregnancy, the methods and definitions of thyroid function test abnormalities were heterogeneous, and the results were conflicting. We hypothesized that maternal thyroid dysfunction as a risk factor in pregnancy could be due to an association between thyroid dysfunction and hypertensive disorders of pregnancy such as gestational hypertension and preeclampsia. We performed a systematic review and individual participant data meta-analysis to assess whether thyroid function test abnormalities were associated with gestational hypertension and preeclampsia.

Methods

We searched MEDLINE (Ovid), Embase, Scopus, and the Cochrane Database of Systematic Reviews from inception to December 27, 2019, for prospective cohort studies with data on maternal thyroid-stimulating hormone (TSH), free thyroxine (FT4), and/or thyroid peroxidase (TPO) antibody concentrations and gestational hypertension and/or preeclampsia, and we issued open invitations to study authors to participate in the Consortium on Thyroid and Pregnancy and share the individual participant data. We excluded participants who had preexisting thyroid disease, were taking medications which affect thyroid function, or had multifetal pregnancy. The primary outcomes were documented gestational hypertension and preeclampsia. Individual participant data were analyzed using logistic mixed-effects regression models adjusting for maternal age, body mass index, smoking, parity, ethnicity, and gestational age at blood sampling. The study protocol was registered at the International Prospective Register of Systematic Reviews, CRD42019128585.

Findings

We identified 1 539 published studies, of which 33 cohorts met the inclusion criteria and 19 cohorts were included after the authors agreed to participate. Our study population comprised 46 528 pregnant women, of whom 39 826 women had sufficient data (TSH and FT4 concentrations

and TPO antibody status) to be classified according to their thyroid function status. Of those, 1 275 (3.2%) had subclinical hypothyroidism, 933 (2.3%) had isolated hypothyroxinemia, 619 (1.6%) had subclinical hyperthyroidism, and 377 (0.9%) had overt hyperthyroidism. Subclinical hypothyroidism was associated with a higher risk of preeclampsia (3.6% *vs* 2.1%; OR, 1.53 [95%CI, 1.09 to 2.15]) compared to euthyroidism. Subclinical hyperthyroidism, isolated hypothyroxinemia, or TPO antibody positivity were not associated with gestational hypertension or preeclampsia. In continuous analyses, both a higher and a lower TSH concentration were associated with a higher risk of preeclampsia (P=0.0001). The FT4 concentration was not associated with the outcomes measured.

Interpretation

Subclinical hypothyroidism during pregnancy was associated with a higher risk of preeclampsia. There was a U-shaped association of TSH with preeclampsia. These results quantify the risks of gestational hypertension or preeclampsia in women with thyroid function test abnormalities, adding to the total body of evidence on the risk of adverse maternofetal outcomes of thyroid dysfunction during pregnancy. These findings have potential implications for defining the optimal treatment target in women treated with levothyroxine during pregnancy, which needs to be assessed in future interventional studies.

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RESEARCH IN CONTEXT

Evidence before this study

Adequate maternal thyroid function during pregnancy is important for an uncomplicated pregnancy. Some studies indicate that thyroid function test abnormalities are associated with hypertensive disorders of pregnancy, but there is considerable heterogeneity and inconsistency in the results. We searched MEDLINE (Ovid), Embase, Scopus, and the Cochrane Database of Systematic Reviews up to December 27, 2019, and we collected data on serum thyroid function tests and antibodies status during pregnancy and gestational hypertension and/or preeclampsia from prospective cohort studies, including treatment-naive pregnant women. There were no individual participant data meta-analyses about this topic identified with our search strategies.

Added value of this study

This individual participant data meta-analysis showed that subclinical hypothyroidism and overt hyperthyroidism are associated with a higher risk of the composite outcome of gestational hypertension or preeclampsia. We also identified that both a higher and a lower thyroid-stimulating hormone (TSH) concentration were associated with a higher risk of preeclampsia.

Implications of all the available evidence

These findings imply that optimal TSH treatment target could be in the middle of the reference range, which highlights the relevance of follow-up of thyroid function tests during pregnancy in women treated with levothyroxine to avoid under- or overtreatment.

INTRODUCTION

Hypertensive disorders of pregnancy are some of the leading causes of maternal, fetal and perinatal mortality worldwide, especially in middle- and low-income countries.[1-3] The group of pregnancy-induced hypertensive disorders includes gestational hypertension, preeclampsia (de novo or superimposed on chronic hypertension), and eclampsia, whose common characteristic is the increase in blood pressure leading to various degrees of multi-organ compromise.[4] Gestational hypertension affects 10-15% of pregnancies and of these, up to 10-25% of women will eventually develop proteinuria and other end-organ failure consistent with the diagnosis of preeclampsia.[5,6] Preeclampsia is a major risk factor for intrauterine growth retardation, placental abruption, and preterm birth.[7,8] Moreover, preeclampsia is a significant risk factor for maternal morbidity including pulmonary edema, liver failure, eclampsia, and cardiovascular events, and may be responsible for approximately 15% of maternal deaths.[9] Despite its relatively high incidence and associated severe complications, the pathogenesis of pregnancy-induced hypertensive disorders is not yet fully elucidated.

