

Association of maternal thyroid function with birth weight: a systematic review and meta-analysis of individual participant data

Arash Derakhshan, MD, MSc^{1,2}; Robin P. Peeters, MD, PhD^{1,2}; Peter N. Taylor, MRCP, PhD³; Sofie Bliddal, MD⁴; David M. Carty, MD^{5,6}; Margreet Meems, MD, PhD⁷; Bijay Vaidya, FRCP, PhD⁸; Liangmiao Chen, MD, PhD⁹; Beverley Shields, PhD¹⁰; Farkhanda Ghafoor, PhD¹¹; Polina V. Popova, MD, PhD^{12,13}; Lorena Mosso, MD, PhD¹⁴; Emily Oken, MD, MPH¹⁵⁻¹⁷; Eila Suvanto, MD, PhD¹⁸; Aya Hisada, PhD¹⁹; Jun Yoshinaga, PhD²⁰; Suzanne J. Brown, PhD²¹; Judith Bassols, MD²²; Juha Auvinen, MD, PhD²³; Wichor M. Bramer²⁴; Abel López-Bermejo, MD, PhD²⁵; Colin Dayan, MD, PhD²⁶; Laura Boucai, MD, MSc²⁷; Marina Vafeiadi, PhD²⁸; Elena N. Grineva, MD, PhD^{12,13}; Alexandra S. Tkachuck, MD^{12,13}; Victor J.M. Pop, MD, PhD⁷; Tanja G. Vrijkotte, PhD²⁹; Mònica Guxens, MD, PhD³⁰⁻³³; Leda Chatzi, MD, PhD³⁴; Jordi Sunyer, MD, PhD^{30-32,35}; Ana Jiménez-Zabala, PhD^{36,37}; Isolina Riaño, MD, PhD^{32,38}; Mario Murcia, PhD^{32,39}; Xuemian Lu, MD, PhD⁹; Amna Pirzada⁴⁰; Christian Delles, MD⁶; Ulla Feldt-Rasmussen, MD, DMSc⁴; Erik K. Alexander, MD⁴¹; Scott M. Nelson, MRCOG, PhD^{42,43}; Layal Chaker, MD, PhD^{1,2}; Tuija Männistö, MD, PhD⁴⁴; Elizabeth N. Pearce, MD⁴⁵; Eric A. P. Steegers, MD, PhD⁴⁶; John P. Walsh, MB, PhD^{21,47}; Tim I. M. Korevaar, MD, PhD^{1,2}

1. Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands.
2. Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands.
3. Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, UK.
4. Department of Medical Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.
5. Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, Glasgow, UK.
6. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.
7. Departments of Medical and Clinical Psychology, Tilburg University, Tilburg, The Netherlands.
8. Department of Endocrinology, Royal Devon and Exeter Hospital NHS Foundation Trust, University of Exeter Medical School, Exeter, UK
9. 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.
10. Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK.

