Appendix

"Association of maternal thyroid function with birth weight: an individual-participant data meta-analysis"

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The association of maternal thyroid function and thyroid autoimmunity with offspring birth-weight

Tim Korevaar, Peter Taylor, Colin Dayan, Robin Peeters

Citation

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Review question

What is the association of maternal TSH, FT4, FT3 and thyroid autoimmunity (TPOAbs or TgAbs) with birth weight?
What is the association of maternal disease entities (i.e. overt and subclinical hypothyroidism, overt and subclinical hyperthyroidism and hypothyroxinemia with birth weight?

Searches

We will search Embase, MEDLINE (Ovid), Web of Science, Cochrane and Google Scholar.
The search strategy will include only terms relating to or describing the exposure and/or intervention.
There will be no language restrictions.
The searches will be re-run before final analyses, if applicable further studies retrieved for inclusion.
In order to obtain unpublished data we will:
- Select from the search, and contact authors that have published studies on thyroid function during pregnancy with different outcomes.
- Use our personal network.
- Publish an invitation to join our research consortium (the consortium on thyroid an pregnancy) in various journals (Thyroid, European Thyroid Journal, Obstetrics & Gynecology).
- Announce our consortium and IPD meta-analysis at various conferences (ETA, ATA, ICE-CSE).
- Advertise our consortium via social media (twitter, researchgate).
Additional details about the search strategy can be found in the attached PDF document (link provided below).

Search strategy

http://www.crd.york.ac.uk/PROSPEROFILES/43496_STRATEGY_20160624.pdf

Types of study to be included

- Non-selected or population-based prospective cohorts. - Data on exposure and outcomes should be obtained/registered prospectively. - Exceptions can be made if authors are willing to retrospectively ascertain data on other covariates that were not prospectively collected during the initial study.

Condition or domain being studied

Birth weight and gestational age-standardized birth weight.

Participants/population

- Non-selected or population-based prospective cohorts.
- Serum TSH, or FT4 or thyroid antibodies measured in pregnant women (any gestational age).
- Follow-up complete until the end of pregnancy.
- Disease-specific prospective cohorts can be included for specific studies when deemed relevant.

Intervention(s), exposure(s)

It is well established that both overt hypothyroidism and overt hyperthyroidism in pregnancy result in profound adverse outcomes particularly premature birth and foetal loss 1,2. Though evidence of its effects on birth-weight are more limited, particularly any occurring independently of gestational age. Subclinical hypothyroidism; (SCH) the presence of an elevated TSH with a normal free thyroxine level is correlated with preterm delivery, placental abruption and need for admission to the special care baby unit (SCBU) 3-7 but its

effect on weight is less well understood. A recent meta-analysis identified that subclinical hypothyroidism, but not IH was associated with intra uterine growth restriction 8 and even variation in TSH within the normal pregnancy reference range was an independent risk factor for being small for gestational age9. Isolated hypothyroxinemia (IH) the presence of a lower free thyroxine with a normal TSH level is associated primarily with impaired neuropsychological development of offspring 10-12 although it has also been associated with both macrosomia 13 and prematurity 14.
Given the growing debate about the need for universal thyroid screening in pregnancy 15 having a greater understanding of TSH and free thyroxine thresholds that might be associated with an unacceptable risk of harm would be desirable. Whilst gestational age also influenced by thyroid status is likely to be a key determinant it is important to ascertain if there is a substantial independent effect on birth-weight. Cohort studies so far have been unable to study effect thresholds and have been unable to quantify precisely the effects of overt or sub-optimal thyroid function, hence the need for this meta-analysis.

Comparator(s)/control
Continuous analyses are preferred, disease entities compared to euthyroid controls.

Context
Exclusion criteria: Fertility treatment, twin pregnancy, thyroid medication usage, pre-existing thyroid disease.

Main outcome(s)
Birth weight.

Additional outcome(s)
Low birth weight, high birth weight, FGR, macrosomia.

Data extraction (selection and coding)
Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors (TK and PT) to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members (TK and PT). Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer (RP). Those responsible for the included studies will be asked to supply line by line individual participant data according to a standardized data codebook file (Excel) and will be cleaned and checked by study lead author (TK).

Risk of bias (quality) assessment
Per cohort, we will check the randomness of missing data and internal data consistency. Any discrepancies or unusual patterns will be checked with the study investigator. Funnel plots will be constructed for the primary outcome. Measures to identify unpublished data have been outlined in above

Strategy for data synthesis
Primary analysis:
1) The continuous association of maternal TSH, FT4 and TPOAbs with birthweight.
- TSH, FT4 and TPOAb SD scores will be calculated per population and studied in order to retain inter-individual differences. Percentile scores will be calculated per cohort and studied to define optimal population-based cut-offs.
Secondary analyses:
1) The association of (sub)clinical thyroid disease entities and TPOAb positivity with birth-weight outcomes.
- Percentile scores will be calculated per cohort and different population-based cut-offs for clinical disease entities will be calculated define optimal population-based cut-offs.
2) The association of TgAbs with birth-weight.
- Similar methodology as for TPOAbs.
Pre-specified sensitivity analyses:
3) Effects of TSH and FT4 in women with and without TPO and/or Tg antibody positivity.
4) Stratification per week of gestational age of serum measurement.
Pre-specified interactions:
5) With known risk factors (maternal age, diabetes, BMI, smoking, ethnicity gestational age).
Additional analysis:

6) Funnel plot to evaluate publication bias.
7) Comparison of women in the cohorts and their offspring in women with and without thyroid function available.
8) Analysis repeated with women with GDM/ or known diabetes excluded.
Statistical analyses:
We will study the above described associations by performing and individual participant based meta-analysis (combining raw data). We will use both a one-step and two-step approach. For the one step, TSH, FT4 and TPOAb concentrations will be standardized to SD scores and per cohort and analyzed utilizing models with random intercepts and slopes per cohort. In addition, we aim to extract effect thresholds by calculating percentile scores per cohort and assess the risk of outcomes per percentile. For the two-step approach, TSH, FT4 and TPOAb concentrations will be standardized to SD scores and/or percentile scores per cohort and analyses performed in each cohort will be pooled.

Analysis of subgroups or subsets
Specified above.

Contact details for further information
Tim Korevaar
t.korevaar@erasmusmc.nl

Organisational affiliation of the review
Erasmus University Medical Center

Review team members and their organisational affiliations
Dr Tim Korevaar. Erasmus University Medical Center
Dr Peter Taylor. Cardiff University
Professor Colin Dayan. Cardiff University
Professor Robin Peeters. Room Na-2913, Department of Epidemiology and Endocrinology, Erasmus Medical Center Postbus 2040, 3000 CA Rotterdam, The Netherlands

Type and method of review
Individual patient data (Individual patient data (IPD) meta-analysis) meta-analysis, Systematic review

Anticipated or actual start date
01 July 2016

Anticipated completion date
01 July 2017

Funding sources/sponsors
The Netherlands Organisation for Health Research and Development (ZonMw), project number 90700412

Conflicts of interest
None known

Language
English

Country
Wales, Netherlands

Published protocol
http://www.crd.york.ac.uk/PROSPEROFILES/43496_PROTOCOL_20160624.pdf

Stage of review
Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Autoimmunity; Birth Weight; Humans; Infant, Extremely Low Birth Weight; Infant Health; Infant, Low Birth Weight; Infant, Newborn; Infant, Very Low Birth Weight; Maternal Health; Pregnancy Outcome; Thyroid Gland; Thyroid Hormones

Date of registration in PROSPERO

10 August 2016

Date of publication of this version

10 August 2016

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

10 August 2016

Supplemental methods:

Search strategies

In addition, we searched in other sources, including bibliographies of key articles in the field and those included in this review. Secondly, to identify cohorts with available data but without published studies, we used our personal contacts in the field, advertised at various conferences, and published open invitations to join the consortium in relevant medical journals and on social media (Twitter and Researchgate).[1,2] For optimal quality and comparability of the studies, we formulated general inclusion criteria *a priori*.

Search terms

Embase.com

('thyroid function'/exp OR 'thyroid function test'/de OR 'thyroid disease'/exp OR 'thyrotropin'/de OR 'thyrotropin blood level'/de OR 'thyroid hormone'/de OR 'thyroid hormone blood level'/exp OR 'thyroid peroxidase antibody'/exp OR 'thyroglobulin antibody'/de OR ((thyroid* NEAR/3 (function* OR dysfunction* OR disorder* OR disease* OR autoimmun* OR auto-immun* OR hormone* OR autoantibod* OR antibod*)) OR thyroidit* OR hyperthyro* OR hypothyro* OR thyrotropin* OR tsh OR ((t4 OR ft4 OR t-4 OR ft-4 OR tsh OR liothyronin* OR thyroxin*) NEAR/3 (free OR plasma OR blood OR serum OR level* OR concentrat* OR low OR high OR elevat* OR decrease* OR increase*)) OR (thyroid* NEAR/3 peroxidase* NEAR/3 antibod*) OR ((tpo OR thyroglobulin* OR thyroperoxidas* OR thyroperoxid*) NEAR/3 (antibod* OR positiv* OR negativ* OR status*)) OR euthyroid* OR graves OR goiter):ab,ti) AND ('pregnancy'/exp OR 'pregnant woman'/de OR 'mother'/de OR 'prenatal exposure'/de OR 'pregnancy outcome'/de OR 'pregnancy disorder'/de OR 'pregnancy complication'/de OR 'prenatal period'/de OR 'prenatal growth'/de OR (pregnan* OR mother* OR prenatal* OR maternal*):ab,ti) AND ('prematurity'/exp OR 'premature fetus membrane rupture'/de OR 'birth weight'/exp OR 'fetus growth'/de OR 'premature labor'/de OR 'prenatal growth'/de OR (prematur* OR preterm* OR pre-term* OR 'birth weight' OR 'neonat* weight' OR 'birthweight' OR lbw OR vlbw OR elbw OR ((fetus OR fetal OR foetal OR foetus) NEAR/3 (growth OR weight)) OR (gestation* NEAR/3 (age OR week*) NEAR/6 (birth OR childbirth OR born OR deliver*))):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Medline Ovid

("Thyroid Function Tests"/ OR exp "Thyroid Diseases"/ OR "Thyrotropin"/ OR exp "Thyroid Hormones"/ OR ((thyroid* ADJ3 (function* OR dysfunction* OR disorder* OR disease* OR autoimmun* OR auto-immun* OR hormone* OR autoantibod* OR antibod*)) OR thyroidit* OR hyperthyro* OR hypothyro* OR thyrotropin* OR tsh OR ((t4 OR ft4 OR t-4 OR ft-4 OR tsh OR liothyronin* OR thyroxin*) ADJ3 (free OR plasma OR blood OR serum OR level* OR concentrat* OR low OR high OR elevat* OR decrease* OR increase*)) OR (thyroid* ADJ3 peroxidase* ADJ3 antibod*) OR ((tpo OR thyroglobulin* OR thyroperoxidas* OR thyroperoxid*) ADJ3 (antibod* OR positiv* OR negativ* OR status*)) OR euthyroid* OR graves OR goiter).ab,ti.) AND (exp "pregnancy"/ OR "pregnant women"/ OR "mothers"/ OR "pregnancy outcome"/ OR "pregnancy complications"/ OR "Fetal Weight"/ OR (pregnan* OR mother* OR prenatal* OR maternal*).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR "Fetal Membranes, Premature Rupture"/ OR "birth weight"/ OR exp "Infant, Low Birth Weight"/ OR (prematur* OR preterm* OR pre-term* OR "birth weight" OR "neonat* weight" OR "birthweight" OR lbw OR vlbw OR elbw OR ((fetus OR fetal OR foetal OR foetus) ADJ3 (growth OR weight)) OR (gestation* ADJ3 (age OR week*) ADJ6 (birth OR childbirth OR born OR deliver*))).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane

(((thyroid* NEAR/3 (function* OR dysfunction* OR disorder* OR disease* OR autoimmun* OR auto-immun* OR hormone* OR autoantibod* OR antibod*)) OR thyroidit* OR hyperthyro* OR hypothyro* OR thyrotropin* OR tsh OR ((t4 OR ft4 OR t-4 OR ft-4 OR tsh OR liothyronin* OR thyroxin*) NEAR/3 (free OR plasma OR blood OR serum OR level* OR concentrat* OR low OR high OR elevat* OR decrease* OR increase*)) OR (thyroid* NEAR/3 peroxidase* NEAR/3 antibod*) OR ((tpo OR thyroglobulin* OR thyroperoxidas* OR thyroperoxid*) NEAR/3 (antibod* OR positiv* OR negativ* OR status*)) OR euthyroid* OR graves OR goiter):ab,ti) AND ((pregnan* OR mother* OR prenatal* OR maternal*):ab,ti) AND ((prematur* OR preterm* OR pre-term* OR 'birth weight' OR 'neonat* weight' OR 'birthweight' OR lbw OR vlbw OR elbw OR ((fetus OR fetal OR foetal OR foetus) NEAR/3 (growth OR weight)) OR (gestation* NEAR/3 (age OR week*) NEAR/6 (birth OR childbirth OR born OR deliver*))):ab,ti)

Web of science
TS=((((thyroid* NEAR/2 (function* OR dysfunction* OR disorder* OR disease* OR autoimmun* OR auto-immun* OR hormone* OR autoantibod* OR antibod*)) OR thyroidit* OR hyperthyro* OR hypothyro* OR thyrotropin* OR tsh OR ((t4 OR ft4 OR t-4 OR ft-4 OR tsh OR liothyronin* OR thyroxin*) NEAR/2 (free OR plasma OR blood OR serum OR level* OR concentrat* OR low OR high OR elevat* OR decrease* OR increase*)) OR (thyroid* NEAR/2 peroxidase* NEAR/2 antibod*) OR ((tpo OR thyroglobulin* OR thyroperoxidas* OR thyroperoxid*) NEAR/2 (antibod* OR positiv* OR negativ* OR status*)) OR euthyroid* OR graves OR goiter)) AND ((pregnan* OR mother* OR prenatal* OR maternal*)) AND ((prematur* OR preterm* OR pre-term* OR "birth weight" OR "neonat* weight" OR "birthweight" OR lbw OR vlbw OR elbw OR ((fetus OR fetal OR foetal OR foetus) NEAR/2 (growth OR weight)) OR (gestation* NEAR/2 (age OR week*) NEAR/5 (birth OR childbirth OR born OR deliver*)))) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR sheep OR ovine OR tadpole* OR frog OR frogs OR ewe OR lamb OR lambs OR pig OR swine OR porcine OR cow OR cows OR bovine OR baboon OR monkey OR primate*) NOT (human* OR patient*))) AND DT=(article)

Google scholar
"thyroid function|dysfunction"|"t4|tsh|tpo level|concentration"|"blood|plasma|serum t4|tsh|tpo" pregnancy|pregnant|mother|prenatal|maternal premature|preterm|"birth weight"|birthweight|"fetal|foetal growth|weight

We identified 4 studies that were published after finalization of our systematic search on March 18th 2018 that would have otherwise been eligible for inclusion.[3-6]

Definition of thyroid disease entities

Subclinical hypothyroidism was defined as a TSH above the cohort-specific 97.5th percentile and a FT4 within the cohort-specific normal range (i.e. 2.5th-97.5th percentile). Subclinical hyperthyroidism was defined as a TSH below the cohort-specific 2.5th percentile and a FT4 within the cohort-specific normal range (i.e. 2.5th-97.5th percentile). Overt hyperthyroidism in the majority of cases represent the physiological response to thyroidal stimulation by high concentrations of hCG and was therefore considered as a mild form of thyroid disease. Overt hyperthyroidism was defined as a TSH below the 2.5th cohort-specific percentile, and a FT4 above the 97.5th cohort-specific percentile. Isolated hypothyroxinemia was defined as a FT4 below the cohort-specific 2.5th percentile and a TSH within the cohort-specific normal range (i.e. 2.5th-97.5th percentile). Cohort-specific cut-offs are provided in Supplemental Table 4.