Adequate maternal thyroid function during pregnancy is important for an uncomplicated pregnancy. Overt hyperthyroidism due to Graves' disease and overt hypothyroidism have both been associated with adverse pregnancy outcomes including pregnancy loss, intrauterine growth retardation, preterm birth, and preeclampsia.[10-15] Thyroid hormones are involved in the regulation of placental development, endothelial function and blood pressure regulation, and therefore, thyroid hormone aberrations might have a relevant role in the development of hypertensive disorders during pregnancy.[16-20] The association of thyroid function test abnormalities with hypertensive disorders of pregnancy has been assessed in multiple prospective and retrospective cohort studies during recent decades. While some studies showed a higher risk of hypertensive disorders of pregnancy in mothers with thyroid function test abnormalities such as subclinical hypothyroidism or overt hyperthyroidism, with odds ratios (ORs) ranging from 1.6 to 3.4,[15,21-25] others did not.[26-30] Several factors, including the use of different definitions of thyroid function test abnormalities, variable gestational age at thyroid function assessment, the lack of controlling for potential confounders, and inadequate statistical power, may explain the considerable heterogeneity and inconsistency in the results of previous studies. In an effort to overcome these methodological issues and to better quantify potential

risks, we performed a systematic literature review and individual participant data meta-analysis to assess the association of thyroid function test abnormalities with gestational hypertension and preeclampsia.

PARTICIPANTS AND METHODS

The current project followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for Individual Patient Data and a protocol of this study has been preregistered in the PROSPERO website (CRD42019128585).

Search strategy and selection criteria

For this systematic review and meta-analysis, with the help of an experienced librarian (L.P.) we searched MEDLINE (Ovid), Embase, Scopus, and the Cochrane Database of Systematic Reviews from database inception to December 27, 2019, with no language restrictions to identify studies on the association of thyroid function and/or autoimmunity with gestational hypertension, preeclampsia, or both (appendix pp 2–3). Additionally, open invitations were sent to relevant journals, international conferences, social media and personal contacts to identify unpublished cohorts.[31,32] We included prospective cohort studies with data available on thyroid-stimulating hormone (TSH), free thyroxine (FT4), and/or thyroid peroxidase (TPO) antibodies as well as gestational hypertension and/or preeclampsia. These studies must have had participants consecutively recruited from the general population or without active selection based on health status (such as comorbidities or thyroid disease). We excluded interventional studies in which participants received treatment based on abnormal thyroid function tests.

Potential studies eligible for inclusion were reviewed independently and in duplicate by two of the authors (F.J.K.T. and S.M.) for inclusion and exclusion criteria, and any disagreement was resolved by consensus. Investigators from each eligible study were invited to participate in the study and join the Consortium on Thyroid and Pregnancy if they were not already members. This consortium is a collaboration of birth cohorts that aims to study the association of maternal thyroid function and autoimmunity with adverse pregnancy and child outcomes. After participation approval, we requested the primary investigators to send us individual participant data using a standardized codebook and the data were checked for completeness, improbable

values, and missing items. Study quality and risk of bias were assessed using the Newcastle-Ottawa Scale.[33] All cohorts were approved by a local review board and had acquired informed consent from participants or had been granted exemption from it by the local ethics committee.

After obtaining individual participant data from the included cohorts and applying exclusion criteria, all participants with data on TSH, FT4, or TPO antibodies, and gestational hypertension or preeclampsia were included in the study. We excluded participants who had preexisting thyroid disease, were taking medications which affect thyroid function and those with multifetal pregnancy.

Primary and secondary outcomes

Primary outcomes were documented gestational hypertension and preeclampsia as separate entities. The secondary outcome was the composite outcome of gestational hypertension or preeclampsia in those cohorts with data on both preeclampsia and gestational hypertension or studies that did not report individually on gestational hypertension and preeclampsia.

Exposures

We assessed the following exposure variables: thyroid function test abnormalities (subclinical hypothyroidism, overt hyperthyroidism, subclinical hyperthyroidism, isolated hypothyroxinemia), continuous thyroid function test measurements (TSH and FT4 concentrations), and TPO antibody positivity. We did not examine the association of overt hypothyroidism with gestational hypertension or preeclampsia because treatment for this disease entity is noncontroversial and because its low prevalence, in combination with the relatively large number of women who were excluded because of pre-existing thyroid disease, indicates that women with true overt hypothyroidism were only selectively represented in the studies included. In contrast, overt hyperthyroidism was examined as this was considered to be a biochemically defined entity without an indication for treatment with antithyroid drugs (participants who were started on antithyroid treatment, presumably for Graves' disease, were excluded from this study). We defined thyroid function test reference ranges using cohort-specific 2.5th and 97.5th population percentiles for TSH and FT4 concentrations after exclusion of TPO antibody positive women, therefore cohorts without TPO antibody data were not

included in analyses on thyroid function test abnormalities. Euthyroidism was defined as TSH and FT4 concentrations within the reference range (2.5th-97.5th percentile). Subclinical hypothyroidism was defined as a TSH concentration above the 97.5th percentile and a FT4 concentration within the reference range (2.5th-97.5th percentile). Overt hyperthyroidism was defined as a TSH concentration below the 2.5th percentile and a FT4 concentration above the 97.5th percentile. Subclinical hyperthyroidism was defined as a TSH concentration below the 2.5th percentile and a FT4 concentration within the reference range. Isolated hypothyroxinemia was defined as a FT4 concentration below the 2.5th percentile and a TSH concentration within the reference range. We defined TPO antibody positivity according to cutoffs established by the manufacturer or cohort-specific cutoffs. Serum values of TSH and FT4 for all cohorts were log-transformed and then standardized to population-specific standard deviation scores (Z-scores) after removal of outliers (±4 SD from the mean).