11. National Health Research Complex, Shaikh Zayed Medical Complex, Lahore, Pakistan.
12. Almazov National Medical Research Centre, Saint Petersburg, Russian Federation.
13. Department of Internal Diseases and Endocrinology, St. Petersburg Pavlov State Medical University, Saint Petersburg, Russian Federation.
14. Departments of Endocrinology, Pontificia Universidad Catolica de Chile, Santiago, Chile.
15. Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School, Boston, Massachusetts, USA.
16. Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA.
17. Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA.
18. Department of Obstetrics and Gynecology and Medical Research Center Oulu, University of Oulu, Oulu, Finland.
19. Center for Preventive Medical Science, Chiba University, Chiba, Japan.
20. Faculty of Life Sciences, Toyo University, Gunma, Japan.
21. Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia.
22. Maternal-Fetal Metabolic Research Group, Girona Biomedical Research Institute (IDIBGI), Dr. Josep Trueta Hospital, Girona, Spain.
23. Medical Research Center Oulu, Oulu University Hospital, and Center for Life Course Health Research, University of Oulu, Oulu, Finland.
24. Medical Library, Erasmus University Medical Centre, Rotterdam, the Netherlands.
25. Pediatric Endocrinology Research Group, Girona Biomedical Research Institute (IDIBGI), Dr. Josep Trueta Hospital, Girona, Spain.
26. Thyroid Research Group, Institute of Molecular and Experimental Medicine, School of Medicine, Cardiff University, Cardiff, United Kingdom.
27. Department of Medicine, Division of Endocrinology, Memorial Sloan-Kettering Cancer Center, Weill Cornell University, New York, NY, USA.
28. Department of Social Medicine, University of Crete, Heraklion, Greece.
29. Department of Public Health, Amsterdam UMC, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands
30. ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.
31. Pompeu Fabra University, Barcelona, Spain.
32. Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain.
33. Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre–Sophia Children’s Hospital, Rotterdam, The Netherlands.
34. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, CA, USA.
35. Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain.
36. BIODONOSTIA Health Research Institute, San Sebastian, Spain.
37. Public Health Division of Gipuzkoa, Basque Government, San Sebastian, Spain.
38. AGC Pediatrics, Hospital Universitario Central de Asturias (Oviedo), Spain.
39. Epidemiology and Environmental Health Joint Research Unit, FISABIO–Universitat Jaume I–Universitat de València, Av. Catalunya 21, 46020 Valencia, Spain.
40. Shifa College of Medicine, Islamabad, Pakistan.
41. Division of Endocrinology, Hypertension and Diabetes, Brigham and Women's Hospital, Harvard Medical School, Boston, USA.
42. School of Medicine, University of Glasgow, Glasgow, United Kingdom.
43. National Institute for Health Research, Bristol Biomedical Research Centre, Bristol, UK.
44. Northern Finland Laboratory Center Nordlab and Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland.

45. Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, Massachusetts, USA.
46. Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.
47. Medical School, University of Western Australia, Crawley, Western Australia, Australia.

Abstract

Background Transplacental passage of maternal thyroid hormone is important for normal fetal growth and development. Maternal overt hypothyroidism and hyperthyroidism are associated with reduced birth weight, but the impact of maternal subclinical thyroid dysfunction is uncertain, partly because of inconsistent definitions of thyroid dysfunction in previous studies. Furthermore, the impact of maternal thyroid function in later pregnancy (when the fetal thyroid has developed) on birth weight remains unknown. The aim of this study was to examine associations of maternal thyroid function with risk of small for gestational age (SGA), large for gestational age (LGA) and birth weight.

Methods For this individual participant data meta-analysis we searched Medline (Ovid), Embase.com, Web-of-Science, Cochrane CENTRAL and Google Scholar from inception to March 18th 2018, and published open invitations to join the Consortium on Thyroid and Pregnancy, to identify published and non-published prospective cohort studies with data on maternal thyroid stimulating hormone (TSH) and/or free thyroxine (FT4) concentrations during pregnancy and birth weight, in which participants did not receive thyroid therapy. We excluded participants with multiple pregnancies, in vitro fertilization, pre-existing thyroid disease or thyroid medication usage, miscarriages and stillbirth. Main outcomes were SGA, LGA and birth weight. We analyzed individual participant data using mixed-effects regression models adjusting for maternal age, body mass index, ethnicity, smoking, parity, gestational age at blood sampling, fetal sex and gestational age at birth (for birth weight only). Effect modification by gestational age at blood sampling, fetal sex, maternal age, body mass index and smoking was also investigated. The study protocol was pre-registered at the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42016043496.