Statistics and sensitivity analyses

We assessed mixed model assumptions and the model fit by inspection of residuals, the Akaike information criteria, non-linearity and log-likelihood tests comparing multilevel models with random intercepts and/or slope per cohort, if applicable.

In the two-step meta-analysis of thyroid function test abnormalities, due to complete or quasi-complete separation of regression models for some cohorts with very small or 0 number of events/exposures, we combined the cohorts with such characteristics to obtain more reliable effect estimates.

References:

1. Korevaar TI, Taylor PN, Dayan CM, Peeters RP. An Invitation to Join the Consortium on Thyroid and Pregnancy. Eur Thyroid J 2016; 5:277

2. Korevaar TI, Taylor PN, Dayan CM, Peeters RP. An Invitation to Join the Consortium on Thyroid and Pregnancy. Obstet Gynecol 2016; 128:913
3. Abel, Marianne Hope, et al. "Iodine intake is associated with thyroid function in mild to moderately iodine deficient pregnant women." Thyroid 28.10 (2018): 1359-1371.
4. Su, P. Y., et al. "Dose-response relationship between maternal thyroid hormones in the first twenty weeks and physical and neuropsychological development of infants: A prospective cohort study in China." Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi 40.2 (2019): 180-185.
5. Han, Yan, et al. "Impact of maternal thyroid autoantibodies positivity on the risk of early term birth: Ma'anshan Birth Cohort Study." Endocrine (2018): 1-10.
6. Gupta, Renu, et al. "A clinical study on thyroid dysfunctions in pregnancy and its effect on maternal and neonatal outcome." Journal Of Evolution Of Medical And Dental Sciences-JEMDS 7.12 (2018): 1520-1523.

Supplemental Table 1A. Maternal demographics per cohort (see Supplemental Table 1E for number (%) of missing data per variable).

Cohort (country)	Age, years	Gestational age*, (weeks)	BMI, (kg/m^2)	Parity				Smoking		Ethnicity	
				0	1	2	≥3	None/past	Current	Native	Non-native
ABCD (Netherlands)	31 (4.8)	13.0 (8.2-22.9)	23.9 (3.7)	2318 (57.6)	1253 (31.2)	329 (8.2)	121 (3.0)	3633 (90.4)	384 (9.6)	2407 (59.9)	1614 (40.1)
ALSPAC (United Kingdom)	28 (4.8)	11 (6-34)	22.9 (3.7)	2153 (42.5)	1643 (32.4)	683 (13.5)	591 (11.7)	3644 (75.8)	1165 (24.2)	5070 (100)	-
Bliddal et al. (Denmark)	31 (4.2)	11.3 (8.9-13.4)	22.8 (4.4)	485 (56.4)	291 (33.8)	84 (9.8)	0	768 (93.4)	54 (6.6)	860 (100)	-
Chen et al. (China)	27 (4.3)	31.1 (6.6-41.0)	NA	7137 (83.1)	1379 (16.1)	61 (0.7)	10 (0.1)	8570 (99.8)	17 (0.2)	8587 (100)	-
EFSOCH (United Kingdom)	30 (5.2)	28 (28-28)	27.9 (4.6)	473 (49.5)	343 (35.8)	101 (10.5)	38 (4.0)	923 (99.8)	2 (0.2)	958 (100)	-
Generation R (Netherlands)	31 (5.0)	13.2 (9.6-17.6)	24.5 (4.4)	3412 (57.4)	1773 (29.8)	549 (9.2)	206 (3.5)	4330 (81.3)	999 (18.7)	3263 (54.5)	2723 (45.5)
Ghafoor et al. (Pakistan)	27 (6.4)	19 (15-31)	NA	620 (34.3)	475 (26.4)	388 (21.5)	319 (17.7)	NA	NA	1803 (100)	-
GIRONA 1 (Spain)	31 (5.0)	26.7 (21.6-28.9)	26.8 (4.3)	147 (50.3)	145 (49.7)	0	0	161 (75.6)	52 (24.4)	326 (100)	-
GIRONA 2 (Spain)	31 (4.6)	25.8 (23.9-27.7)	26.4 (3.9)	192 (51.9)	132 (35.7)	46 (12.4)	0	310 (84.7)	56 (15.1)	370 (100)	-
HAPPY (Netherlands)	30 (3.7)	12 (12-12)	23.8 (3.9)	1008 (49.7)	795 (39.2)	198 (9.8)	29 (1.4)	1721 (92.7)	136 (7.3)	2067 (100)	-
Hisada et al. (Japan)	34 (4.7)	11 (7-15)	20.6 (2.7)	87 (48.9)	74 (41.6)	16 (9.0)	1 (0.6)	157 (91.3)	15 (8.7)	179 (100)	-
INMA (Spain)	31 (4.3)	13 (11-20)	23.5 (4.2)	1240 (56.4)	806 (36.7)	133 (6.1)	18 (0.8)	1474 (68.4)	681 (31.6)	2199 (100)	-
Mosso et al. (Chile)	25 (6.5)	8.4 (5-14)	26.0 (5.0)	288 (53.5)	147 (27.3)	103 (19.2)	0	474 (88.1)	64 (11.9)	538 (100)	-
NFBC (Finland)	27 (5.4)	10 (6-20)	22.2 (3.4)	1961 (33.8)	1954 (33.7)	1056 (18.2)	835 (14.4)	5586 (97.4)	148 (2.6)	5827 (100)	-
PIP Study (United Kingdom)	30 (6.0)	13 (10-17)	26.1 (5.4)	1520 (45.2)	1192 (35.5)	422 (12.6)	226 (6.7)	2877 (85.5)	487 (14.5)	3099 (92.1)	265 (7.9)
Popova et al. (Russia)	29 (4.6)	11 (6-14)	23.8 (4.9)	278 (61.2)	138 (30.4)	34 (7.5)	4 (0.9)	344 (75.8)	110 (24.2)	454 (100)	-
Rhea (Greece)	29 (4.9)	13 (9-23)	25.0 (4.6)	333 (39.7)	334 (39.8)	138 (16.4)	34 (4.1)	666 (82.6)	140 (17.4)	856 (100)	-
VIVA (United States)	32 (4.7)	9.5 (6.9-16.7)	24.5 (5.1)	370 (49.9)	258 (34.8)	88 (11.9)	25 (3.4)	592 (80.1)	147 (19.9)	595 (80.3)	146 (19.7)
Western Australia	31 (5.2)	11.1 (9.7-13.4)	NA	NA	-	-	-	2160 (90.3)	233 (9.7)	2393 (100)	-

Values are mean (SD), median (95% range) or n (valid %). NA: not available.

ABCD: Amsterdam Born Children and their Development; ALSPAC: Avon Longitudinal Study of Parents and Children; EFSOCH: The Exeter Family Study of Childhood Health; HAPPY: Holistic Approach to Pregnancy and the first Postpartum Year; INMA: Infancia y Medio Ambiente; NFBC: Northern Finland Birth Cohort; PIP Study: The Proteomics In Pre-eclampsia.

*Gestational age at the time of blood sampling.

Supplemental Table 1B. Maternal thyroid function test results per cohort.

Cohort (country)	TSH		FT4		TPOAb status*, N (%)		TgAb status*, N (%)	
	N	Median (IQR)	N	Median (IQR)	Negative	Positive	Negative	Positive
ABCD (Netherlands)	3998	1.16 (0.8-1.8)	4020	9.48 (8.7-10.4)	3780 (94.0)	241 (6.0)	NA	NA
ALSPAC (United Kingdom)	4908	1.02 (0.7-1.5)	4948	16.1 (14.7-17.7)	4366 (87.8)	609 (12.2)	NA	NA
Bliddal et al. (Denmark)	857	1.36 (0.9-2.0)	854	14.3 (13.2-15.6)	732 (85.2)	127 (14.8)	784 (91.2)	76 (8.8)
Chen et al. (China)	8587	1.74 (1.2-2.6)	8587	9.04 (8.0-10.2)	8027 (94.8)	438 (5.2)	8130 (95.8)	359 (4.2)
EFSOCH (United Kingdom)	955	1.87 (1.4-2.5)	957	12.0 (11.1-13.0)	885 (92.9)	68 (7.1)	NA	NA
Generation R (Netherlands)	5595	1.34 (0.8-2.0)	5633	12.0 (10.6-13.6)	5265 (94.4)	315 (5.6)	NA	NA
Ghafoor et al. (Pakistan)	1803	1.69 (1.26-2.2)	1803	17.4 (15.3-19.2)	1645 (91.2)	158 (8.8)	NA	NA
GIRONA 1 (Spain)	326	1.81 (1.3-2.4)	326	11.3 (10.3-12.2)	286 (89.4)	34 (10.6)	NA	NA
GIRONA 2 (Spain)	370	2.18 (1.6-2.9)	370	12.2 (11.3-13.2)	299 (92.0)	26 (8.0)	NA	NA
HAPPY (Netherlands)	2067	1.46 (1.0-2.1)	2067	14.3 (13.2-15.4)	1903 (92.1)	164 (7.9)	NA	NA
Hisada et al. (Japan)	179	1.10 (0.6-1.8)	NA	-	NA	NA	NA	NA
INMA (Spain)	2199	1.26 (0.8- 1.8)	2199	10.4 (9.5-11.4)	NA	NA	NA	NA
Mosso et al. (Chile)	538	2.06 (1.3-3.0)	538	14.5 (13.2-15.8)	482 (89.6)	56 (10.4)	NA	NA
NFBC (Finland)	5803	1.21 (0.7-1.8)	5747	15.0 (13.7-16.6)	5542 (95.3)	275 (4.7)	5479 (95.2)	278 (4.8)
PIP Study (United Kingdom)	3358	1.30 (0.8-1.9)	3363	14.2 (13.1-15.5)	NA	NA	NA	NA
Popova et al. (Russia)	454	1.35 (0.7-2.1)	447	14.8 (13.4-16.4)	399 (89.3)	48 (10.7)	NA	NA
Rhea (Greece)	856	1.10 (0.7-1.6)	855	15.1 (14.0-16.7)	777 (90.8)	79 (9.2)	810 (94.6)	46 (5.4)
VIVA (United States)	732	1.20 (0.7-1.9)	741	2.1 (1. 9-2.3)**	639 (86.2)	102 (13.8)	NA	NA
Western Australia	2393	0.79 (0.5-1.2)	2393	13.0 (12.0-15.0)	2142 (89.5)	251 (10.5)	2089 (87.3)	304 (12.7)

Values are median (IQR) or n (valid %). NA: not available.

ABCD: Amsterdam Born Children and their Development; ALSPAC: Avon Longitudinal Study of Parents and Children; EFSOCH: The Exeter Family Study of Childhood Health; HAPPY: Holistic Approach to Pregnancy and the first Postpartum Year; INMA: Infancia y Medio Ambiente; NFBC: Northern Finland Birth Cohort; PIP Study: The Proteomics In Pre-eclampsia.

*According to cohort-specific assay manufacturer cut-offs.

** Values are FT4 index, calculated from the total T4 and T3 uptake values (reference range, 1.0-4.0; doi: 10.4158/EP.14.1.33).

Supplemental Table 1C. Description of euthyroidism and thyroid function test abnormalities per cohort.

Cohort (country)	N	Euthyroid, N (%)	Subclinical hypothyroidism, N (%)	Subclinical hyperthyroidism, N (%)	Hyperthyroidism, N (%)	Hypothyroxinemia, N (%)	Hypothyroidism, N (%)
ABCD (Netherlands)	3998	3662 (91.1)	131 (3.24)	56 (1.38)	45 (1.11)	83 (2.05)	21 (0.52)
ALSPAC (United Kingdom)	4803	4376 (86.3)	184 (3.80)	68 (1.41)	41 (0.86)	102 (2.1)	32 (0.67)
Bliddal et al. (Denmark)	854	791 (92.0)	21 (2.8)	10 (1.2)	8 (0.9)	21 (2.4)	3 (0.5)
Chen et al. (China)	8587	7966 (92.8)	210 (2.4)	145 (1.7)	60 (0.7)	195 (2.3)	11 (0.1)
EFSOCH (United Kingdom)	954	877 (91.5)	30 (3.1)	18 (1.9)	5 (0.5)	22 (2.3)	2 (0.2)
Generation R (Netherlands)	5554	5093 (85.1)	176 (3.2)	80 (1.4)	54 (1.0)	137 (2.5)	15 (0.3)
Ghafoor et al. (Pakistan)	1803	1690 (93.7)	29 (1.6)	33 (1.8)	9 (0.5)	38 (2.1)	5 (0.3)
GIRONA 1 (Spain)	326	299 (91.7)	8 (2.4)	7 (2.1)	1 (0.3)	10 (3.1)	1 (0.3)
GIRONA 2 (Spain)	370	370 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HAPPY (Netherlands)	2067	1902 (92.0)	66 (3.2)	27 (1.4)	17 (0.8)	50 (2.4)	5 (0.2)
Hisada et al. (Japan)*	NA	NA	NA	NA	NA	NA	NA
INMA (Spain)*	NA	NA	NA	NA	NA	NA	NA
Mosso et al. (Chile)	538	488 (90.7)	19 (3.3)	4 (0.7)	9 (1.6)	13 (2.3)	5 (1.1)
NFBC (Finland)	5736	5248 (90.1)	188 (3.3)	107 (1.9)	31 (0.5)	128 (2.2)	34 (0.6)
PIP Study (United Kingdom)*	NA	NA	NA	NA	NA	NA	NA
Popova et al. (Russia)	447	412 (90.7)	12 (2.7)	8 (1.8)	3 (0.7)	10 (2.2)	2 (0.4)
Rhea (Greece)	855	791 (92.4)	25 (3.0)	9 (1.0)	11 (1.2)	19 (2.2)	0 (0)
VIVA (United States)	732	674 (91.0)	31 (4.2)	7 (1.0)	7 (1.0)	10 (1.0)	3 (0.4)
Western Australia	2393	2199 (91.9)	92 (3.8)	9 (0.4)	24 (1.0)	56 (2.3)	13 (0.5)
Total	40,018	36,838 (1.7)	1,222 (3.05)	588 (1.46)	325 (0.81)	894 (2.23)	152 (0.37)

Values are n (valid %). NA: not available.

ABCD: Amsterdam Born Children and their Development; ALSPAC: Avon Longitudinal Study of Parents and Children; EFSOCH: The Exeter Family Study of Childhood Health; HAPPY: Holistic Approach to Pregnancy and the first Postpartum Year; INMA: Infancia y Medio Ambiente; NFBC: Northern Finland Birth Cohort; PIP Study: The Proteomics In Pre-eclampsia.

*Cohorts marked as NA did not have data on TPOAb and were not included in the analysis of thyroid function tests abnormalities.

Supplemental Table 1D. Description of pregnancy characteristics per cohort.