Statistical analyses

We studied the association of thyroid function test abnormalities (with euthyroid women as the reference group), TSH and FT4 concentrations as continuous variables, and TPO antibody positivity with gestational hypertension, preeclampsia, and the composite outcome of gestational hypertension or preeclampsia using generalized logistic mixed models with a random intercept for each cohort. Binomial distribution with logit link function was used to fit generalized linear mixed model. The primary analyses were repeated with a 2-step approach by using random effect models according to the Der-Simonian and Laird method to pool estimates and the Firth bias reduction method in case of near or complete separation in smaller cohorts.[34,35] Heterogeneity across studies was assessed using the I^2 statistic. To evaluate potential publication bias, funnel plots and Egger's tests were used.[36] All analyses were adjusted for maternal age, body mass index (BMI), smoking, parity, ethnicity and gestational age at blood sampling. Results are reported as adjusted odds ratio (OR) and 95% confidence interval. Natural splines with 3 knots were used to assess non-linear associations according to Type III Wald chi-square tests. We used multilevel multiple imputation for missing data on covariates.[37] Five imputed datasets were created and pooled for analyses using Rubin's rules.[38] We performed prespecified sensitivity analyses to explore whether the association of TSH and FT4 concentration differed according to differences in gestational age at the time of blood sampling (≥24 weeks *vs* <24

weeks) or TPO antibody status. A 2-sided threshold for statistical significance of <0.05 was used. All statistical analyses were performed using SPSS, RevMan and R version 3.6.2 (R Project for Statistical Computing).

Role of the funding source

The funders had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, in the preparation, review, approval of the manuscript, or the decision to submit the manuscript for publication. The corresponding author had full access to all the data and the final responsibility to submit for publication.

RESULTS

From the initial literature search, 1 539 published studies were identified, which included 79 publications involving cohort studies that were potentially eligible for inclusion based on title/abstract review (Figure 1). There were no individual participant data meta-analyses about this topic identified with our search strategies. After the evaluation of full text, a total of 33 cohorts were identified and invited to participate in this meta-analysis. Finally, a total of 19 cohorts from Denmark, Chile, the Netherlands, Spain, Finland, Greece, United Kingdom, Russia, Japan, China, Australia, and the United States, with data collection dates from July 1985 to December 2016, responded to the invitation and were able to participate. Of those, all cohorts had data on TSH concentration, one cohort did not have data on FT4 concentration but had data on FT4 index, three cohorts did not have data on TPO antibody status, and five cohorts did not have data on either gestational hypertension [three] or preeclampsia [two].

After applying the exclusion criteria, the final study population comprised 46 528 participants with a mean maternal age of 29.1 years (SD 5.2) and median gestational age at blood sampling of 12.5 weeks (95% range 7.0–39.7) (Table 1). Gestational hypertension and preeclampsia occurred in 1 717/43 082 (4.0%) and 809/38 147 (2.1%) pregnancies, respectively. The composite outcome occurred in 1 963/34 973 (5.6%) pregnancies. Discrepancies between the composite outcome with the sum of its individual components are explained by the way the composite outcome was defined (please refer to participants and methods section) and because

women who developed both gestational hypertension and preeclampsia were only counted once for the composite outcome.

Of the entire population, 39 826 women had sufficient data (TSH and FT4 concentrations, and TPO antibody status) to be classified according to their thyroid function status. Of those, 1 275 (3.2%) had subclinical hypothyroidism, 933 (2.3%) had isolated hypothyroxinemia, 619 (1.6%) had subclinical hyperthyroidism, and 337 (0.9%) had overt hyperthyroidism (appendix p 4). Additionally, 3 005/39 736 (7.6%) were TPO antibody positive (appendix p 6). Cohort-specific population characteristics, cohort-specific number of participants with available thyroid function measurements, data quality assessment by the Newcastle-Ottawa Scale, missing data on specific covariates and cohort-specific percentile cutoffs for thyroid function test abnormalities are shown in the appendix (appendix pp 5-10). Data on covariates were missing for participants [and cohorts] as follows: maternal age: 1.1% [0 cohorts], gestational age at the time of blood sampling: 0.6% [0 cohorts], parity: 7.1% [1 cohort], smoking status: 3.1% [0 cohorts], and BMI: 29.8% [2 cohorts] (appendix p 7). Pregnant women who were not included due to missing outcome data had a similar mean TSH and FT4 concentrations to those who were included (0.02 SD *vs* -0.0008 SD; P =0.38, and 0.016 SD *vs* -0.0006 SD; P =0.47, respectively), but had a higher proportion of TPO antibody positivity (9.9% *vs* 6.5%; P < .001) (appendix p 11).

Compared with euthyroidism, subclinical hypothyroidism was associated with a higher risk of preeclampsia (3.6% *vs* 2.1%; OR, 1.53 [95%CI, 1.09 to 2.15]), but not with gestational hypertension (5.7% *vs* 4.2%; OR, 1.18 [95%CI, 0.91 to 1.53]) (Figure 2). Subclinical hypothyroidism was also associated with a higher risk of the composite outcome (8.9% *vs* 5.6%; OR, 1.45 [95%CI, 1.14 to 1.85], appendix p 14). Overt hyperthyroidism was not associated with gestational hypertension (6.0% *vs* 4.2%; OR, 1.59 [95%CI, 0.97 to 2.60]) or preeclampsia (2.9% *vs* 2.1%; OR, 1.43 [95%CI, 0.70 to 2.92]), but was associated with a higher risk of the composite outcome (9.3% *vs* 5.6%; OR, 1.90 [95%CI, 1.21 to 2.99]) (Figure 2 and appendix p 14). Neither subclinical hyperthyroidism nor isolated hypothyroxinemia were associated with the outcomes evaluated (Figure 2 and appendix p 14).