Results From 2,526 published reports, 35 cohorts were invited to participate. After addition of 5 unpublished datasets, a total of 19 cohorts were included. After exclusions, the study population comprised 46,599 mother-child pairs with a maternal mean (SD) age of 29 years (5.2) and median gestational age at blood sampling of 13 weeks (95% range: 7 to 39.7). Thyroid function test abnormalities were defined in 40,019 participants (16 cohorts with available TPOAb data) of whom 1,222 (3.1%) had subclinical hypothyroidism (increased TSH with normal FT4) and 894 (2.2%) had isolated hypothyroxinemia (decreased FT4 with normal TSH). Of the offspring, 4,574 (9.9%) were SGA and 4,510 (9.8%) were LGA. Maternal subclinical hypothyroidism was associated with a higher risk of SGA than euthyroidism (11.5% vs. 10.0% respectively, absolute risk difference 2.0% [95% CI, 0.1 to 4.5]; odds ratio (OR) 1.20 [95% CI 1.00-1.44], $P=0.04$) and lower mean birth weight (absolute difference -34.5g [95% CI -58.6 to -10.4], $P=0.005$) with a higher effect estimate for sampling in the 3rd trimester compared with the 1st or 2nd trimester. Isolated hypothyroxinemia was associated with a lower risk of SGA than euthyroidism (OR, 0.71 [95% CI 0.55-0.92], $P=0.01$) and higher mean birth weight (difference, 42g [95% CI 14 to 70], $P=0.003$). Each 1-SD higher maternal TSH concentration was associated with lower birth weight (-5.4g [-9.4 to -1.4], per SD, $P=0.008$), with higher effect estimates in TPOAb-positive than TPO-negative women. Each 1-SD higher FT4 concentration was associated with lower birth weight (-21.2g [95% CI -25 to -17] per SD, $P<0.001$), with a higher effect estimate for sampling in the 3rd trimester compared with the 1st or 2nd trimester. Results were similar for TSH and FT4 within the normal range.

Interpretation Maternal subclinical hypothyroidism in pregnancy is associated with a higher risk of SGA and lower birth weight, whereas isolated hypothyroxinemia is associated with lower risk of SGA and higher birth weight. There was an inverse, dose-response association of maternal TSH and FT4 (even within the normal range) with birth weight. These results

advance understanding of the complex relationships between maternal thyroid function and fetal outcomes, and should prompt careful consideration of potential risks as well as benefits of levothyroxine therapy during pregnancy.

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Introduction

Birth weight is an important marker of fetal growth, development, nutrition and other *in utero* exposures. Low birth weight or being born small for gestational age (SGA) are major risk factors for neonatal mortality and morbidity, and are associated with a higher risk of non-communicable diseases in later life such as type 2 diabetes, cardiovascular diseases and cancer.¹⁻⁴ At the other end of the spectrum, being large for gestational age (LGA) is a risk factor for cesarean section, postpartum hemorrhage, newborn hypoglycemia and is associated with obesity in later life.⁵⁻⁷ Thyroid hormone regulates fetal growth and development throughout gestation. Fetal thyroid hormone availability largely depends on the placental transfer of maternal thyroid hormone, particularly during the first 18-20 weeks of pregnancy.⁸ Overt maternal thyroid disease such as hypothyroidism or Graves' hyperthyroidism are well known risk factors for SGA and occur in 0.3% and 0.05% of pregnancies, respectively.⁸ Although mild thyroid function test abnormalities such as subclinical hypothyroidism, hypothyroxinemia and subclinical hyperthyroidism are much more frequent, it remains to be elucidated whether these are risk factors for SGA or LGA.

Levothyroxine is one of the most commonly prescribed drugs during pregnancy worldwide.⁹⁻¹³ However, there is currently insufficient evidence to recommend for or against levothyroxine treatment for mild thyroid function test abnormalities. The guidelines of the American Thyroid Association indicate that treatment can be considered for mild thyroid function test abnormalities such as subclinical hypothyroidism or thyroid peroxidase antibody (TPOAb) positive women with a TSH above 2.5 mU/L.¹⁴ To date, it remains common practice to titrate levothyroxine therapy to high-normal free thyroxine (FT4) concentrations and/or low-normal TSH concentrations as the potential benefits are believed to outweigh potential harms. However, some observational studies suggest that already a high-normal FT4