Cohort (Country)	N	Birth weight (grams)	Low birth weight, N (%)	Macrosomia, N(%)	Child sex, N (%)*	
					Female	Male
ABCD (Netherlands)	4021	3450 (578)	176 (4.4)	559 (13.9)	2062 (51.3)	1959 (48.7)
ALSPAC (United Kingdom)	5070	3431 (525)	179 (3.5)	621 (12.2)	2457 (48.5)	2613 (51.5)
Bliddal et al. (Denmark)	860	3544 (542)	25 (2.9)	148 (17.2)	NA	NA
Chen et al. (China)	8587	3338 (433)	187 (2.2)	466 (5.4)	NA	NA
EFSOCH (United Kingdom)	958	3453 (522)	34 (3.5)	127 (13.3)	465 (48.5)	493 (51.4)
Generation R (Netherlands)	5986	3416 (563)	297 (5.0)	782 (13.1)	2969 (49.6)	3017 (50.4)
Ghafoor et al. (Pakistan)	1803	2952 (571)	212 (11.8)	20 (1.1)	943 (52.3)	860 (47.7)
GIRONA 1 (Spain)	326	3276 (464)	16 (4.9)	17 (5.2)	149 (45.7)	177 (54.3)
GIRONA 2 (Spain)	370	3296 (481)	15 (4.1)	25 (6.8)	185 (50.0)	185 (50.0)
HAPPY (Netherlands)	2067	3452 (530)	69 (3.3)	278 (13.4)	1050 (50.8)	1017 (49.2)
Hisada et al. (Japan)	179	2975 (362)	12 (6.7)	0 (0)	90 (50.3)	89 (49.7)
INMA (Spain)	2199	3259 (470)	111 (5.0)	106 (4.8)	1058 (48.1)	1141 (51.9)
Mosso et al. (Chile)	538	3355 (513)	28 (5.2)	51 (9.5)	259 (48.1)	279 (51.9)
NFBC (Finland)	5827	3576 (526)	158 (2.7)	1090 (18.7)	2825 (48.5)	3002 (51.5)
PIP Study (United Kingdom)	3364	3421 (556)	166 (4.9)	468 (13.9)	1699 (50.5)	1665 (49.5)
Popova et al. (Russia)	454	3477 (528)	18 (4.0)	55 (12.1)	205 (45.2)	249 (54.8)
Rhea (Greece)	856	3188 (447)	43 (5.0)	32 (3.7)	418 (48.8)	438 (51.2)
VIVA (United States)	741	3519 (556)	26 (3.5)	127 (17.1)	361 (48.7)	380 (51.3)
Western Australia	2393	3408 (523)	95 (4.0)	264 (11.0)	1144 (47.8)	1249 (52.2)

Values are mean (SD) or n (valid %). NA: not available.

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Per definition, the percentage of small or large for gestational age per cohort was 10%.

*For number (%) of missing on child sex see Supplemental Table 1E.

Supplemental Table 1E. Number (%) of missing data of covariates per cohort.

Cohort (country)	N	Maternal age	Gestational age at the time of blood sampling	Parity	Smoking	BMI	Child sex
ABCD (Netherlands)	4021	93 (2.3)	19 (0.5)	0	4 (0.1)	922 (22.9)	1 (0.0)
ALSPAC (United Kingdom)	5070	0	0	0	261 (5.1)	791 (15.6)	0
Bliddal et al. (Denmark)	860	0	0	0	38 (4.4)	41 (4.7)	NA
Chen et al. (China)	8587	20 (0.2)	0	0	0	NA	NA
EFSOCH (United Kingdom)	958	0	0	3 (0.3)	33 (3.4)	5 (0.5)	0
Generation R (Netherlands)	5986	0	20 (0.3)	46 (0.8)	657 (11.0)	34 (0.6)	0
Ghafoor et al. (Pakistan)	1803	4 (0.2)	0	1 (0.1)	NA	NA	6 (0.3)
GIRONA 1 (Spain)	326	6 (1.8)	65 (20.2)	34 (10.4)	113 (34.7)	60 (18.4)	0
GIRONA 2 (Spain)	370	0	2 (0.5)	0	4 (1.1)	2 (0.5)	0
HAPPY (Netherlands)	2067	0	0	37 (1.8)	210 (10.2)	78 (3.7)	3 (0.1)
Hisada et al. (Japan)	179	2 (1.1)	31 (17.1)	1 (0.6)	7 (3.9)	1 (0.6)	1 (0.6)
INMA (Spain)	2199	1 (0.0)	1 (0.0)	2 (0.1)	44 (2.0)	0	0
Mosso et al. (Chile)	538	0	0	0	0	1 (0.2)	5 (0.9)
NFBC (Finland)	5827	0	15 (0.3)	21 (0.4)	93 (1.6)	142 (2.4)	0
PIP Study (United Kingdom)	3364	9 (0.3)	13 (0.4)	4 (0.1)	0	317 (9.4)	12 (0.4)
Popova et al. (Russia)	454	1 (0.2)	0	0	0	0	1 (0.2)
Rhea (Greece)	856	8 (0.9)	0	17 (2.0)	50 (5.8)	43 (6.7)	0
VIVA (United States)	741	3 (0.4)	0	0	2 (0.3)	2 (0.3)	0
Western Australia	2393	0	0	NA	0	NA	0
Total	46,599	147 (0.3%)	166 (0.35%)	2559 (5.5%)	3319 (7.1%)	15222 (32.7%)	9476 (20.3)

Values are n (valid %).

NA: not available (100% missing).

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Supplemental Table 2. Date and place of data collection for the included cohorts.

Cohort	Date	Place
ABCD	between January 2003 and March 2004	Amsterdam, The Netherlands
ALSPAC	between April 1991 and December 1992	former Avon county, UK
Bliddal et al.	throughout 2008	Copenhagen, Denmark
Chen et al.	February 2009 until February 2012	Wenzhou, China
EFSOCH	throughout 2006	Exeter, UK
Generation R	April 2002 until January 2006	Rotterdam, The Netherlands
Ghafoor et al.	July 2000 to July 2002	Lahore, Pakistan
GIRONA 1&2	May 2008 until May 2010	Girona, Catalonia, Spain
HAPPY	throughout 2012	South-East Brabant, The Netherlands
Hisada et al.	2009 to 2011	Tokyo, Japan
INMA	between 2003 and 2008	Valencia, Sabadell (Catalonia), Asturias, and Gipuzkoa (Basque Country), Spain
Mosso et al.	the first half of 2014	Santiago, Chile
NFBC	July 1, 1985, until June 30, 1986	northernmost provinces of Finland
PIP Study	between 2007 and 2010	West of Scotland, UK
Popova et al.	January 2012 to December 2016	St. Petersburg, Russia
Rhea	starting February 2007	Heraklion, Crete, Greece
VIVA	between 1999 and 2002	Eastern Massachusetts, USA
Western Australia	October 2006 until February 2007	Western Australia, Australia

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Supplemental Table 3. Newcastle - Ottawa Quality Assessment Scale per cohort.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES Selection	Generation R	GIRONA 1	GIRONA 2	Chen et al.	Western Australia	Rhea	Mosso et al.	VIVA
1) Representativeness of the exposed cohort								
a) truly representative of the average pregnant woman in the community *	*	*	*	*	*	*	*	*
b) somewhat representative of the average pregnant woman in the community *								
c) selected group of users eg nurses, volunteers								
d) no description of the derivation of the cohort								
2) Selection of the non exposed cohort								
a) drawn from the same community as the exposed cohort *	*	*	*	*	*	*	*	*
b) drawn from a different source								
c) no description of the derivation of the non exposed cohort								
3) Ascertainment of exposure								
a) secure record (laboratory measurement) *	*	*	*	*	*	*	*	*
b) structured interview *								
c) written self report								
d) no description								
4) Demonstration that outcome of interest was not present at start of study								
a) yes *	*	*	*	*	*	*	*	*
b) no								
Comparability								
1) Comparability of cohorts on the basis of the design or analysis								
a) study controls for maternal age *	*	*	*	*	*	*	*	*
b) study controls formaternal smoking *	*	*	*	*	*	*	*	*
Outcome								
1) Assessment of outcome								
a) either independent blind assessment * or (combined with) b) record linkage *	*	*	*	*	*	*	*	*
c) self report								
d) no description								
2) Was follow-up long enough for outcomes to occur								
a) yes (select an adequate follow up period for outcome of interest) *	*	*	*	*	*	*	*	*
b) no								
3) Adequacy of follow up of cohorts								
a) complete follow up - all subjects accounted for *			*		*			*
b) subjects lost to follow up unlikely to introduce bias - small number lost - < 5% or no differential missing *	*	*		*		*	*	
c) follow up rate < 85% with no difference in thyroid function								
d) no statement								
Total Score (Stars out of a max. 9)	9	9	9	9	9	9	9	9

Supplemental Table 3 continued

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES	ABCD	Popova et al.	Hisada et al.	HAPPY	EFSOCH	Ghafoor et al	INMA	Bliddal et al	NFBC	PIP Study	ALSPAC
Selection											
1) Representativeness of the exposed cohort											
a) truly representative of the average pregnant woman in the community *	*	*	*	*	*		*		*	*	*
b) somewhat representative of the average pregnant woman in the community *						*		*			
c) selected group of users eg nurses, volunteers											
d) no description of the derivation of the cohort											
2) Selection of the non exposed cohort											
a) drawn from the same community as the exposed cohort *	*	*	*	*	*	*	*	*	*	*	*
b) drawn from a different source											
c) no description of the derivation of the non exposed cohort											
3) Ascertainment of exposure											
a) secure record (laboratory measurement) *	*	*	*	*	*	*	*	*	*	*	*
b) structured interview *											
c) written self report											
d) no description											
4) Demonstration that outcome of interest was not present at start of study											
a) yes *	*	*	*	*	*	*	*	*	*	*	*
b) no											
Comparability											
1) Comparability of cohorts on the basis of the design or analysis											
a) study controls for maternal age *	*	*	*	*	*	*	*	*	*	*	*
b) study controls formaternal smoking *	*	*	*	*	*	X	*	*	*	*	*
Outcome											
1) Assessment of outcome											
a) either independent blind assessment * or (combined with) b) record linkage *	*	*	*	*	*	*	*	*	*	*	*
c) self report											
d) no description											
2) Was follow-up long enough for outcomes to occur											
a) yes (select an adequate follow up period for outcome of interest) *	*	*	*	*	*	*	*	*	*	*	*
b) no											
3) Adequacy of follow up of cohorts											
a) complete follow up - all subjects accounted for *			*		*						
b) subjects lost to follow up unlikely to introduce bias - small number lost - < 5% or no differential missing *	*	*		*		*	*		*	*	*
c) follow up rate < 85% but no difference in thyroid function tests								X			
d) no statement											
Total Score (Stars out of a max. 9)	9	9	9	9	9	8	9	8	9	9	9

Supplemental Table 4. Cohort-specific cut-offs of TSH and FT4 for defining thyroid function test abnormalities.

	TSH (mU/L)		FT4 (pmol/L)	
Cohort	**2.5th percentile**	**97.5th percentile**	**2.5th percentile**	**97.5th percentile**
ABCD	0.12	3.09	7.19	12.6
ALSPAC	0.08	2.59	12.4	22.4
Bliddal et al.	0.10	3.69	11.4	19.2
Chen et al.	0.37	5.37	6.19	13.2
EFSOCH	0.63	4.46	9.35	15.7
Generation R	0.03	4.04	10.4	22.0
Ghafoor et al.	0.48	3.00	11.4	23.2
GIRONA 1	0.43	4.26	9.00	15.1
GIRONA 2	0.58	4.62	9.45	15.8
HAPPY	0.23	4.00	11.5	18.0
Hisada et al.	NA	NA	NA	NA
INMA	NA	NA	NA	NA
Mosso et al.	0.10	6.00	11.0	19.0
NFBC	0.09	3.82	11.5	22.6
PIP Study	NA	NA	NA	NA
Popova et al.	0.07	4.06	11.7	20.2
RHEA	0.11	3.21	11.2	20.1
VIVA	0.06	3.66	1.5*	3.0*
Western Australia	0.02	2.25	11.0	18.0

Lower and upper percentiles of TSH and FT4 were defined after exclusion of TPOAb positive participants. Cohorts marked as NA did not have data on TPOAb and were not included in the analysis of defining thyroid function tests abnormalities.

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* Values are FT4 index, calculated from the total T4 and T3 uptake values (reference range, 1.0-4.0; doi: 10.4158/EP.14.1.33).

Supplemental Table 5. Comparison of TSH, FT4, T3 and T4 concentrations or TPOAb positivity between women with or without data on birth weight.

	N	BW available	N	BW missing	P value
TSH (SD)	45,978	0.0 (0.004)	339	-0.01 (0.05)	0.82
FT4 (SD)	45,848	-0.001 (0.004)	344	-0.01 (0.05)	0.79
		BW available	**N**	**BW missing**	**P value**
TPOAb positivity, N (%)		2991 (7.4)	317	40 (12.6)	<0.0001

Data are mean (standard error of mean) or N (percentage), as appropriate. BW; birth weight. P values are calculated using Student's t-test or Mann-Whitney U test.

Supplemental Table 6. Association of thyroid antibodies with birth weight.

	Small for Gestational Age			Large for Gestational Age			Birth weight (grams)	
	N of events/ Total (%)	OR (95% CI)	*P* value	N of events/ Total (%)	OR (95% CI)	*P* value	Beta (95% CI)	P value
TPOAb negative	3711/37169 (10.0)	Ref	Ref	3677/37169 (9.9)	Ref	Ref	Ref	Ref
TPOAb Positivity	266/2991 (8.9)	0.92 (0.81 to 1.05)	0.25	299/2991 (10.0)	0.95 (0.84 to 1.08)	0.46	3.0 (-13 to 19)	0.71
TgAb negative	1737/17292 (10.0)	Ref	Ref	1699/17292 (9.8)	Ref	Ref	Ref	Ref
TgAb positivity	85/1063 (8.0)	0.82 (0.65 to 1.03)	0.10	117/1063 (11.0)	1.07 (0.88 to 1.31)	0.46	21.8 (-4.1 to 47)	0.099

Table shows the association of thyroid antibodies with small for gestational age (SGA), large for gestational age (LGA) and continuous birth weight (grams). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex and gestational age at birth.

Supplemental Table 7A. P values for the interaction terms of thyroid function test abnormalities as well as thyroid function tests with relevant variables in association with main birth weight.

	Subclinical hypothyroidism	**Subclinical hyperthyroidism**	**Overt hyperthyroidism**	**Isolated hypothyroxinemia**	**TSH**	**FT4**	**TPOAb**
Gestational age*	**0.054**	0.81	0.95	0.21	0.41	**0.0004**	0.35
Fetal sex	0.76	0.96	0.50	0.32	0.17	0.23	0.93
Maternal age	0.25	0.33	0.82	0.24	0.16	**0.051**	0.63
BMI	0.83	0.74	0.64	0.25	0.57	**0.002**	0.86
Smoking	0.24	0.31	0.88	0.24	0.36	0.30	0.12

Table shows P values for product interaction terms of thyroid function test abnormalities as well as thyroid function tests with gestational age at the time of sampling, fetal sex, maternal age, maternal BMI and smoking status in association with birth weight (grams) in multivariable regression models adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex and gestational age at birth. For *P* values<0.15 stratified analysis was performed.

* Denotes gestational age at the time of maternal blood sampling.

Supplemental Table 7B. Association of FT4, subclinical hypothyroidism or isolated hypothyroxinemia with birth weight outcomes according to trimesters of pregnancy.

	1st trimester N=14,971	**2nd trimester N=23,082**	**3rd trimester N=7,795**	
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	*P* for interaction
FT4 (Z-score)	-12.3 (-19 to -5.0)	-22.0 (-27 to -16)	-35.8 (-46 to -26)	0.0004
	1st trimester **N*=437**	2nd trimester **N*=522**	3rd trimester **N*=263**	
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	*P* for interaction
Subclinical hypothyroidism	-15.5 (-56 to 25)	-28.2 (-65 to 9.0)	-74.8 (-124 to -25)	0.054

Table shows the association of FT4 Z-scores and subclinical hypothyroidism with birth weight according to trimesters of pregnancy. All analyses are adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex and gestational age at birth. Trimester of pregnancy were defined as <week 12 weeks, weeks 12-25 and >week 25 of pregnancy.
* Versus euthyroid population. N is the number of subclinical hypothyroidism. N of euthyroid participants per trimester is 13015, 16900 and 7224, respectively.