When TSH and FT4 were examined as continuous variables, there was a U-shaped association of TSH with preeclampsia (P=0.0001; Figure 3) and the composite outcome (P<0.0001; appendix p 15). When this analysis was restricted to TSH within the reference range, the association of a lower TSH with a higher risk of preeclampsia (Figure 3) and the composite outcome persisted (appendix p 15). There was no association of FT4 with any of the outcomes evaluated, neither when the full range nor the normal range was assessed (Figure 4 and appendix p 15).

There was no association of TPO antibody positivity, as compared to TPO antibody negativity with gestational hypertension or preeclampsia (appendix p 16). Similar results were found in subsequent stratified analyses of TPO antibody positive women with TSH within normal range, TSH concentration above 2.5 mIU/L and TSH concentration above 4.0 mIU/L (appendix p 16).

The results of the primary analyses were similar using a 2-step approach (appendix pp 17-21), except that in a two-step analysis subclinical hyperthyroidism was associated with preeclampsia (OR 2.02, [95%CI 1.14 to 3.59]. Neither the funnel plots or Egger's tests indicated relevant publication bias (all *P* values for the tests for asymmetry ranged from 0.06 to 0.85) and the I^2 values were less than or equal to 7%.

In prespecified sensitivity analyses, the association of TSH and FT4 or thyroid function test abnormalities with gestational hypertension, preeclampsia or its composite outcome did not differ according to the gestational age at blood sampling, parity or TPO antibody status (appendix pp 12-13). Out of all subsequent stratified analyses (selected based on P for interaction ≤0.15), those with a clinically relevant point estimate indicated a higher risk of preeclampsia for high TSH and a higher risk of the composite outcome of gestational hypertension or preeclampsia especially towards later pregnancy (e.g., 24 weeks *vs* 12 weeks), but these analyses lacked adequate statistical power (appendix p 22).

DISCUSSION

In this individual participant data meta-analysis, maternal subclinical hypothyroidism was associated with a higher risk of preeclampsia. Additionally, both subclinical hypothyroidism and

overt hyperthyroidism during pregnancy were associated with a higher risk of the composite outcome of gestational hypertension or preeclampsia. In contrast, there was no association of subclinical hyperthyroidism, isolated hypothyroxinemia, or TPO antibody positivity with any of the studied outcomes. Additionally, both a higher and lower maternal TSH concentration were associated with a higher risk of preeclampsia in a dose-dependent manner.

This study shows that subclinical hypothyroidism was associated with a higher risk of preeclampsia. Various mechanisms, which can be extrapolated from experimental studies on the effects of thyroid hormones on vascular function and placental formation, could explain how a (relative) lack of thyroid hormones, as is likely reflected by subclinical hypothyroidism, might influence the development of pregnancy-induced hypertension. Hypothyroidism has been associated with endothelial cell dysfunction likely secondary to decreased production of vasoactive substances (e.g., nitric oxide) which leads to impaired vasorelaxation, increased sympathetic tone, and vascular resistance and finally hypertension.[18,20,39,40] Critical processes during placental formation, such as decidual cell migration and angiogenesis are regulated by inflammatory mediators (e.g., interleukin-10, leptin, and nitric oxide synthase 2) and at least in part influenced by thyroid hormones.[41-43] Consequently, conditions with a low thyroid hormone availability may result in an inadequate anti-inflammatory environment in the developing placenta and therefore in placental vascularity disturbances, which have been associated with adverse pregnancy outcomes such as preeclampsia and miscarriage.[16]

Alternatively, it may be that the association of subclinical hypothyroidism with preeclampsia is due to reverse causation. One of the major pathophysiological mechanisms that underlies preeclampsia is excessive release of antiangiogenic proteins, most notably soluble FMS-like tyrosine kinase-1 (sFlt1) from the placenta into the maternal circulation.[44] Interestingly, one longitudinal study showed that the increase in the serum sFlt1 concentration was associated with an increase in the serum TSH concentrations and a higher risk of subclinical hypothyroidism[45] and similar results were obtained in a cross sectional study.[46] As such, rather than subclinical hypothyroidism increasing the risk of preeclampsia, it may be that the anti-angiogenic profile that arises already in early stages of preeclampsia adversely affects thyroid gland vascularization, as demonstrated in animal studies.[47] Further evidence in favor of reverse causation is the lack of

any signal that levothyroxine treatment of subclinical hypothyroidism reduces the risk of preeclampsia,[48-51] while potential overtreatment of women with a normal thyroid function could increase the risk of preeclampsia.[48] Further studies on these underlying mechanisms are required to understand the clinical relevance of slight thyroid hypofunction as a risk factor or marker of preeclampsia.

Previous studies examining the associations of overt hyperthyroidism with hypertensive disorders of pregnancy identified conflicting results. This may be because of heterogeneity in study design and definitions of thyroid function test abnormalities.[15,23,24,26-28,52-55] In the current study, we identified that overt hyperthyroidism was associated with a higher risk of a composite outcome of gestational hypertension or preeclampsia. Hyperthyroidism contributes to endothelial cell dysfunction through impairment of protective mechanisms against endothelial damage, such as tissue plasminogen activator and plasminogen activator inhibitor secretion, regulation of interleukin-18 and soluble vascular cell adhesion molecule 1 (VCAM-1).[17,19,56] Higher FT4 concentrations in early pregnancy have been associated with higher vascular resistance in both the maternal and fetal placental compartment, which may induce adverse pregnancy outcomes.[57] Additionally, the association of hyperthyroidism with hypertensive disorders of pregnancy could in part be related to dysregulation of placental deiodinases, which activate or deactivate thyroid hormones in local tissues (placental deiodinases type 1 [DIO1] and type 2 [DIO2] convert T4 to T3 whereas placental deiodinase type 3 [DIO3] inactivates T4).[16] It has been suggested that since both hypothyroidism and hyperthyroidism are risk factors for preeclampsia, the existence of divergent molecular mechanisms of placental deiodinase dysregulation in preeclampsia could be implied.[16] Future clinical studies could assess this possibility, for example by assessing the association of maternal FT3 or the FT4/FT3 ratio with gestational hypertension and preeclampsia.[16]