concentrations are associated with impaired fetal growth and lower birth weight, suggesting that levothyroxine treatment comes with the potential risk of overtreatment.¹⁵⁻¹⁸ Moreover, four out of the five randomized clinical trials on the treatment of women with thyroid function test abnormalities or autoimmunity with levothyroxine report non-statistically significant lower birth weight in the treatment group, but this could be due to the limited number of participants.¹⁹⁻²³ Overall, previous observational studies on the association of mild thyroid function test abnormalities with birth weight show conflicting results,^{14,24-29} partly due to relatively small sample sizes and use of widely varying definitions to define abnormal thyroid function. Furthermore, the majority of studies have focused on early pregnancy, and both the clinical relevance of mild thyroid function test abnormalities as well as treatment aims for the second half of pregnancy remain to be elucidated.

The aim of this study was to investigate the associations of maternal thyroid function tests with SGA, LGA and birth weight.

Methods

The Consortium on Thyroid and Pregnancy is a collaboration of prospective birth cohorts that aims to study the association of maternal thyroid function and autoimmunity with adverse pregnancy and child outcomes.³⁰ For the current study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data guidelines and pre-registered our study protocol (PROSPERO ID CRD42016043496, together with protocol deviations shown in the appendix). To identify studies for inclusion, we conducted a systematic search of literature for the publications on the association of thyroid function or autoimmunity with birth weight, published from inception to March 18th 2018, with no language restrictions and using several databases (Medline (Ovid), Embase.com, Web-of-Science, Cochrane CENTRAL and Google Scholar, detailed search terms and strategy are in

the appendix), and identified unpublished studies through personal contacts, advertisements at scientific conferences and invitations to join the consortium in medical journals and on social media.^{31,32} We included prospective cohort studies that consecutively included participants from the general population and/or without active selection based on health status and had either TSH or FT4 measurements and data on birth weight available. We excluded studies in which participants received treatment based on (abnormal) thyroid function tests (predominantly hospital-based cohorts) or studies that only included women with (overt) thyroid disease. Possible studies for inclusion were independently assessed for suitability by two authors (TIMK and PNT) and any disagreement was resolved by discussion with a third author (RPP). Investigators from each eligible study were invited to join the consortium using the contact details on the identified reports, when unsuccessful we used contact details of other published studies, contacted their co-authors or department. Upon participation, we collected individual-participant data using a standardized codebook. Quality of the studies and risk of bias was assessed using the Newcastle-Ottawa scale. All cohorts were approved by a local review board and acquired participants informed consent. All participants with either TSH, FT4 or TPOAbs measurements and birth weight data available were included, any data on thyroglobulin antibodies was collected upon availability. We excluded participants with a miscarriage/stillbirth, pre-existing thyroid disease or thyroid-interfering medication usage, IVF treatment or twin pregnancies.

Exposures

Exposures included thyroid function test abnormalities, continuous thyroid function test measurements (TSH and FT4) and TPOAb and thyroglobulin antibody (TgAb) positivity. Thyroid function test abnormalities were defined according to cohort-specific 2.5th and 97.5th population percentiles for TSH and FT4 concentrations, in cohorts with available TPOAb data, after exclusion of TPOAb positive women. Subclinical hypothyroidism was defined as

TSH above the 97.5th percentile and a FT4 within the normal range (i.e. 2.5th-97.5th percentile). Overt hyperthyroidism was defined as TSH below the 2.5th percentile, and a FT4 above the 97.5th percentile. Subclinical hyperthyroidism was defined as a TSH below the 2.5th percentile and a FT4 within the normal range. Isolated hypothyroxinemia was defined as a FT4 below the 2.5th percentile and a TSH within the normal range. TPOAb and TgAb positivity were based on cohort-specific cut-offs recommended by the manufacturer. For continuous TSH and FT4 concentrations as exposure variables, concentrations for all cohorts were log-transformed and then transformed to population-specific standard deviation (SD) scores after removal of outliers (± 4 SD from the mean) to enable comparison between different cohorts and assays.