Supplemental Table 7C. Association of FT4 with birth weight according to maternal age.

	Maternal age <30 years N= 25,128	**Maternal age ≥30 years N= 20,748**	
	Beta (95% CI)	Beta (95% CI)	*P* for interaction
FT4 (Z-score)	-23.6 (-29 to -18)	-18.9 (-25 to -13)	0.051

Table shows the association of FT4 Z-scores with birth weight according maternal age. All analyses are adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex and gestational age at birth.

Supplemental Table 7D. Association of FT4 with birth weight according to maternal body mass index (BMI).

	BMI<20 kg/m^2 N=7,340	**20≤BMI<25 kg/m^2 N= 22,691**	**25≤BMI<30 kg/m^2 N= 12,870**	**BMI≥30 kg/m^2 N=2,975**	
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	*P* for interaction
FT4 (Z-score)	-20.1 (-33 to -7.3)	-13.3 (-19 to -7.4)	-28.8 (-36 to -20.1)	-39.8 (-56 to -23)	0.002

Table shows the association of FT4 Z-scores with birth weight according to maternal body mass index (BMI). All analyses are adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex and gestational age at birth.

Supplemental Table 8. Association of TSH, FT4 with birth weight according to TPOAb status.

	Birth weight						
	TPOAb negative			TPOAb positive			
	N	Beta (95% CI)	*P* value	N	Beta (95% CI)	*P* value	*P* for interaction with TPOAb
Z-scores							
TSH	36,627	-4.2 (-8.8 to 0.4)	0.072	2944	-16.1 (-31 to -0.66)	0.041	0.144
FT4	36,678	-21.8 (-26 to -17)	<0.0001	2957	-10.5 (-25 to 4.2)	0.16	0.087

Table shows the association of maternal TSH, FT4 and T3 (Z-scores) with continuous birth weight (grams) according to TPOAb status. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex and gestational age at birth.

Supplemental Table 9. Association of thyroid function test abnormalities as well as TSH, FT4 and T4 concentrations with very small for gestational age, low birth weight or macrosomia.

	LBW			Macrosomia		
	N of events/total(%)	OR (95% CI)	*P* value	N of events*(%)	OR (95% CI)	*P* value
Thyroid function test abnormalities						
Euthyroid	1398/36838 (3.8)	Ref	Ref	4140 (11.2)	Ref	Ref
Subclinical Hypothyroidism	71/1221 (5.8)	1.70 (1.23 to 2.34)	0.001	145 (11.9)	0.96 (0.80 to 1.16)	0.70
Subclinical Hyperthyroidism	27/588 (4.6)	1.02 (0.60 to 1.73)	0.91	73 (12.4)	1.15 (0.89 to 1.51)	0.27
Overt hyperthyroidism	14/325 (4.3)	1.22 (0.62 to 2.39)	0.55	30 (9.2)	0.90 (0.60 to 1.34)	0.61
Isolated hypothyroxinemia	36/894 (4)	0.67 (0.41 to 1.09)	0.11	110 (12.3)	1.06 (0.85 to 1.32)	0.56
Z-scores						
TSH	1847/45978 (4)	1.07 (1.00 to 1.14)	0.031	5134 (11.2)	0.96 (0.93 to 0.99)	0.038
FT4	1838/45848 (4)	1.14 (1.07 to 1.21)	<0.0001	5137 (11.2)	0.93 (0.90 to 0.96)	<0.001
TPOAb negative	1379/37169 (3.7)	Ref	Ref	4241 (11.4)	Ref	Ref
TPOAb Positivity	170/2991 (5.7)	1.31 (1.03 to 1.65)	0.022	358 (12)	1.02 (0.90 to 1.15)	0.69
TgAb negative	479/17292 (2.8)	Ref	Ref	1867 (10.8)	Ref	Ref
TgAb positivity	23/1063 (2.2)	0.78 (0.47 to 1.30)	0.35	117 (11)	0.97 (0.78 to 1.19)	0.78

Table shows the association of maternal thyroid function test abnormalities with very small for gestational age (vSGA), low birth weight (LBW) or macrosomia. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling, fetal sex and gestational age at birth (for LBW and macrosomia).

*Total N is the same as stated in the 2nd column.

Supplemental Table 10. Association of thyroid function test abnormalities as well as TSH and FT4 concentrations with small for gestational age according to adjustment with gestational diabetes mellitus (GDM).

	Small for Gestational Age					
			Not adjusted with GDM*		+ GDM*	
	N	GDM cases (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Thyroid function test abnormalities						
Euthyroid	33776	861 (2.5)	Ref	Ref	Ref	Ref
Subclinical Hypothyroidism	1152	21 (1.8)	1.21 (1.01 to 1.45)	0.029	1.21 (1.01 to 1.45)	0.031
Subclinical Hyperthyroidism	537	14 (2.6)	0.88 (0.65 to 1.18)	0.41	0.88 (0.65 to 1.18)	0.40
Overt hyperthyroidism	303	9 (3.0)	1.05 (0.73 to 1.51)	0.77	1.05 (0.73 to 1.52)	0.76
Isolated hypothyroxinemia	821	36 (4.4)	0.73 (0.56 to 0.95)	0.018	0.73 (0.57 to 0.95)	0.021
Continuous						
TSH	42,469	1057 (2.5)	1.03 (1.00 to 1.07)	0.027	1.03 (1.00 to 1.07)	0.029
FT4	42,357	1047 (2.5)	1.09 (1.05 to 1.12)	<0.0001	1.09 (1.05 to 1.12)	<0.0001

Table shows the association of maternal thyroid function test abnormalities as well as continuous TSH and FT4 Z-scores with small for gestational age (SGA) in a subset with available data on gestational diabetes mellitus (GDM). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

* Missing in cohorts: Mosso et al., EFSOCH and Ghafoor et al.

Supplemental Table 11. Association of thyroid function test abnormalities as well as TSH and FT4 concentrations with large for gestational age according to adjustment with gestational diabetes mellitus (GDM).

	Large for Gestational Age					
			Not adjusted with GDM*		+ GDM*	
	N	GDM cases (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Thyroid function test abnormalities						
Euthyroid	33776	861 (2.5)	Ref	Ref	Ref	Ref
Subclinical Hypothyroidism	1152	21 (1.8)	1.04 (0.85 to 1.26)	0.68	1.04 (0.85 to 1.27)	0.65
Subclinical Hyperthyroidism	537	14 (2.6)	0.79 (0.58 to 1.08)	0.14	0.79 (0.58 to 1.08)	0.15
Overt hyperthyroidism	303	9 (3.0)	0.92 (0.63 to 1.37)	0.71	0.93 (0.63 to 1.37)	0.72
Isolated hypothyroxinemia	821	36 (4.4)	1.14 (0.92 to 1.42)	0.20	1.13 (0.91 to 1.40)	0.24
Continuous						
TSH	42,469	1057 (2.5)	0.99 (0.96 to 1.02)	0.72	0.99 (0.96 to 1.02)	0.76
FT4	42,357	1047 (2.5)	0.88 (0.85 to 0.91)	<0.0001	0.88 (0.85 to 0.91)	<0.0001

Table shows the association of maternal thyroid function test abnormalities as well as continuous TSH and FT4 Z-scores with large for gestational age in a subset with available data on gestational diabetes mellitus (GDM). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

* Missing in cohorts: Mosso et al., EFSOCH and Ghafoor et al.

Supplemental Table 12. Association of thyroid function test abnormalities as well as TSH and FT4 concentrations with birth weight according to adjustment with gestational diabetes mellitus (GDM).

			Birth weight (grams)			
			Not adjusted with GDM*		+ GDM*	
	N	GDM cases (%)	Beta (95% CI)	*P* value	Beta (95% CI)	*P* value
Thyroid function test abnormalities						
Euthyroid	33776	861 (2.5)	Ref	Ref	Ref	Ref
Subclinical Hypothyroidism	1152	21 (1.8)	-35.7 (-60 to -11)	0.004	-35.0 (-59 to -10)	0.005
Subclinical Hyperthyroidism	537	14 (2.6)	14.5 (-21 to 51)	0.43	14.8 (-21 to 51)	0.42
Overt hyperthyroidism	303	9 (3.0)	-22.9 (-70 to 24)	0.34	-23.1 (-70 to 24)	0.33
Isolated hypothyroxinemia	821	36 (4.4)	33.9 (4.7 to 63)	0.022	32.0 (2.9 to 61)	0.031
Continuous						
TSH	42469	1057 (2.5)	-6.6 (-10 to -3.5)	0.001	-6.5 (-10 to -2.3)	0.002
FT4	42357	1047 (2.5)	-20.8 (-25 to -17)	<0.0001	-20.5 (-25 to -16)	<0.001

Table shows the association of maternal thyroid function test abnormalities as well as continuous TSH and FT4 Z-scores with birth weight (grams) in a subset with available data on gestational diabetes mellitus (GDM). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling, fetal sex and gestational age at birth.

* Missing in cohorts: Mosso et al., EFSOCH and Ghafoor et al.

Supplemental Table 13. Association of thyroid function test abnormalities as well as TSH and FT4 concentrations with small for gestational age according to adjustment with preeclampsia.

	Small for Gestational Age					
			Not adjusted with Preeclampsia*		+ Preeclampsia*	
	N	GDM cases (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Thyroid function test abnormalities						
Euthyroid	26585	588 (1.6)	Ref	Ref	Ref	Ref
Subclinical Hypothyroidism	866	30 (2.5)	1.31 (1.06 to 1.62)	0.009	1.30 (1.05 to 1.60)	0.013
Subclinical Hyperthyroidism	427	9 (1.5)	0.96 (0.68 to 1.35)	0.81	0.95 (0.67 to 1.34)	0.79
Overt hyperthyroidism	233	6 (1.8)	0.81 (0.50 to 1.33)	0.42	0.81 (0.49 to 1.32)	0.41
Isolated hypothyroxinemia	644	16 (1.8)	0.69 (0.51 to 0.94)	0.022	0.69 (0.51 to 0.94)	0.021
Continuous						
TSH	32,488	721 (1.6)	1.07 (1.03 to 1.11)	0.0004	1.07 (1.03 to 1.11)	0.0005
FT4	32,343	718 (1.6)	1.05 (1.01 to 1.10)	0.003	1.05 (1.01 to 1.10)	0.003

Table shows the association of maternal thyroid function test abnormalities as well as continuous TSH and FT4 Z-scores with small for gestational age (SGA) in a subset with available data on preeclampsia. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

* Missing in cohorts: Mosso et al., HAPPY, EFSOCH, Ghafoor et al., INMA and ALSPAC.

Supplemental Table 14. Association of thyroid function test abnormalities as well as TSH and FT4 concentrations with large for gestational age according to adjustment with preeclampsia.

	Large for Gestational Age					
			Not adjusted with Preeclampsia*		+ Preeclampsia*	
	N	Preeclampsia cases (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Thyroid function test abnormalities						
Euthyroid	26585	588 (1.6)	Ref	Ref	Ref	Ref
Subclinical Hypothyroidism	866	30 (2.5)	0.93 (0.74 to 1.18)	0.57	0.94 (0.74 to 1.18)	0.60
Subclinical Hyperthyroidism	427	9 (1.5)	0.94 (0.68 to 1.31)	0.75	0.95 (0.68 to 1.31)	0.75
Overt hyperthyroidism	233	6 (1.8)	0.76 (0.47 to 1.23)	0.26	0.76 (0.47 to 1.23)	0.27
Isolated hypothyroxinemia	644	16 (1.8)	1.13 (0.88 to 1.45)	0.31	1.13 (0.89 to 1.45)	0.30
Continuous						
TSH	32,488	721 (1.6)	0.98 (0.95 to 1.02)	0.58	0.98 (0.95 to 1.02)	0.58
FT4	32,343	718 (1.6)	0.92 (0.89 to 0.96)	0.0001	0.92 (0.89 to 0.96)	0.0001

Table shows the association of maternal thyroid function test abnormalities as well as continuous TSH and FT4 Z-scores with large for gestational age in a subset with available data on preeclampsia. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

* Missing in cohorts: Mosso et al., HAPPY, EFSOCH, Ghafoor et al., INMA and ALSPAC.

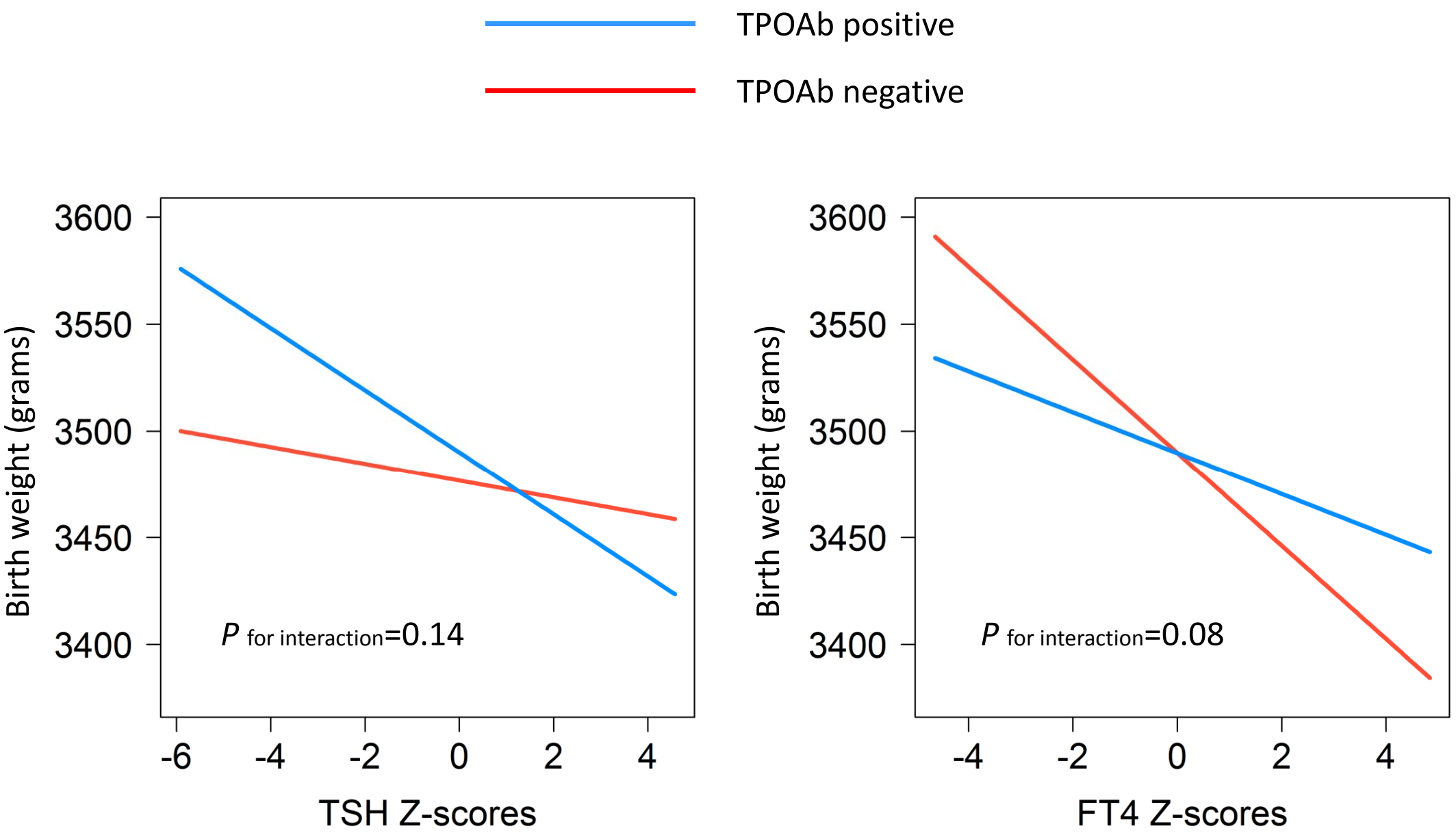
Supplemental Table 15. Association of thyroid function test abnormalities as well as TSH and FT4 concentrations with birth weight according to adjustment with preeclampsia.