The higher risk of preeclampsia in women with overt hyperthyroidism identified in this study may depend on the underlying etiology. Overt hyperthyroidism during pregnancy (gestational hyperthyroidism) is often transient and caused by an early pregnancy, physiological increase in human chorionic gonadotropin (hCG), which stimulates thyroid hormone production through its affinity for the TSH receptor.[58,59] Overt hyperthyroidism can also be caused by underlying

thyroid pathology such as Graves' disease or toxic adenoma.[58,59] It has been reported that women with both high FT4 and high hCG concentrations do not have a higher risk of developing preeclampsia, whereas women with a high FT4 concentration despite a low hCG have a 3.4 to 4.9-fold higher risk of preeclampsia.[60] On the other hand, a higher hCG concentration during early pregnancy in the absence of hyperthyroidism, has been associated with a higher risk of preeclampsia.[61] These findings suggest that according to the etiology of hyperthyroidism during pregnancy, there may be different mechanisms underlying the higher risk of preeclampsia. More studies are required to further elucidate the pathophysiologic mechanisms underlying the relationships of thyroid function test abnormalities with hypertensive disorders of pregnancy.

In the current study, we also identified that pregnant women with the lowest and highest concentrations of TSH had a higher risk of preeclampsia, even within the reference range. The current findings indicate that women with a TSH concentration in the middle of the TSH reference range have the lowest risk of preeclampsia. Given the lack of clinical trials on the effects of different levothyroxine treatment targets on adverse pregnancy outcomes, optimal TSH treatment targets can only be extrapolated from observational studies. In line with other observational studies[62,63], our data indicate that an optimal TSH treatment target could be in the middle of the reference range, which highlights the relevance of follow-up of thyroid function tests during pregnancy in women treated with levothyroxine to avoid under- or overtreatment. It has been described that hyperthyroidism in otherwise healthy women or those overtreated with levothyroxine (e.g., iatrogenic hyperthyroidism or treatment for a gestational TSH 2.5-4.0 mIU/L, especially in TPO antibody negative women) was associated with a higher risk of preeclampsia, preterm delivery, gestational diabetes, small for gestational age, attention-deficit/hyperactivity disorder and behavioral problems.[48,64] Additional studies that assess how the changes in thyroid function in patients on pharmacological therapy during pregnancy could be translated to clinical benefits or harms are needed.

Finally, we did not identify any association of TPO antibody positivity with any of the outcomes assessed, which is consistent with results from previous studies [10,28,54,65] Furthermore, studies in specific subgroups that did not meet the inclusion criteria for the current study, such as women with previous pregnancy losses, showed similar results.[66] A synergistically higher risk of TPO

antibody positivity with thyroid function test abnormalities and preeclampsia[67] as well as other adverse pregnancy outcomes[68-70] has been previously described. However, in the current study we did not identify any evidence of a synergistic risk between TPO antibody positivity and high TSH.

This study included 19 prospective, population-based birth cohorts from 12 countries with detailed data on thyroid function tests in early pregnancy, adverse pregnancy outcomes and potential confounding factors. The analysis of individual participant data allowed standardization of thyroid function test abnormalities and consistent statistical analyses across cohorts. One of the main limitations of this study derives from the observational nature of the studies included in this meta-analysis, such as residual or unmeasured confounding. Our inability to include all the published cohorts in our analyses due to data-sharing regulations and restrictions, lack of interest or failure to obtain a response from contact authors, and publication date during or after conducting the statistical analyses for the current study may have affected our results. The nature of individual participant data meta-analysis, requiring extensive time to coordinate data sharing, prohibited an updated search strategy. Also, the use of Firth bias reduction method in case of near or complete separation in smaller cohorts may have produced hyperinflated estimates when the 2-step approach was used; this may account for the discrepant results as regards the association of subclinical hyperthyroidism with preeclampsia. Finally, we were unable to include personal or familial history of hypertensive gestational disorders as part of our exclusion criteria, and to assess the differential risk of frequently used subcategories of hypertensive disorders of pregnancy based on the gestational age at the time of onset (i.e., early *vs* late), which may have influenced the identification of a clinically meaningful difference in the effects of thyroid function test abnormalities across gestation or new insights into the pathophysiology underlying thyroid hormones and hypertensive disorders of pregnancy.[71,72]

In conclusion, this individual participant data meta-analysis shows that subclinical hypothyroidism during pregnancy was associated with a higher risk of preeclampsia, and that there was a U-shaped association of TSH with preeclampsia. These findings add to the total body of evidence on the risk of adverse maternofetal outcomes of thyroid dysfunction during

pregnancy and indirectly informs on the optimal TSH treatment target in women treated with levothyroxine during pregnancy, which needs to be assessed in future interventional studies.

Contributors

FJKT, AD, TIMK, and SM made the analysis plan, performed analyses, and were involved in writing of the manuscript. LP performed the systematic search and FJKT and SM were involved in study selection. All other authors were involved in data collection and provided substantial contributions to drafting of the work including critical revision for important intellectual content. TIMK and SM verified the underlying data, supervised analyses, and directed the project.