Outcomes

The primary outcomes were SGA, LGA and birth weight (as a continuous variable). To define SGA and LGA, birth weight was standardized to gestational age at birth (weeks) and fetal sex per cohort. SGA was defined as a standardized birth weight below the 10th cohort-specific percentile, and LGA as a standardized birth weight above the 90th cohort-specific percentile, according to the definition of a World Health Organization expert committee.³³ Secondary outcomes were low birth weight (LBW; birth weight below 2500 grams) and macrosomia (birth weight above 4000 grams).

Sensitivity analyses

First, we assessed differential data availability within cohorts by comparing thyroid function between women with and without available data on birth weight. Second, main analyses for thyroid function tests were also performed in women with TSH, FT4 concentrations within the normal range (2.5th-97.5th percentiles). Third, we investigated whether the association of thyroid function test abnormalities or TSH and FT4 concentrations with birth weight differed according to gestational age at the time of blood sampling, fetal sex, maternal age, BMI and

smoking by adding a product interaction term into the models. Fourth, we studied whether the association of TSH or FT4 with birth weight differed according to TPOAb or TgAb positivity by adding product interaction terms to the models and stratifying the analysis if required. We subsequently quantified potential relevant differences by performing stratified analyses by the above factors if there was any indication of effect modification. Finally, we studied if maternal gestational diabetes mellitus or preeclampsia could be mediators in the association of interest by adding these variables to the regression models.

Statistical analyses

We used linear mixed effect regression models with a random intercept for each cohort to study the association of thyroid function test abnormalities (compared with euthyroidism), TSH, FT4 concentrations or TPOAb, TgAb positivity with birth weight. We used generalized logistic mixed regression models with a random intercept for each cohort to study SGA, LGA, LBW and macrosomia. All main analyses (primary outcomes) were also performed with a two-step approach using a random-effect models according to DerSimonian and Laird to pool estimates and assess heterogeneity across studies using the I^2 statistic and 95% confidence interval. We evaluated for potential publication bias using funnel plots and Egger tests. All models were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling, fetal sex and gestational age at birth (the latter two for birth weight only). We used multilevel multiple imputation for missing data on covariates creating five imputed datasets for pooled analyses.³⁴ All statistical analyses were performed using R statistical software version 3.5.1 (R Development Core Team (2008), Vienna, Austria; packages *lme4*, *mice*, *micemd*, *miceadds*, *metafor*, *sjPlot*).

Results

We identified 2,244 reports of which 130 were eligible for inclusion based on title and abstract screening (Figure 1). After reading full texts, and addition of five cohorts from other sources, a total of 35 cohorts were invited for participation. Subsequently, 19 cohorts from Europe, USA, Chile, Pakistan, Japan and Australia responded to our invitation and were able to participate. After exclusions, the final study population included 46,599 participants (Figure 1) with a mean birth weight of 3,400 (SD 535) grams and median gestational age at birth of 39.9 (95% range: 35.4 to 42.0) weeks; 4,574 newborns were born SGA (9.9%) and 4,510 (9.8%) were born LGA (Table). Subclinical hypothyroidism occurred in 1,222 women (3.1%), isolated hypothyroxinemia occurred in 894 women (2.2%) out of 40,019 from 16 cohorts with available data on TPOAb. Cohort-specific characteristics, Newcastle-Ottawa Quality Assessment Scales, number of participants with available thyroid function and birth weight and percentiles for definition of thyroid function test abnormalities are provided in the appendix. Data on specific covariates were missing in up to 33% and from as many as 3 cohorts (total percentage missing [number of cohorts] maternal age 0.3% [0], gestational age at the time of blood sampling 0.35% [0], parity 5.5% [1], smoking status 7.1% [1], BMI 32.7% [3], fetal sex 20.3% [2], see appendix). Compared with participants included in the study, women who were not included because of missing data on birth weight had similar TSH and FT4 concentrations, but a higher rate of TPOAb positivity (12.6% vs. 7.4 %, $P<0.0001$; appendix).