	Birth weight (grams)					
			Not adjusted with Preeclampsia*		+ Preeclampsia*	
	N	Preeclampsia cases (%)	Beta (95% CI)	*P* value	Beta (95% CI)	*P* value
Thyroid function test abnormalities						
Euthyroid	26585	588 (1.6)	Ref	Ref	Ref	Ref
Overt hypothyroidism	100	2 (1.3)	60.0 (-21 to 142)	0.15	58.8 (-23 to 140)	0.15
Subclinical Hypothyroidism	866	30 (2.5)	-44.7 (-73 to -16)	0.002	-43.1 (-71 to -14)	0.002
Subclinical Hyperthyroidism	427	9 (1.5)	5.45 (-34 to 45)	0.79	5.79 (-34 to 45)	0.77
Overt hyperthyroidism	233	6 (1.8)	-24.9 (-79 to 29)	0.36	-24.1 (-78 to 29)	0.38
Isolated hypothyroxinemia	644	16 (1.8)	45.4 (12 to 78)	0.007	45.1 (12 to 78)	0.007
Continuous						
TSH	32,488	721 (1.6)	-6.7 (-11 to -1.9)	0.006	-6.7 (-11 to -1.9)	0.006
FT4	32,343	718 (1.6)	-20.9 (-25 to -16)	0.0009	-20.7 (-25 to -15)	0.0008

Table shows the association of maternal thyroid function test abnormalities as well as continuous TSH and FT4 Z-scores with birth weight (grams) in a subset with available data on preeclampsia. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling, fetal sex and gestational age at birth.

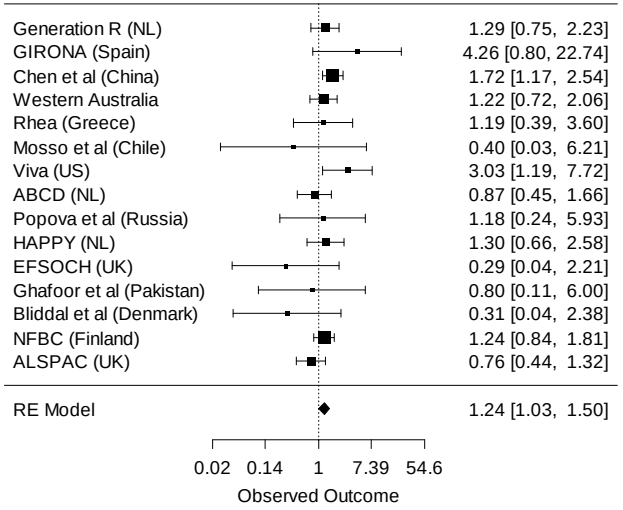
* Missing in cohorts: Mosso et al., HAPPY, EFSOCH, Ghafoor et al., INMA and ALSPAC.

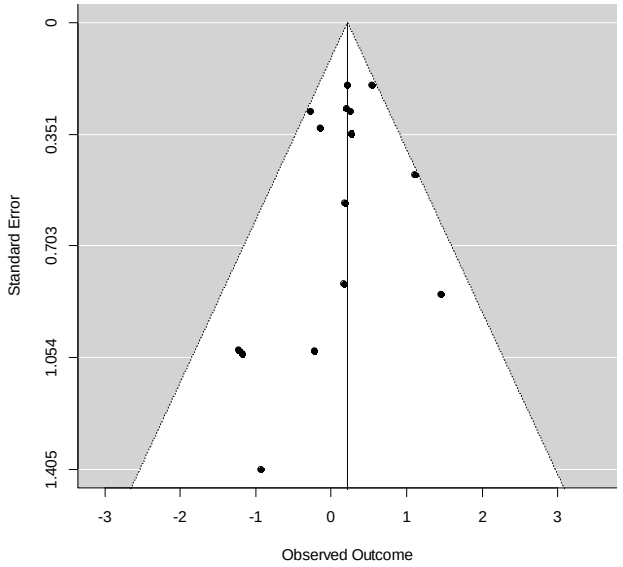
Supplemental Figure 1. Association of TSH or FT4 with birth weight according to TPOAb status.



Supplemental Figure 2. Two-step meta-analyses and funnel plots for the association of subclinical hypothyroidism with SGA, LGA or BW.

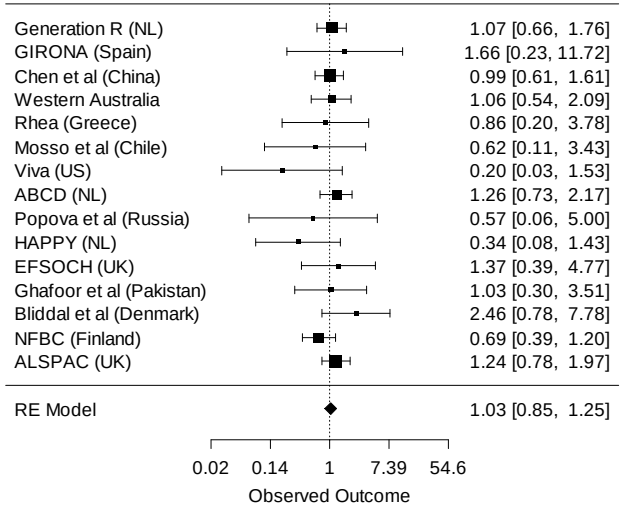
SGA

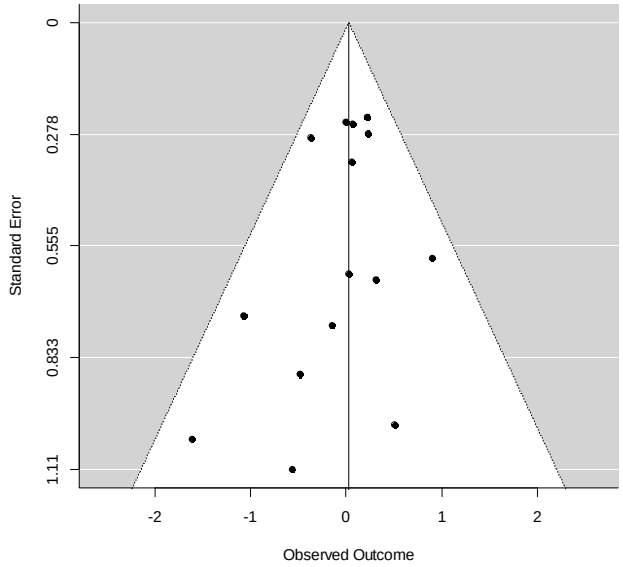




test for funnel plot asymmetry:
z = -1.0537, p = 0.2920
I^2(%)=6.78 (0.0-82.5)
H^2=1.07 (1.0-5.72)

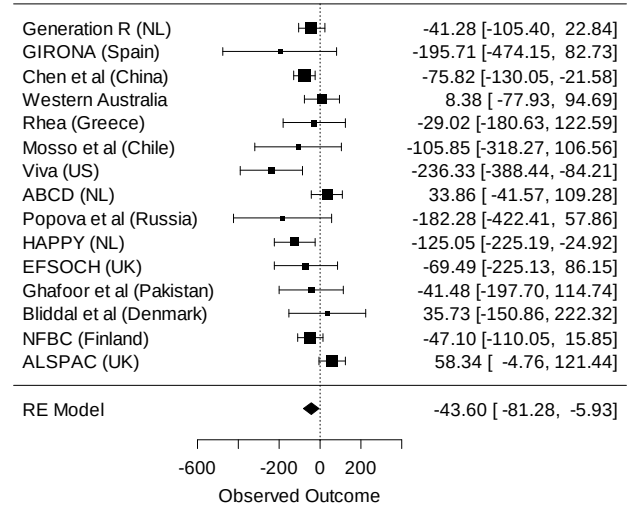
LGA

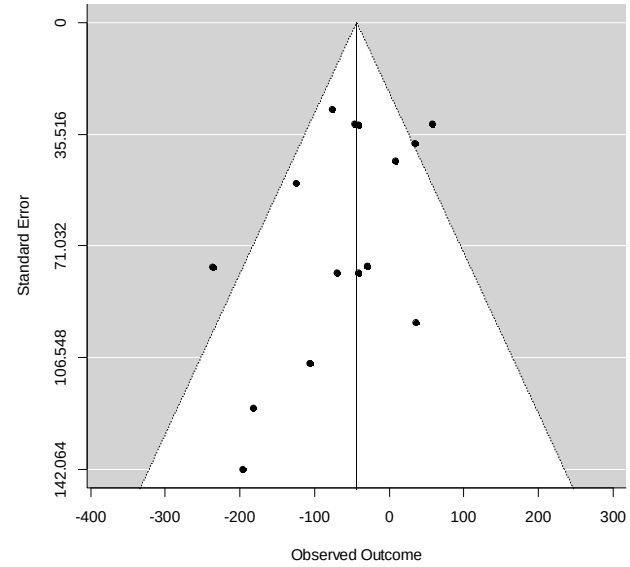




test for funnel plot asymmetry:
z = -0.9774, p = 0.3284
I^2(%)=0.0 (0.0-68.2)
H^2=1.0 (1.0-3.14)

BW

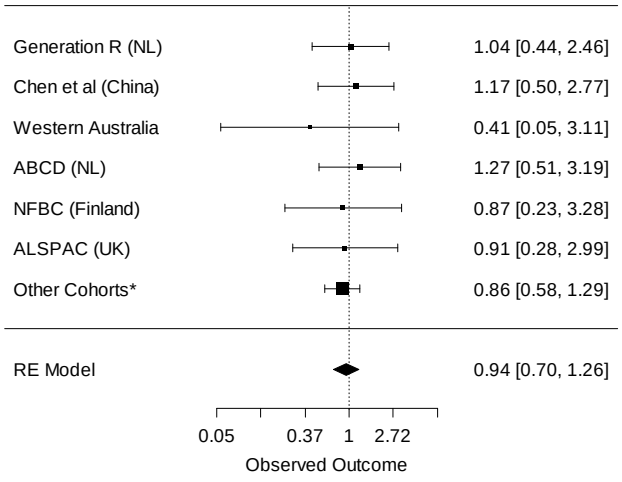




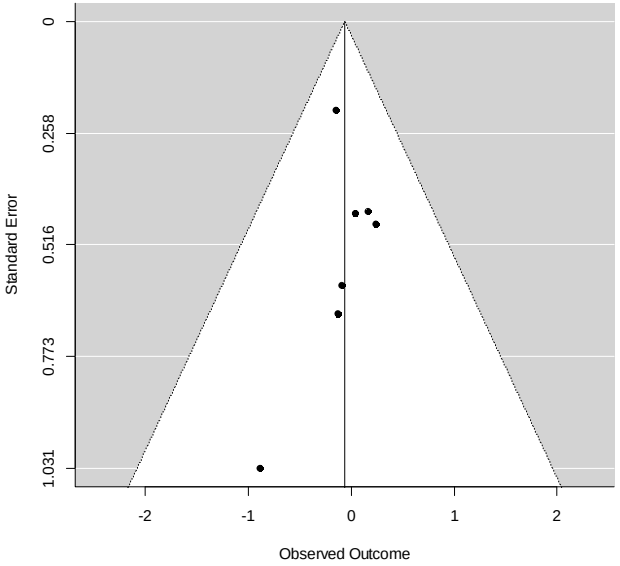
test for funnel plot asymmetry:
z = -1.8034, p = 0.0713
I^2(%)=48.4 (7.0-84.2)
H^2=1.93 (1.07-6.33)

Supplemental Figure 3. Two-step meta-analyses and funnel plots for the association of overt hyperthyroidism with SGA, LGA or BW.

SGA

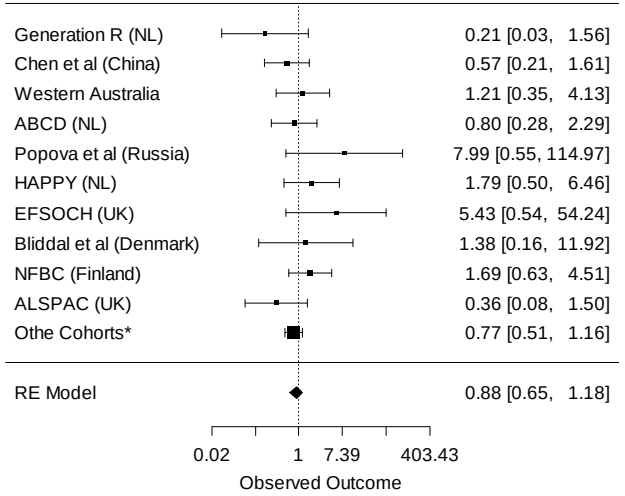


*The following cohorts were pooled as one due to complete or quasi-complete separation: GIRONA, Rhea, Mosso et al, Viva, Popova et al, HAPPY, EFSOCH, Ghafoor et al and Bliddal et al.