Declaration of interests

EO reports grants from the National Institutes of Health. TGMV reports grants from the Netherlands Organization for Health Research and Development. EKA reports consultancy with Roche Diagnostics. CD reports grants from the Chief Scientist Office (Scotland) and the British Heart Foundation. SMN has received consultancy, speakers' fees, or travel support from Access Fertility, Beckman Coulter, Ferring Pharmaceuticals, Merck, Modern Fertility, Roche Diagnostics, and The Fertility Partnership. SMN also declares payments for medical-legal work and investment in The Fertility Partnership. ENG received speaker's fees and payment for expert testimony from Merck and consulting fees from Brunel Rus LLC. PT reports a travel grant from Society for Endocrinology (leadership development award). LC received travel support by Pfizer. SB declares consulting fees from Sonic Healthcare. JRVL declares grant or contract support from the Dutch Heart Foundation and Amryt. TIMK reports lectureship fees from Berlin-Chemie, Goodlife Healthcare, IBSA, Merck, and Quidel. All other authors declare no competing interests.

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Data sharing

A protocol of this study is available at the PROSPERO website (CRD42019128585). Deidentified individual participant data are available from the Consortium on Thyroid and Pregnancy. A data dictionary with details of the definitions of the variables used in the study is available upon request.

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Figure legends

Figure 1. Flowchart of the study and participant selections

Figure 2. Association of thyroid function test abnormalities with gestational hypertension and preeclampsia

Figure 3. Association of thyroid-stimulating hormone (TSH) concentrations with gestational hypertension (HTN) and preeclampsia

Figure 4. Association of free thyroxine (FT4) concentrations with gestational hypertension (HTN) and preeclampsia

1539 Studies identified through database searching

1460 Studies excluded after title/abstract review

79 Potentially relevant studies identified for further review

25 Studies excluded
- **12** No exposure or outcome of interest
- **10** Selected population
- **3** No prospective study

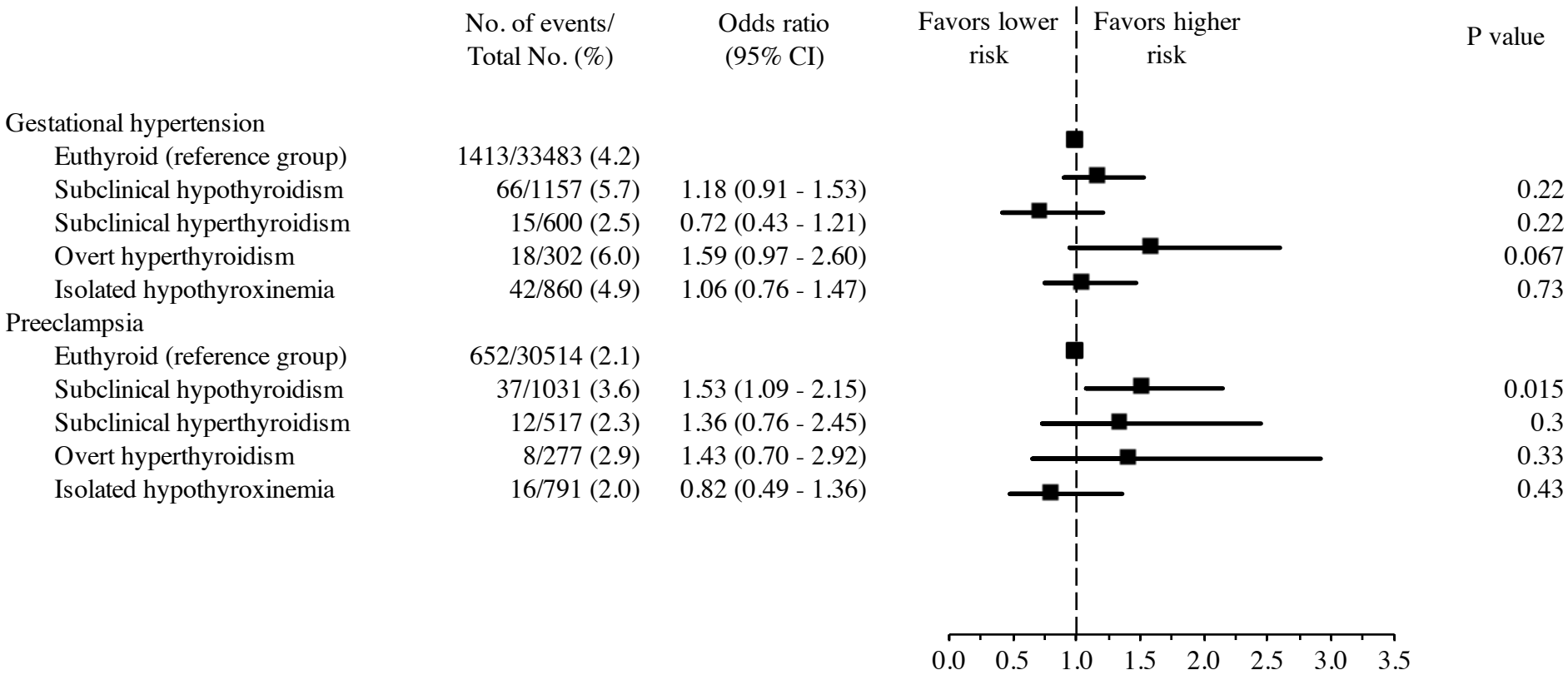
54 Eligible studies based on full review
- **33** Data sets of cohorts