Compared with euthyroidism, maternal subclinical hypothyroidism was associated with a higher risk of SGA (10.0% vs 11.5%, absolute risk difference 2.0 % [95% CI, 0.1 to 4.5]; odds ratio [95% CI]: 1.20 [1.00 to 1.44, $P=0.042$]; Figure 2A) and lower mean birth weight (estimated mean difference -34.5g [95% CI -59 to -10]; Figure 2C). Isolated

hypothyroxinemia was associated with a lower risk of SGA (10.0% vs 7.4%, absolute risk difference -2.9 % [95% CI, -4.8 to -0.8]; odds ratio [95% CI]: 0.71 [0.55 to 0.92, $P=0.01$]; Figure 2A) and higher mean birth weight (estimated mean difference 42.4g [95% CI 14 to 70]; Figure 2C). Subclinical hyperthyroidism and overt hyperthyroidism were not associated with SGA or birth weight (Figure 2A), and there was no association of thyroid function test abnormalities with LGA (Figure 2B).

When analyzed as a continuous variable, each 1-SD higher maternal TSH concentration was associated with a higher risk of SGA (OR 1.04 [95% CI 1.00 to 1.08] per SD) and lower mean birth weight (-5.4g [95% CI -9.4 to -1.4], Figure 3). Each 1-SD higher FT4 concentration was associated with a higher risk of SGA (OR 1.08 [95% CI 1.05 to 1.12] per SD), a lower risk of LGA (OR 0.91 [95% CI 0.89 to 0.94] per SD) and lower mean birth weight (-21.2g [95% CI -25 to -17] per SD, Figure 3). When considered across the full FT4 range, this approximated a difference in birth weight of ~200 grams (Figure 3B). Effect estimates remained similar when analysis was confined to TSH or FT4 concentrations within the normal range (Figure 3B). TPOAb and TgAb positivity were not associated with SGA, LGA or birth weight (appendix).

The association of FT4 with birth weight differed according to the gestational age at blood sampling (P for interaction 0.0004). Subsequent stratified analyses showed that the effect estimates of the association of FT4 with birth weight were 2 and 3-fold larger when the FT4 concentration was measured during the 2nd or 3rd trimesters compared to the 1st trimester (β [95% CI] for birth weight: -12.3 , -22.0 and -35.8 in 1st, 2nd and 3rd trimesters, respectively; Figure 4, appendix). Also, the association of subclinical hypothyroidism with birth weight were 2 and 5-fold larger when the FT4 concentration was measured during the 2nd or 3rd trimesters compared to the 1st trimester (β [95% CI] for birth weight: -15.5, -28.2 and -74.8 in 1st, 2nd and 3rd trimesters, respectively; appendix)

There was evidence that the association of TSH and FT4 with birth weight differed according to TPOAb status (P for interaction=0.14 and 0.08, respectively). In the subsequent stratified analysis, effect estimates of the negative association of TSH with birth weight were 4-fold higher for TPOAb positive women than TPOAb negative women (β [95% CI] -16.1 [-31 to -0.66] per SD vs -4.2 [-8.8 to 0.4] per SD, respectively; appendix). In contrast, for FT4, the negative effect estimate of the association with birth weight in TPOAb positive women was almost half the estimate for TPOAb negative women (β [95% CI] -10.5 [-25 to 4.2] per SD vs -21.8 [-26 to -17] per SD, respectively; appendix). Results did not meaningfully differ according to TgAb positivity (appendix).