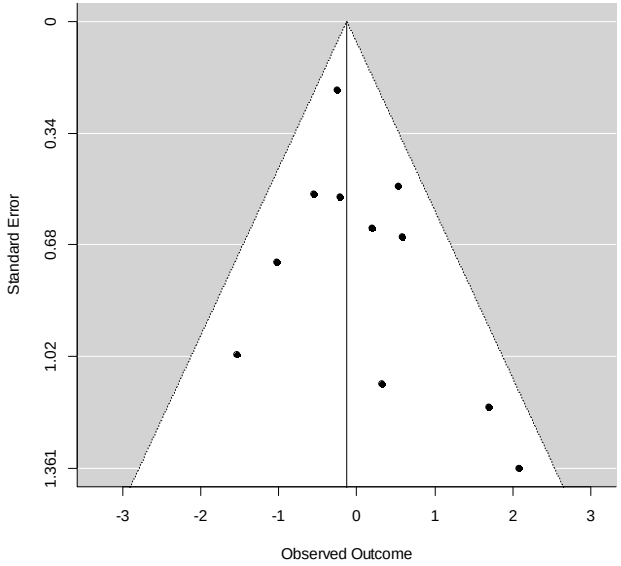


test for funnel plot asymmetry:
z = 0.0023, p = 0.9982
I^2(%)=0.0 (0.0-23.25)
H^2=1.0 (1.0-1.30)

LGA

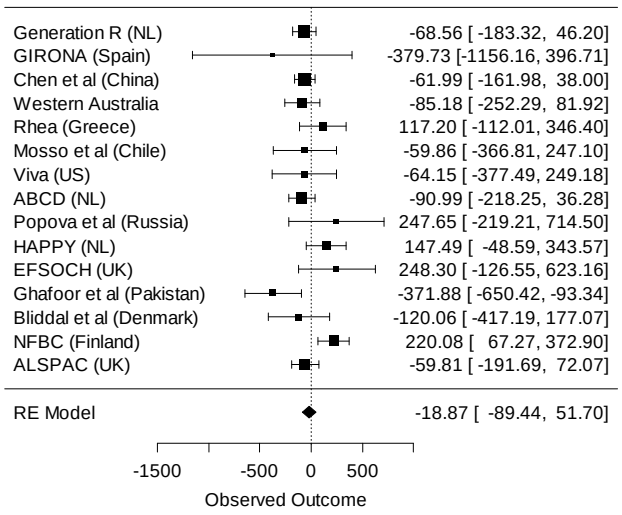


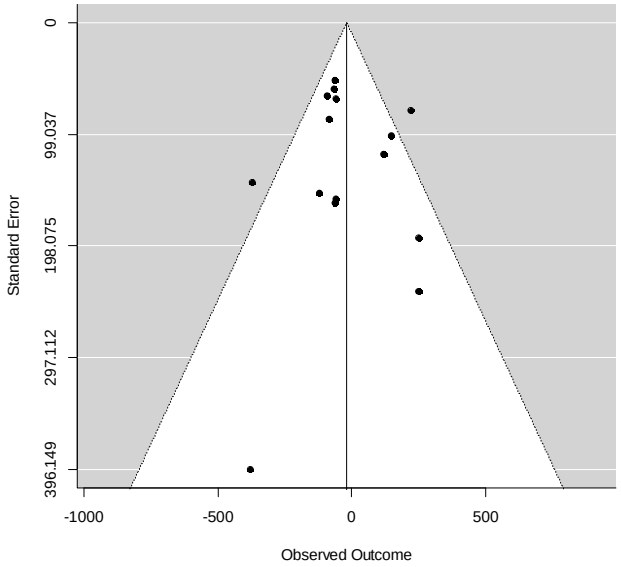
*The following cohorts were pooled as one due to complete or quasi-complete separation: GIRONA, Rhea, Mosso et al, Viva and Ghafoor et al..



test for funnel plot asymmetry:
z = 1.2463, p = 0.2126
I^2(%)=0.0 (0.0-87.9)
H^2=1.0 (1.0-8.3)

BW

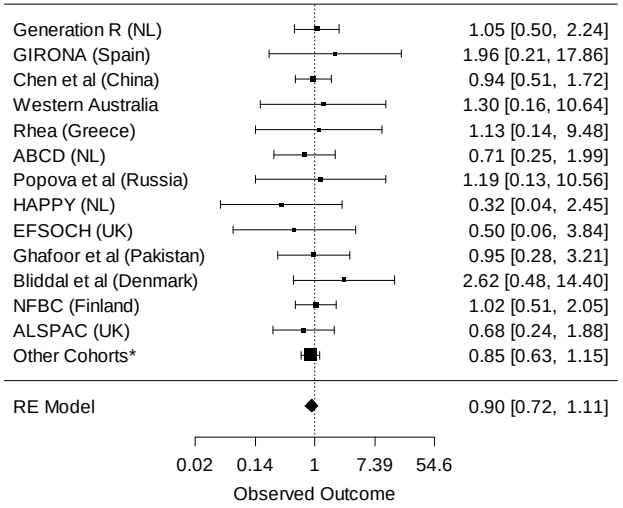




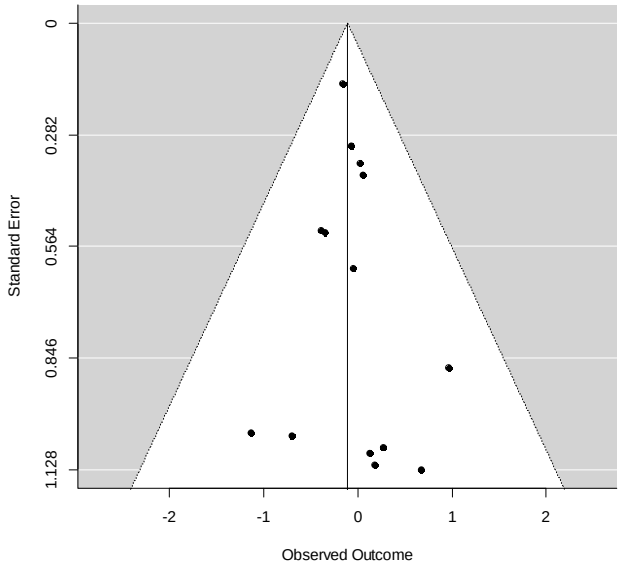
test for funnel plot asymmetry:
z = 0.0877, p = 0.9301
I^2(%)=46.8 (6.35-86.7)
H^2=1.88 (1.06-7.53)

Supplemental Figure 4. Two-step meta-analyses and funnel plots for the association of subclinical hyperthyroidism with SGA, LGA or BW.

SGA

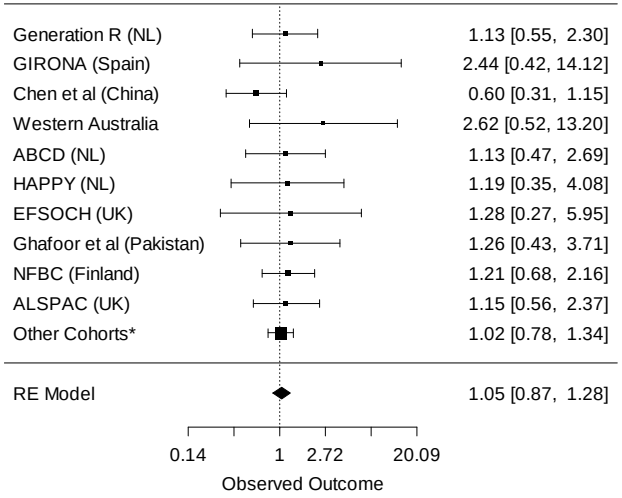


*The following cohorts were pooled as one due to complete or quasi-complete separation: Mosso et al and Viva.

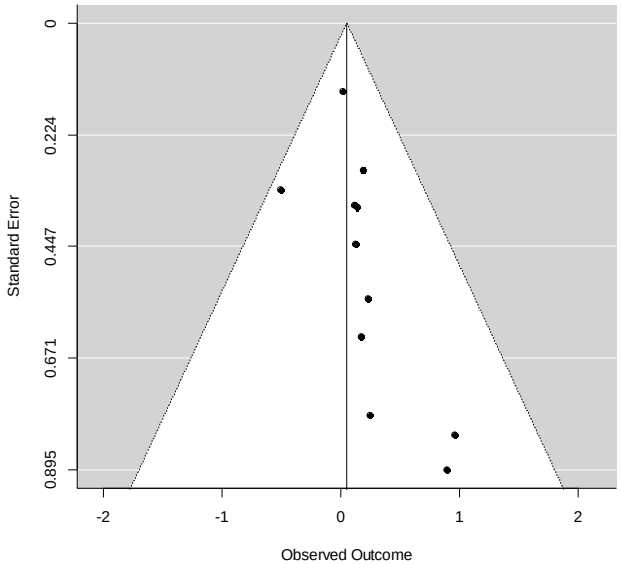


test for funnel plot asymmetry:
z = 0.4046, p = 0.6858
I^2(%)=0.0 (0.0-0.0)
H^2=1.0 (1.0-1.0)

LGA

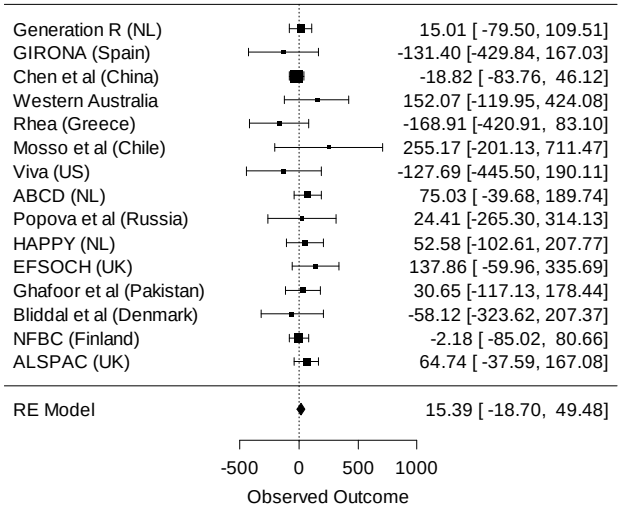


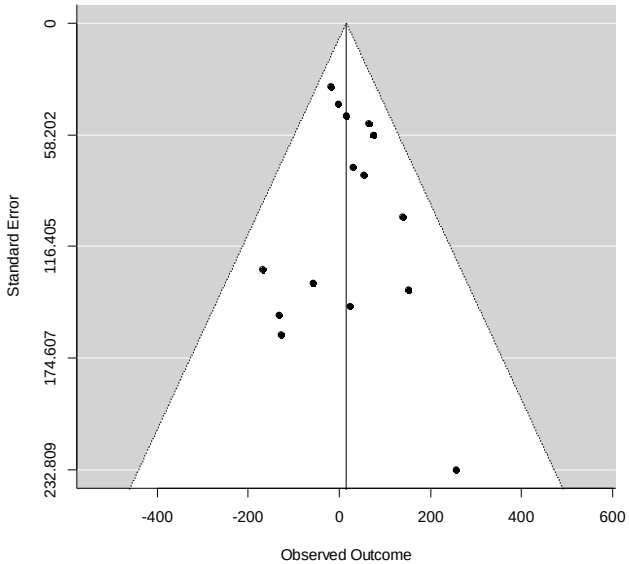
*The following cohorts were pooled as one due to complete or quasi-complete separation: Rhea, Mosso et al, Viva, Popova et al and Bliddal et al.



test for funnel plot asymmetry:
z = 1.0821, p = 0.2792
I^2(%)=0.0 (0.0-49.9)
H^2=1.0 (1.00-1.99)

BW

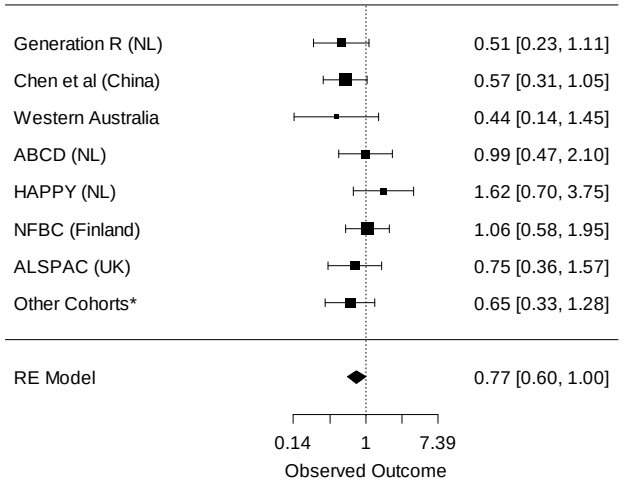




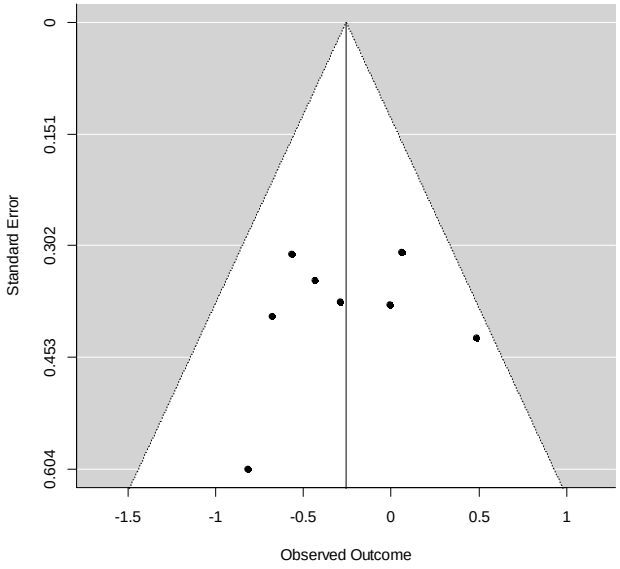
test for funnel plot asymmetry:
z = 0.3338, p = 0.7385
I^2(%)=0.0 (0.0-1.96)
H^2=1.0 (1.0-1.02)

Supplemental Figure 5. Two-step meta-analyses and funnel plots for the association of hypothyroxinemia with SGA, LGA or BW.

SGA

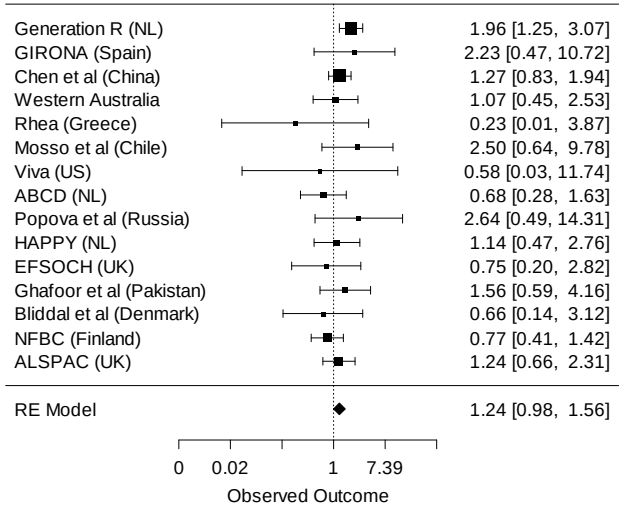


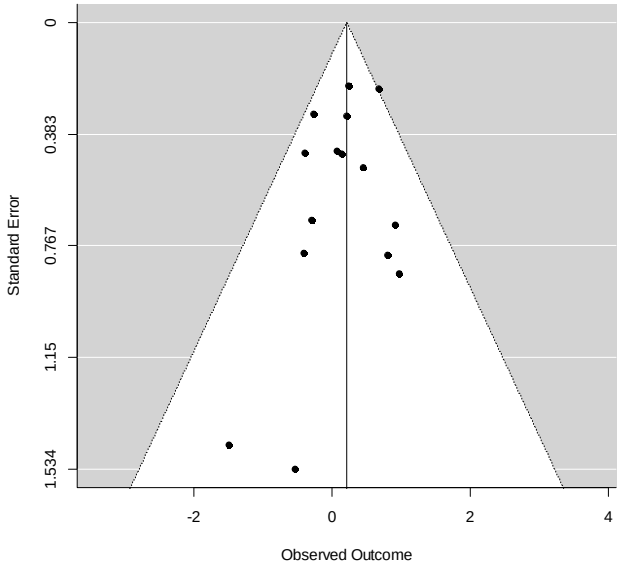
*The following cohorts were pooled as one due to complete or quasi-complete separation: GIRONA, Rhea, Mosso et al, Viva, Popova et al, EFSOCH, Ghafoor et al and Bliddal et al.



test for funnel plot asymmetry:
z = -0.3338, p = 0.7385
I^2(%)=0.0 (0.0-80.5)
H^2=1.0 (1.0-5.13)