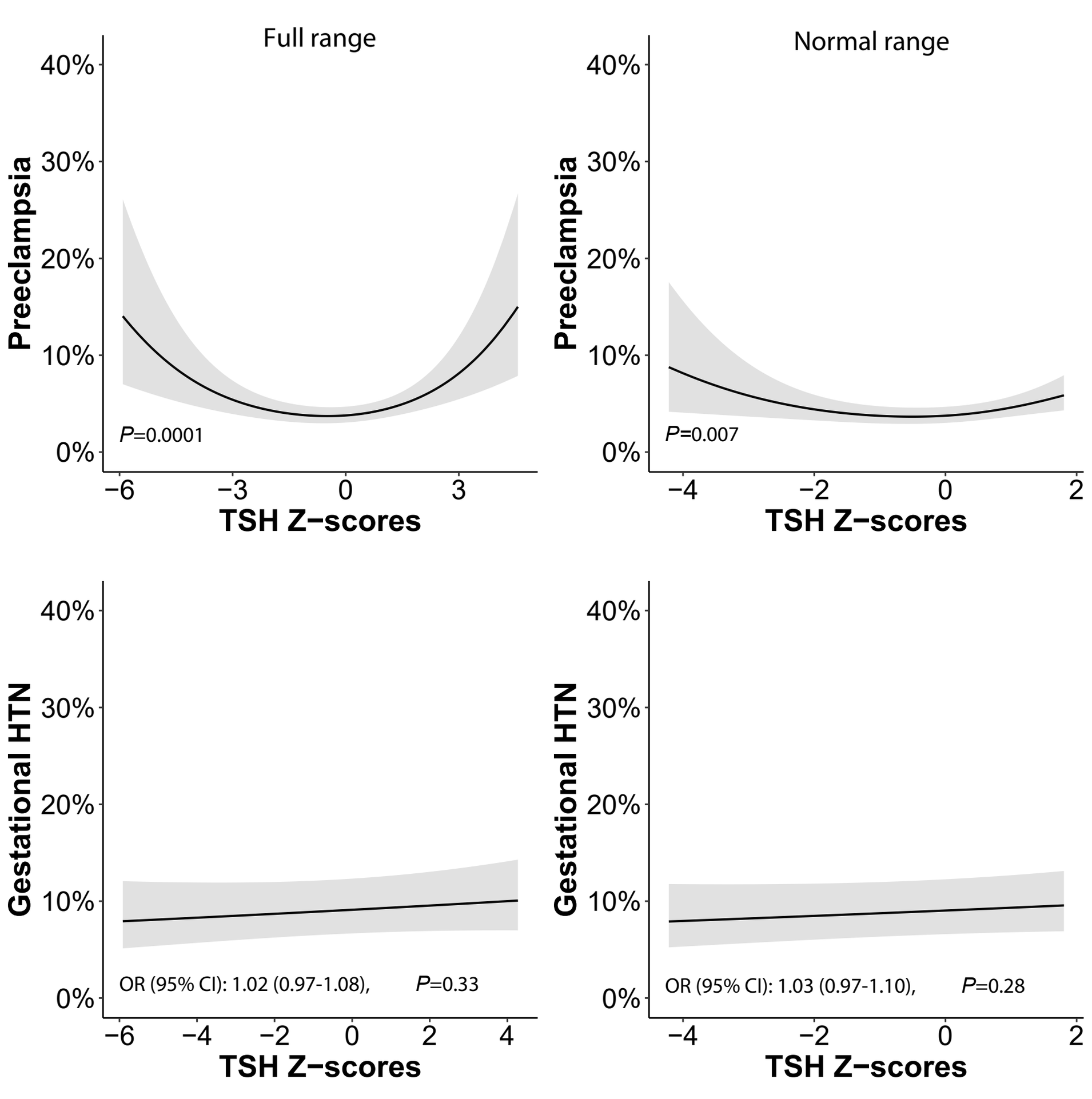
14 Cohorts excluded
- **9** Investigators not reachable
- **5** Declined participation (primary investigator retired or data sharing issue)

19 Data sets included
- **55246** Pregnant women

8718 Women excluded
- **7469** Data unavailable for exposure or outcomes
- **815** Preexisting thyroid disease or thyroid-interfering medication usage
- **434** Multiple gestation

46528 Women with available data
- **45877** Thyroid-stimulating hormone
- **45930** Free thyroxine
- **39736** Thyroid peroxidase antibody


No. of events/ Total No. (%)
Odds ratio (95% CI)
Favors lower risk
Favors higher risk
P value
Gestational hypertension
Euthyroid (reference group) 1413/33483 (4.2)
Subclinical hypothyroidism 66/1157 (5.7) 1.18 (0.91 - 1.53) 0.22
Subclinical hyperthyroidism 15/600 (2.5) 0.72 (0.43 - 1.21) 0.22
Overt hyperthyroidism 18/302 (6.0) 1.59 (0.97 - 2.60) 0.067
Isolated hypothyroxinemia 42/860 (4.9) 1.06 (0.76 - 1.47) 0.73
Preeclampsia
Euthyroid (reference group) 652/30514 (2.1)
Subclinical hypothyroidism 37/1031 (3.6) 1.53 (1.09 - 2.15) 0.015
Subclinical hyperthyroidism 12/517 (2.3) 1.36 (0.76 - 2.45) 0.3
Overt hyperthyroidism 8/277 (2.9) 1.43 (0.70 - 2.92) 0.33
Isolated hypothyroxinemia 16/791 (2.0) 0.82 (0.49 - 1.36) 0.43
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5


Full range
Normal range
Preeclampsia
Gestational HTN
40%
30%
20%
10%
0%
P=0.0001
P=0.007
OR (95% CI): 1.02 (0.97-1.08), P=0.33
OR (95% CI): 1.03 (0.97-1.10), P=0.28
−6
−4
−3
−2
0
2
3
4
TSH Z−scores