The association of FT4 with birth weight differed according to maternal age and BMI (P for interaction 0.051 and 0.002, respectively) but not fetal sex or smoking status (appendix). Stratified analyses showed that the negative effect estimate of the association of FT4 with birth weight was larger in women with a BMI ≥ 30 kg/m² compared to those with a BMI of 20-25 kg/m² (appendix). Finally, when stratified by maternal age (below 30 or higher than 30 years) there was not a meaningful difference in the association of FT4 with birth weight among the two groups (β [95% CI] for birth weight: -23.6 [-29 to -18] and -18.9 [-25 to -13] for maternal age <30 or ≥ 30 years, respectively; appendix). There was no evidence that the association of TSH with birth weight differed meaningfully according to gestational age at the time of sampling, fetal sex, maternal age, BMI, or smoking (appendix). Results of analyses on low birth weight or macrosomia yielded results similar to those of SGA or LGA (appendix). Additional adjustment for gestational diabetes mellitus or preeclampsia did not change the results (appendix). Results of two-step meta-analyses were similar to one-step

analyses and funnel plots did not indicate publication bias or unexpected differences in effect estimates between the included studies (appendix).

Discussion

In this individual participant data meta-analysis, we show that maternal subclinical hypothyroidism during pregnancy is a risk factor for SGA and is associated with lower birth weight. By contrast, isolated hypothyroxinemia was associated with higher birth weight. Maternal TSH and FT4 concentrations were both inversely associated with birth weight, with the association of FT4 being most apparent during later pregnancy, whereas the association of TSH with birth weight was most apparent in TPOAb-positive women.

Levothyroxine is one of the most commonly prescribed drugs during pregnancy⁹⁻¹³, and is commonly targeted to achieve high-normal FT4 concentrations. This study in untreated, otherwise healthy women, shows that a higher maternal FT4 concentration within the normal range is associated with lower birth weight and a higher risk of SGA. This suggests that levothyroxine therapy comes with a potential risk of overtreatment, especially when targeting high-normal FT4 concentrations. Consistent with the results of this study, recent randomized trials showed that low-dose levothyroxine treatment of either subclinical hypothyroidism or isolated hypothyroxinemia was associated with a higher risk of SGA, albeit statistically non-significant (for subclinical hypothyroidism, levothyroxine 10% vs placebo 8%; for isolated hypothyroxinemia, levothyroxine 9% vs placebo 8%).²³ Further studies are needed to investigate whether the changes in TSH or FT4 concentrations that occur during levothyroxine therapy in pregnancy are related to treatment benefits and/or harms.

The contrasting results for subclinical hypothyroidism and isolated hypothyroxinemia with regard to birth weight in the current study suggest differences in the underlying

pathophysiological mechanisms. Subclinical hypothyroidism is more common in TPOAb positive women and likely reflects a lower thyroid functional capacity. The latter is reflected by a considerable attenuation of the hCG-mediated increase in FT4 and decrease in TSH concentrations in women with subclinical hypothyroidism as compared to euthyroid women.³⁵ On the other hand, neither TPOAb positivity nor an impaired thyroïdal response to hCG seem to play a role in women with isolated hypothyroxinemia.³⁵ We speculate that isolated hypothyroxinemia is a thyroid function test abnormality that is specific for pregnancy and may not necessarily represent thyroid gland hypofunction.⁸ It has also been suggested that minor aberrations of thyroid function during pregnancy may arise from dysfunction of the uteroplacental unit, rather than from thyroid dysfunction.³⁶ Further studies are required to elucidate the underlying physiology of such gestational thyroid function test abnormalities.

The mechanisms underlying the association of isolated hypothyroxinemia with lower birth weight, and the negative relationship between maternal FT4 and birth weight are uncertain. Since circulating maternal (F)T4 crosses the placenta, and maternal FT4 concentrations are correlated with newborn FT4 concentrations,^{37,38} the negative association of maternal FT4 with birth weight could reflect a direct thyroid hormone effect. This dose-dependent association can also be further extrapolated to fetal growth restriction typically seen in pregnancies complicated by Graves' hyperthyroidism.^{39,40} We hypothesize that such an effect is mediated by an increase in newborn lipid and protein catabolism effectuating a reduction in caloric availability, which could be further complicated by a higher placenta vascular resistance.^{41,42} The point estimates in this study indicate a lower risk of SGA for women with overt hyperthyroidism which warrants further studies. This could be explained via high hCG concentrations, since overt hyperthyroidism in the current study may reflect transient

gestational thyrotoxicosis rather than Graves' hyperthyroidism and high hCG concentrations have been associated with a higher birth weight.⁴³