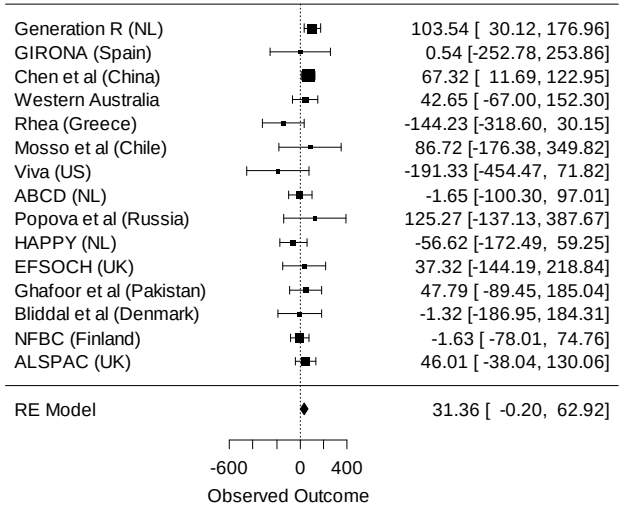
LGA

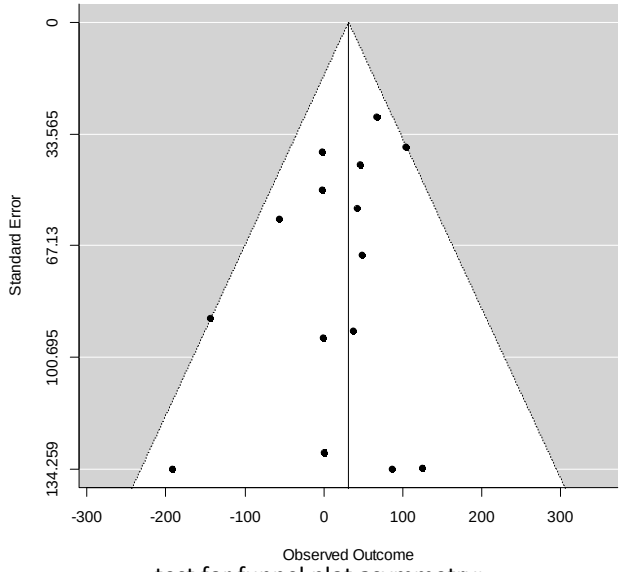




test for funnel plot asymmetry:
z = -0.9477, p = 0.3433
I^2(%)=9.62 (0.0-63.0)
H^2=1.10 (1.0-2.70)

BW

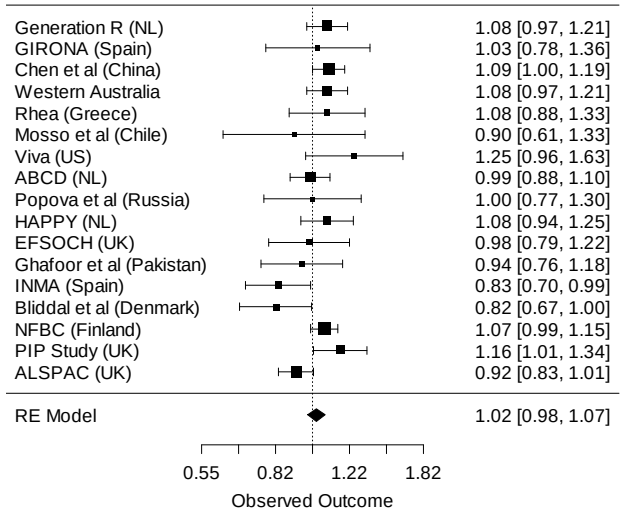


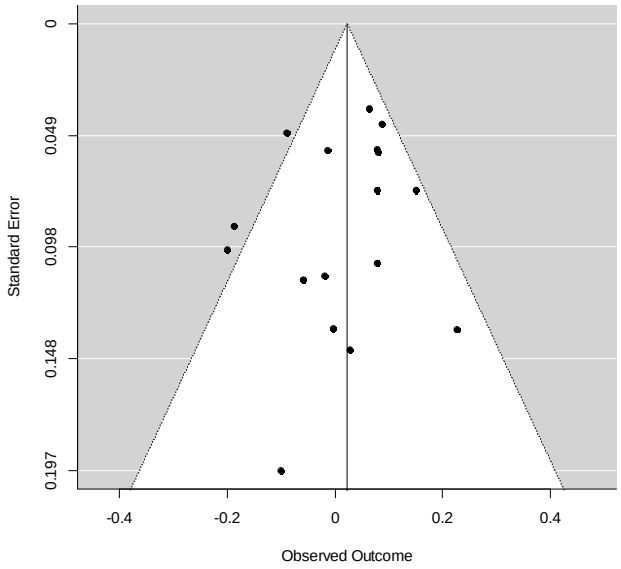


test for funnel plot asymmetry:
z = -1.7285, p = 0.0839
I^2(%)=14.1 (0.0-62.1)
H^2=1.16 (1.0-2.64)

Supplemental Figure 6. Two-step meta-analyses and funnel plots for the association of TSH with SGA, LGA or BW.

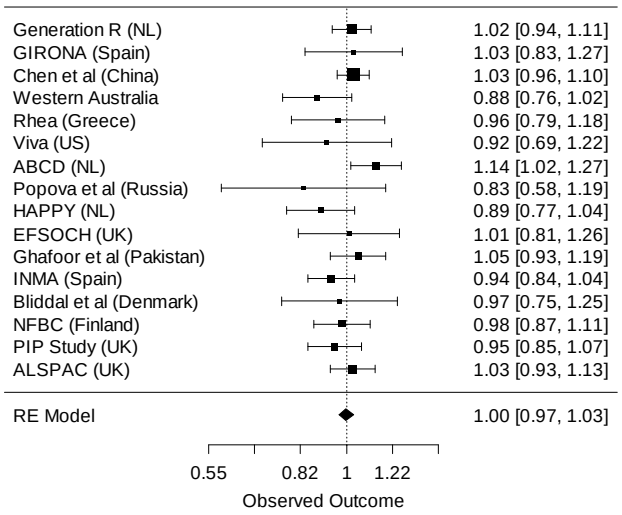
SGA

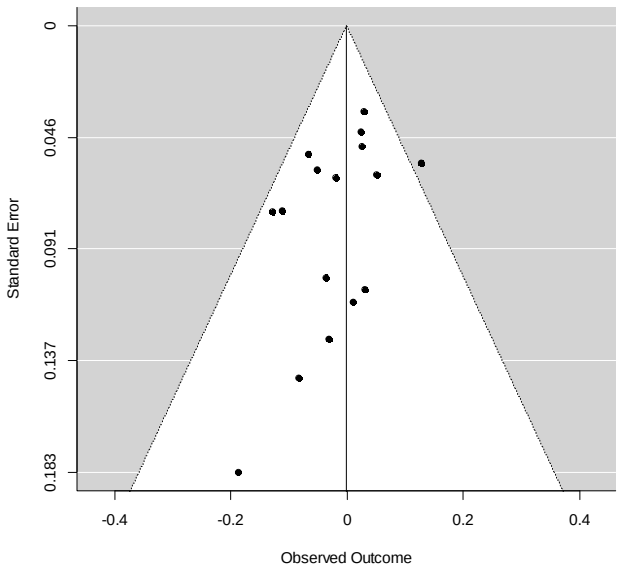




test for funnel plot asymmetry:
z = -0.8105, p = 0.4177
I^2(%)=41.7 (0.0-80.0)
H^2=1.71 (1.0-5.02)

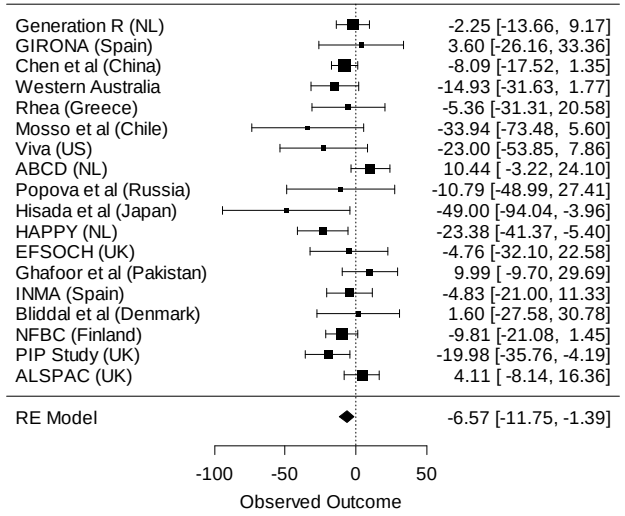
LGA

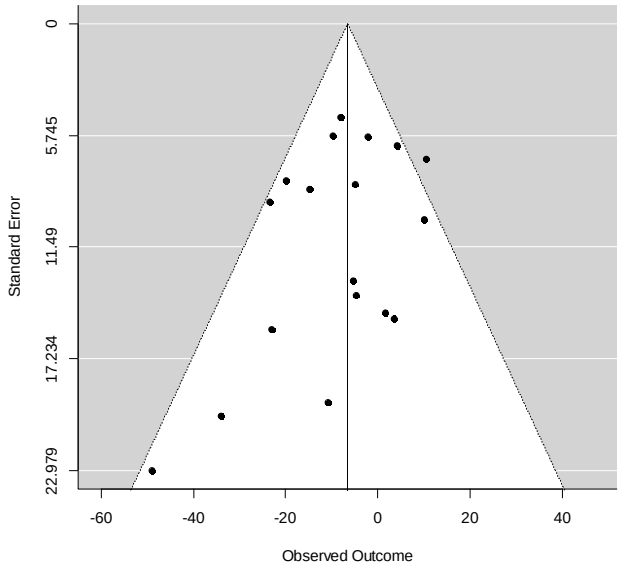




test for funnel plot asymmetry:
z = -1.6860, p = 0.0918
I^2(%)=8.02 (0.0-61.9)
H^2=1.08 (1.0-2.63)

BW

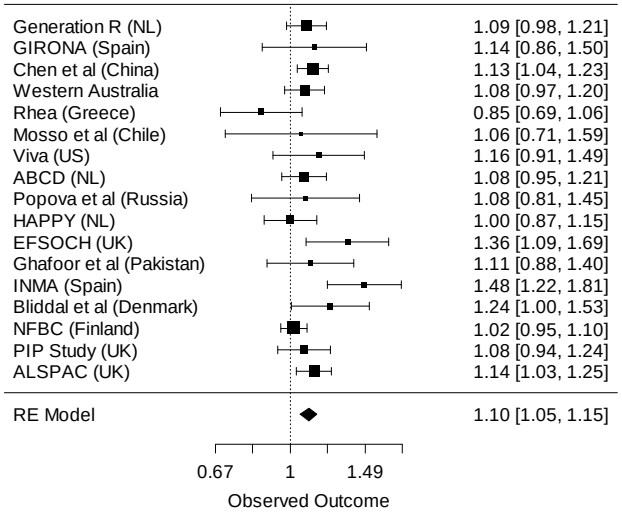


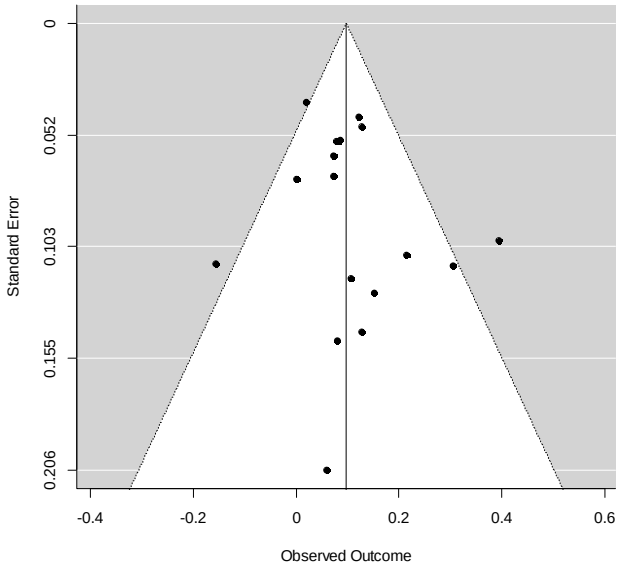


test for funnel plot asymmetry:
z = -1.4895, p = 0.1364
I^2(%)= 31.5 (0.00-78.9)
H^2=1.46 (1.0- 4.74)

Supplemental Figure 7. Two-step meta-analyses and funnel plots for the association of FT4 with SGA, LGA or BW.

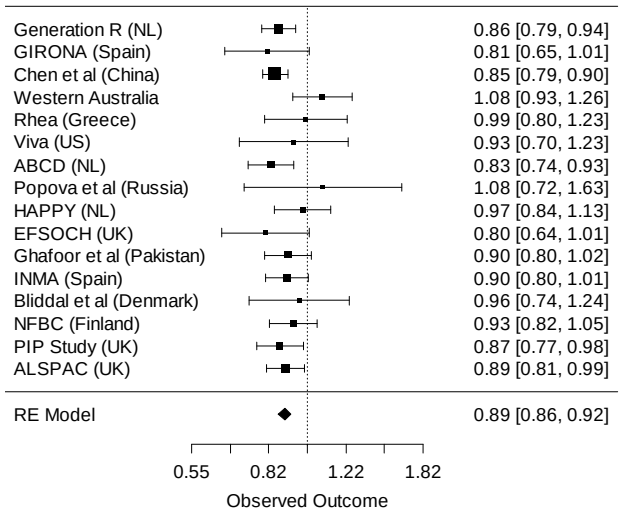
SGA

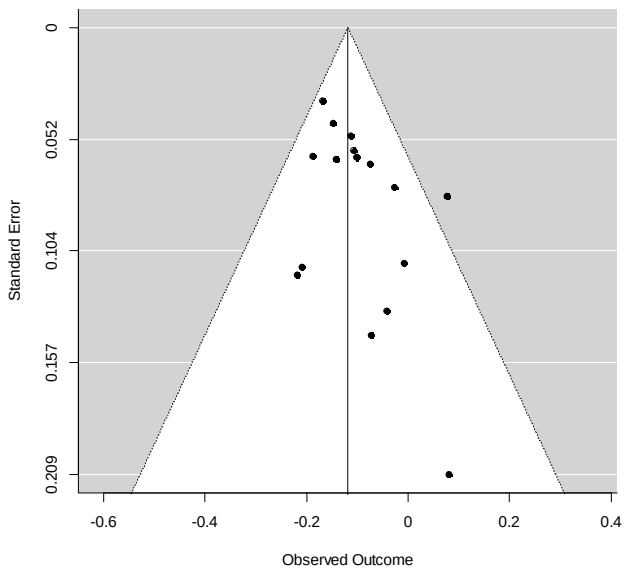




test for funnel plot asymmetry:
z = 0.9637, p = 0.3352
I^2(%)=38.9 (0.0-82.4)
H^2=1.63 (1.0-5.69)

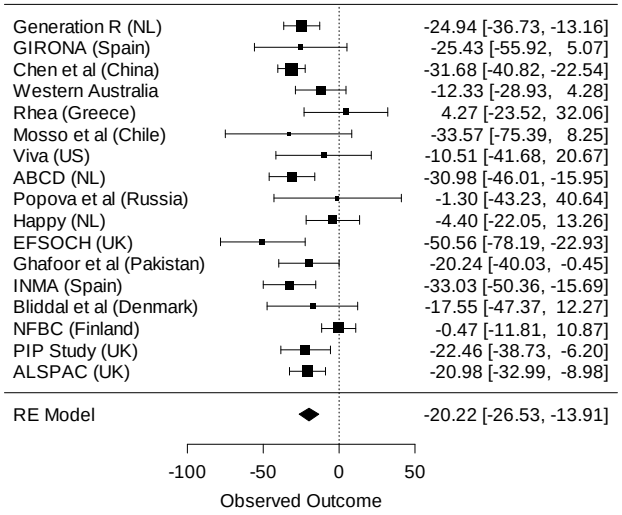
LGA

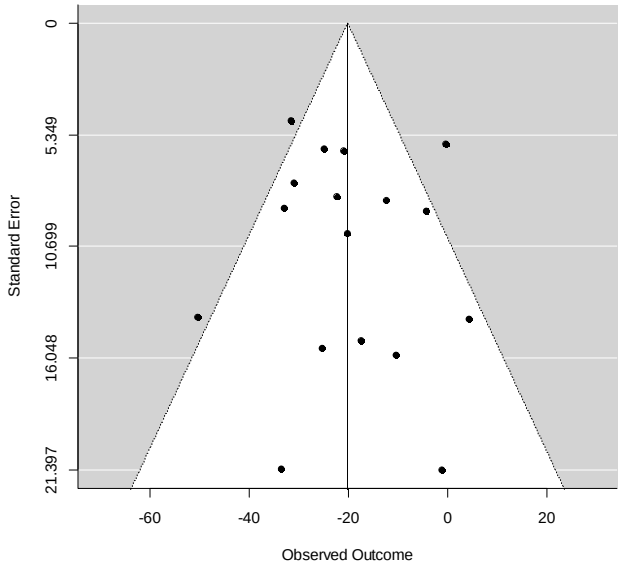




test for funnel plot asymmetry:
z = 1.8542, p = 0.0637
I^2(%)=6.48 (0.0-67.0)
H^2=1.06 (1.0-3.03)