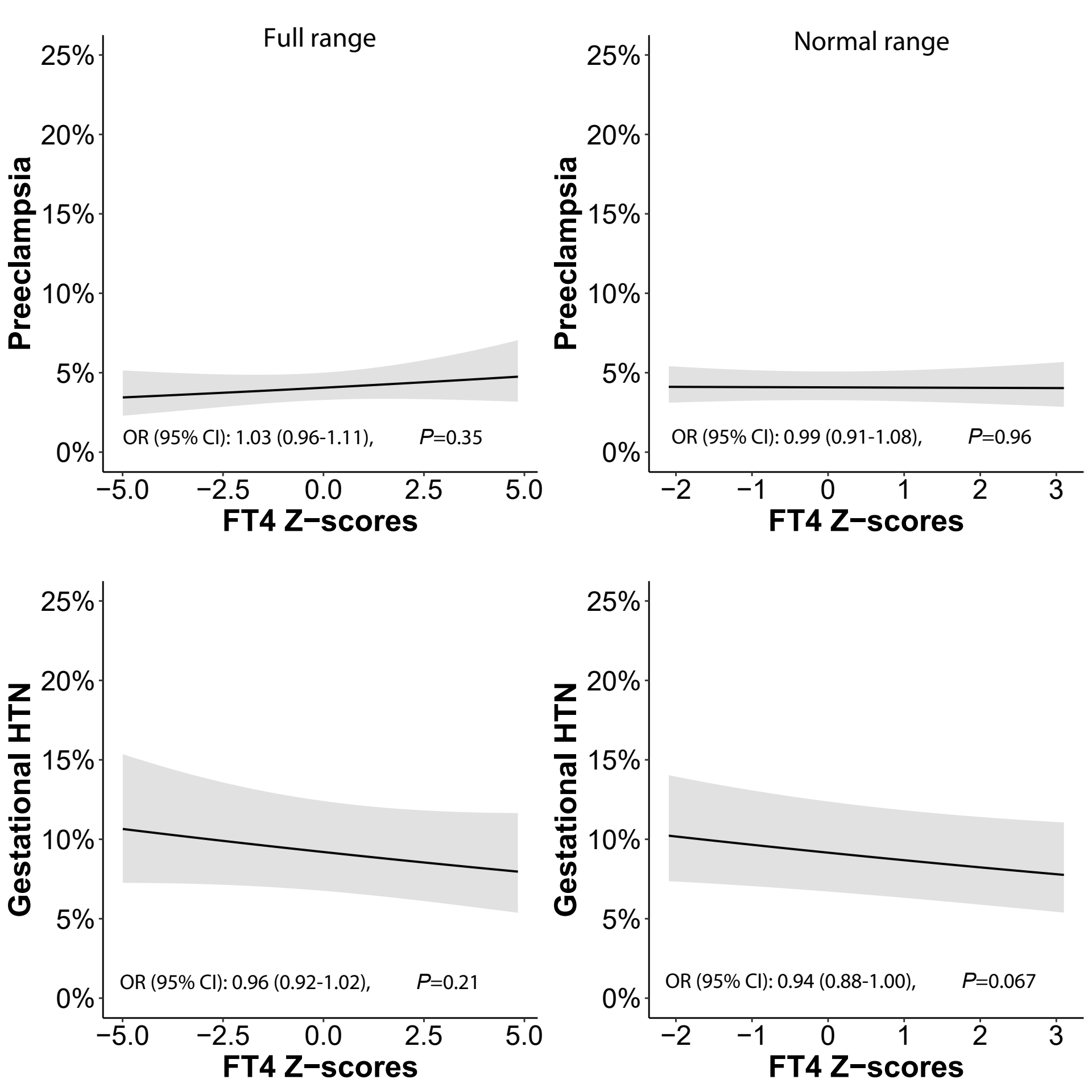

Full range
Normal range
Preeclampsia
Gestational HTN
25%
20%
15%
10%
5%
0%
OR (95% CI): 1.03 (0.96-1.11), P=0.35
OR (95% CI): 0.99 (0.91-1.08), P=0.96
OR (95% CI): 0.96 (0.92-1.02), P=0.21
OR (95% CI): 0.94 (0.88-1.00), P=0.067
−5.0
−2.5
0.0
2.5
5.0
−2
−1
0
1
2
3
FT4 Z−scores

Table 1. Characteristics of total study population (n=46528)

	No. of participants / Total No.	**(%)**	**Median (95% range)**
Maternal demographics			
Age, years	46017		29.1 (5.2)[a]
Gestational age at blood sampling, weeks	46262		12.5 (7.0-39.7)
Body mass index	32665		23.8 (4.4)[a]
Parity			
0	23759/43202	55.0	
1	13279/43202	30.7	
2	4036/43202	9.3	
≥3	2128/43202	4.9	
Smoking status			
Nonsmoker or past smoker	39949/45081	88.6	
Current smoker	5132/45081	11.4	
Educational level			
Primary school	10471/33655	31.1	
High school	11495/33655	34.2	
College or higher education	11689/33655	34.7	
Maternal thyroid function tests			
Thyrotropin, mIU/L	45877		1.29 (0.11-4.56)
Free thyroxine, ng/dL	45930		1.01 (0.56-1.73)[b]
Thyroid peroxidase antibody positivity	3005/39736	7.6	
Outcomes			
Preeclampsia	809/38147	2.1	
Gestational hypertension	1717/43082	4.0	
Composite outcome [c]	1963/34973	5.6	

[a] Expressed as mean (SD)

[b] pmol/L: 13.1 (7.2-22.3)

[c] Refers to either studies with data on both preeclampsia and gestational hypertension or studies that did not report individually on gestational hypertension and preeclampsia. Studies with data only on preeclampsia or gestational hypertension are not included here.