Thyroid hormone regulates fetal growth by facilitating placentation and regulation of metabolism, fetal glucose and oxygen consumption as well as other co-factors directly affecting skeletal growth, tissue differentiation and accretion.⁴⁴⁻⁴⁶ One of the sensitivity analyses in this study showed that the negative association of FT4 with birth weight is amplified during the 2nd and 3rd trimester. These differences most likely reflect an amplification of the metabolic effect of thyroid hormone on fetal growth due to an increased fetal nutritional demand and increased fetal growth rate with the progression of pregnancy.^{44,47} Our results indicate that maternal thyroid function during later pregnancy is still closely related to pregnancy outcome or child development. These results highlight the relevance of follow-up thyroid function testing when levothyroxine therapy is started during early pregnancy and warrant further studies preferably utilizing repeated measurements.

Strengths and limitations

In the current study, we were able to utilize detailed individual-participant data on thyroid function, birth weight and potential confounders from 19 prospective, population-based cohorts, allowing standardization of the definition of thyroid function test abnormalities and analyzing potential dose-dependent associations. One of the limitations of the current study is the interpretation of the results on overt hyperthyroidism, since we had limited statistical power for this group and TSH receptor antibody concentrations were not available. Another potential limitation of this study is that the interpretation of the results could be interfered by pregnancy-related changes in thyroid binding proteins that could interfere with FT4 immunoassays. However, gestational changed in FT4 concentrations as assessed by immunoassays are highly similar to those measured with liquid chromatography-mass

spectrometry or equilibrium dialysis.^{48,49} Another potential limitations is that we could not include studies that were published while conducting statistical analyses for the current study. Finally, due to the observational nature of the included studies, we cannot exclude any residual or unmeasured confounding, and does not allow us to draw conclusions about causality.

Conclusion

This large individual participant data meta-analysis shows that subclinical hypothyroidism is a risk factor for SGA and that isolated hypothyroxinemia is associated with higher birth weight. Furthermore, we identified a dose-dependent negative association of maternal FT4 with birth weight that was most prominent during late pregnancy. This indicates that there is a potential risk of overtreatment when titrating levothyroxine to high-normal FT4 concentrations and underlines the importance of follow-up thyroid function testing when levothyroxine therapy is started during early pregnancy.

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Author Contributions

AD, TIMK and MM performed analyses and were involved in writing of the manuscript. PNT, CD, EAPS, LC, EKA, TIMK and RPP made the analysis plan and were involved in the writing of the manuscript. WMB performed the systematic search and PNT, TIMK and RPP were involved in study selection. All authors were involved in data collection and provided substantial contributions to drafting of the work including critical revision for important intellectual content. TIMK and RPP supervised analyses, were involved in writing of the manuscript and directed the project.

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Figure 1. Flowchart of the study and population selection.

Figure 2. Association of thyroid function test abnormalities with small or large for gestational age and birth weight.

All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling, fetal sex and gestational age at birth (for birth weight only). Risk differences and 95% CIs were back-calculated from the results of multivariable models and adjusted for baseline risk imprecision.

Figure 3. Association of TSH and FT4 concentrations with small or large for gestational age and birth weight.

Figures show the association of maternal TSH and FT4 in full range or within the normal range (2.5th-97.5th percentiles) with small or large for gestational age (panel A) and birth weight in grams (panel B). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling, fetal sex and gestational age at birth (for birth weight only).

* Normal range (2.5th-97.5th percentiles) is defined based on cohort-specific absolute measurements of TSH or FT4, which in the standardized data corresponds to TSH Z-score range of -4.2 to 1.8 and FT4 Z-score range of -2.2 to 2.5.

Figure 4. Association of FT4 Z-scores with birth weight according to gestational age at the time of sampling.

Figure shows the association of FT4 Z-scores with birth weight (grams) stratified by gestational age at the time of sampling. The analysis was adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex and gestational age at birth.