BW

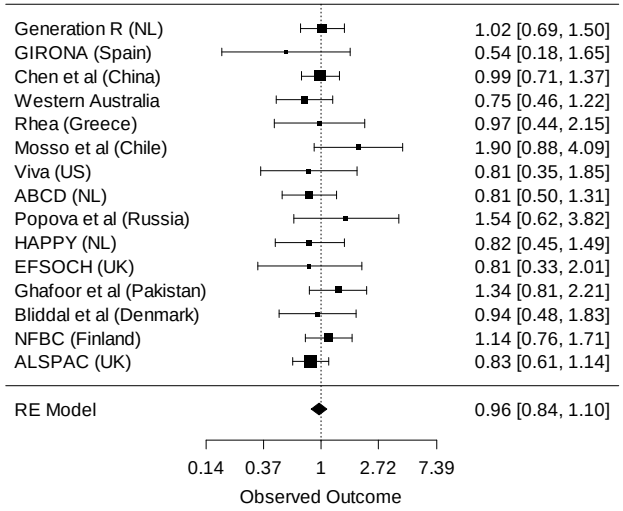


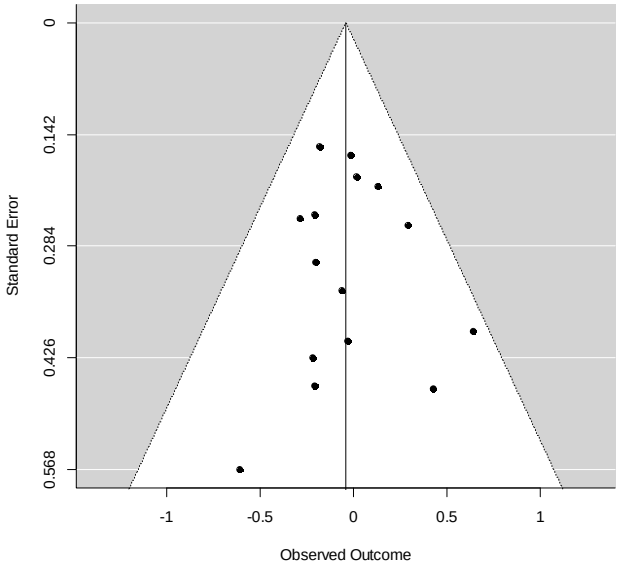


test for funnel plot asymmetry:
z = 0.2746, p = 0.7836
I^2(%)=50.6 (13.4-81.0)
H^2=2.02 (1.15-5.26)

Supplemental Figure 8. Two-step meta-analyses and funnel plots for the association of TPOAb positivity with SGA, LGA or BW.

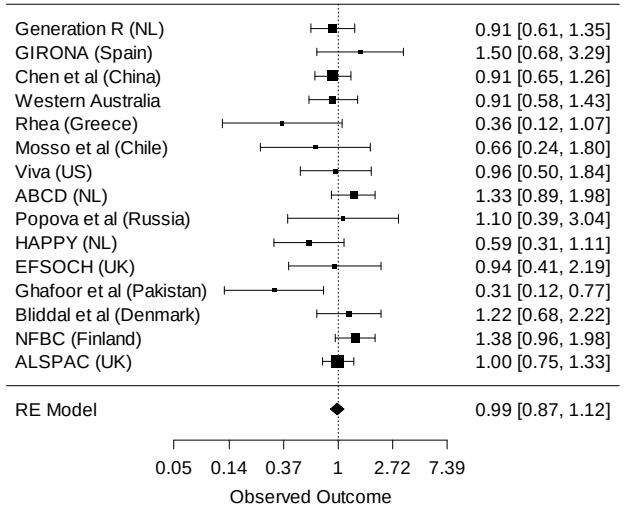
SGA

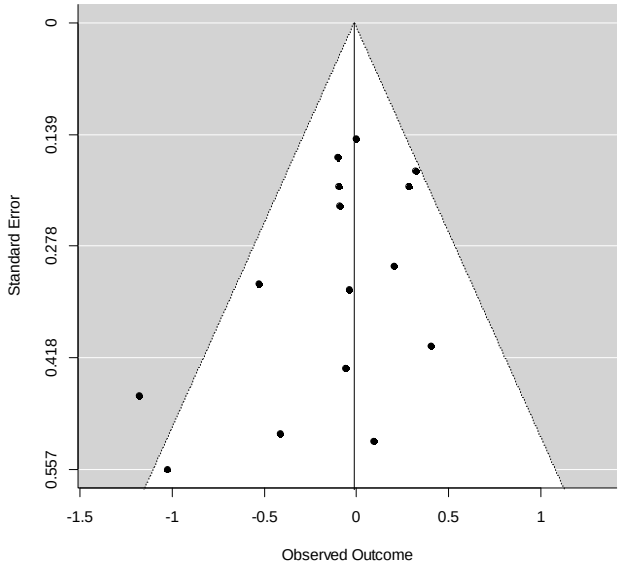




test for funnel plot asymmetry:
z = 0.2613, p = 0.7939
I^2(%) =0.0 (0.0-54.1)
H^2=1.0 (1.0-2.18)

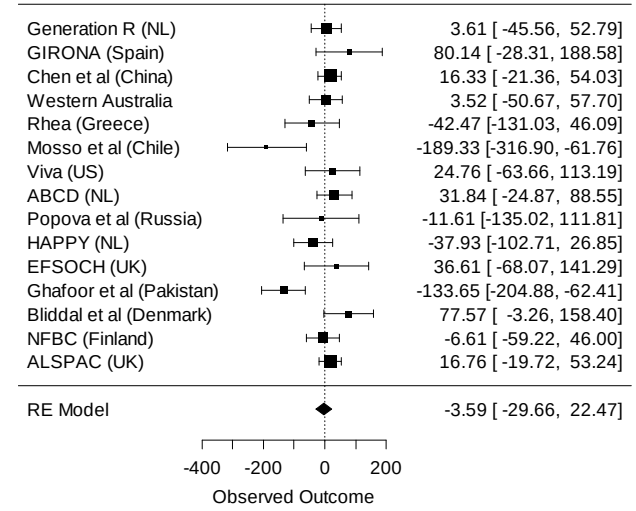
LGA

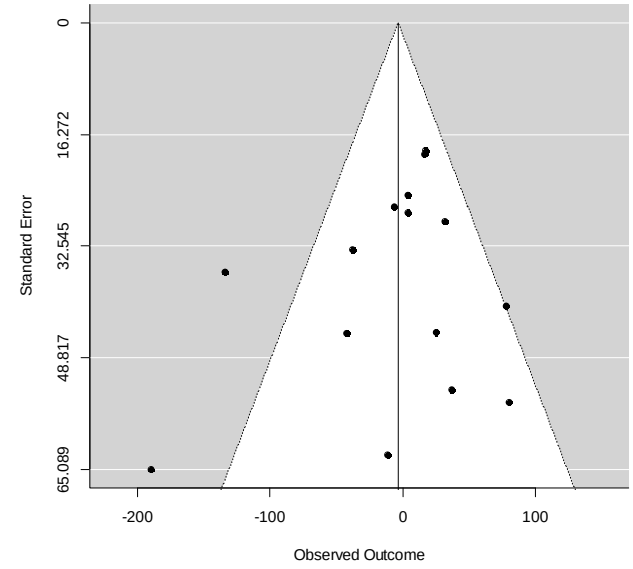




test for funnel plot asymmetry:
z = -1.9278, p = 0.0539
I^2(%)=1.58 (0.0-83.5)
H^2=1.01 (1.0-6.0)

BW

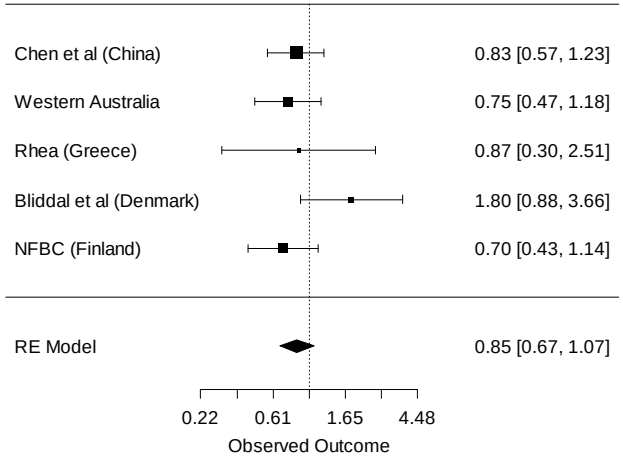


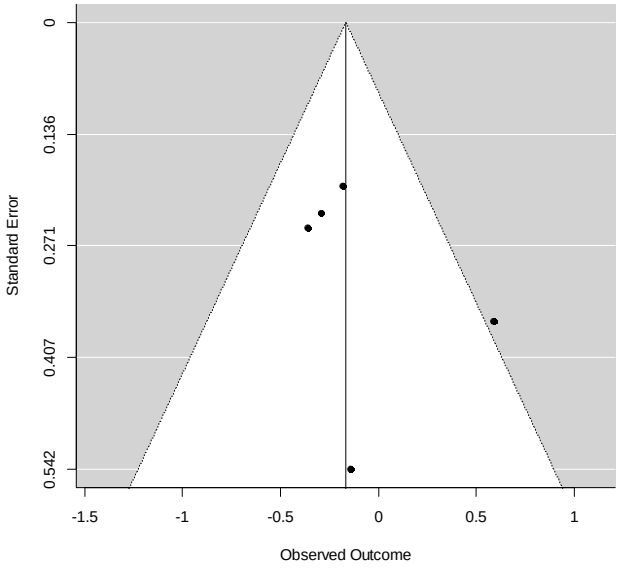


test for funnel plot asymmetry:
z = -0.9639, p = 0.3351
I^2(%)=56.8 (31.0-90.8)
H^2=2.31 (1.45-10.8)

Supplemental Figure 9. Two-step meta-analyses and funnel plots for the association of TgAb positivity with SGA, LGA or BW.

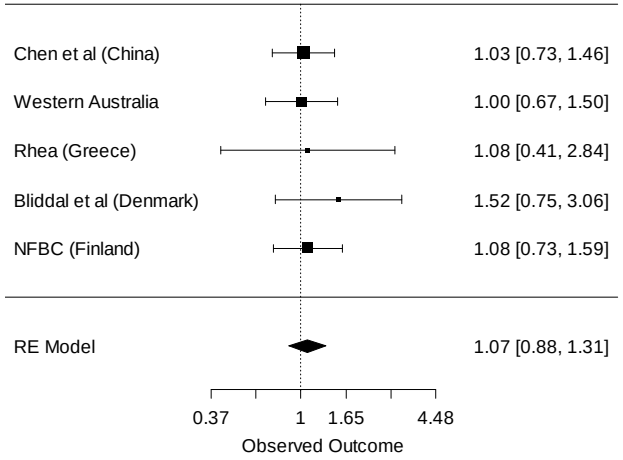
SGA

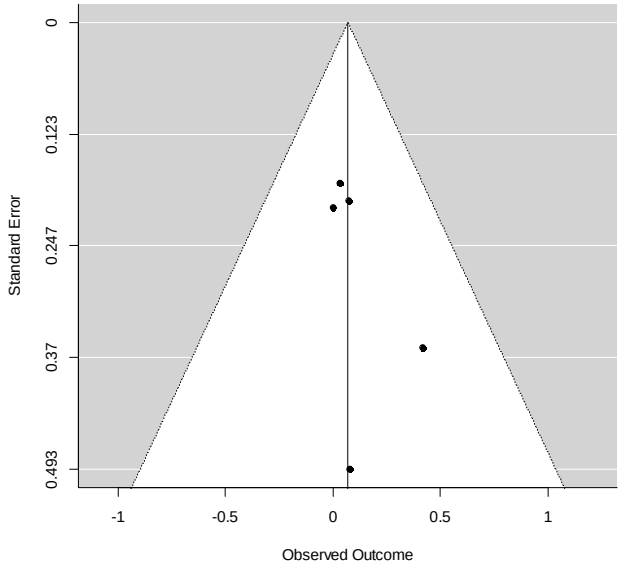




test for funnel plot asymmetry:
z = -1.4895, p = 0.1364
I^2(%)=31.5 (0.0-78.9)
H^2=1.46(1.0-4.74)

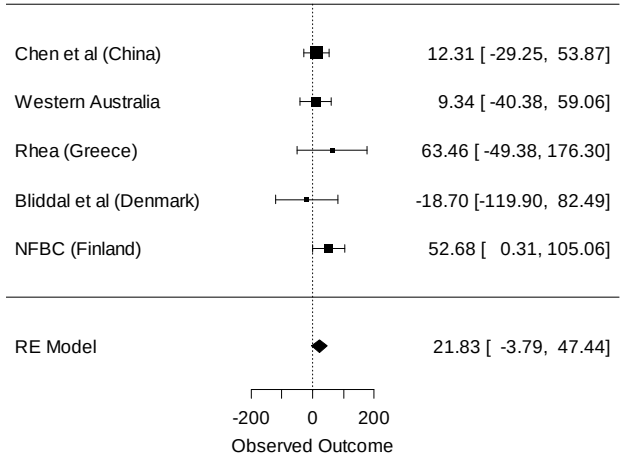
LGA

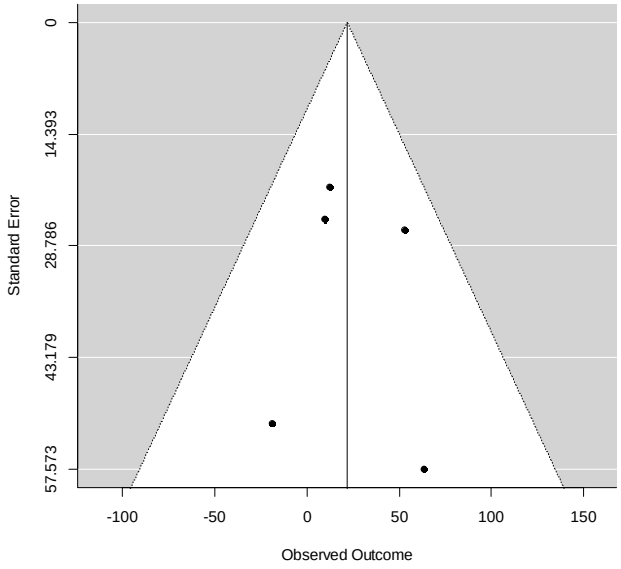




test for funnel plot asymmetry:
z = 0.6250, p = 0.5320
I^2(%)=0.0 (0.0-68.1)
H^2=1.0 (1.0-3.14)

BW





test for funnel plot asymmetry:
z = 0.1982, p = 0.8429
I^2(%)=0.0 (0.0-9.55)
H^2=1.0 (1.0-1.10)

Supplemental acknowledgements and grant details

ABCD

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Bliddal et al. cohort

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Generation R

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Ghafoor et al. cohort

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GIRONA

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