Supplementary Online Content

The Consortium on Thyroid and Pregnancy–Study Group on Preterm Birth. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2019.10931

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods: Details on search strategy and systematic search and statistics

Additional 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 97.5[th] percentile and a FT4 within the cohort-specific normal range (i.e. 2.5[th]-97.5[th] percentile). Subclinical hyperthyroidism was defined as a TSH below the cohort-specific 2.5[th] percentile and a FT4 within the cohort-specific normal range (i.e. 2.5[th]-97.5[th] 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 2.5[th] cohort-specific percentile, and a FT4 above the 97.5[th] cohort-specific percentile. Isolated hypothyroxinemia was defined as a FT4 below the cohort-specific 2.5[th] percentile and a TSH within the cohort-specific normal range (i.e. 2.5[th]-97.5[th] percentile). Cohort-specific cut-offs are provided in eTable 4.

Data collection

Upon agreement, we requested individual-participant data via a standardized codebook, which included any thyroid function measurements, individual demographic characteristics, thyroid interfering medication usage, in vitro fertilization treatment, multiple pregnancies and outcome data.

Statistics and sensitivity analyses

We assessed differential data availability within cohorts by comparing thyroid function and TPOAb positivity between women with and without data on gestational age at birth.

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

We studied if the association of TSH or FT4 with preterm birth differed according to gestational age at blood sampling, parity or BMI using a stepwise approach in order to overcome multiple testing issues. First, we screened for potential modifiers by adding a product interaction term of the continuous variable(s) to the models. To reduce the risk of a type II error, we used a P-value below 0.15 to progress to stratification of analyses, this value was chosen based on suggestions by Selvin [7] and personal experience. To identify whether the modifier is also of clinical relevance we stratified the analyses according to clinical cut-offs only and we quantified the potential relevance of any differences according to the point estimates.

For some cohorts, and for most two-step analyses on very preterm birth, it was necessary to use Firth bias reduction in order to obtain any or reliable effects estimates for meta-analysis, these analyses tended to show higher effect estimates than those from the one-step analyses.

Absolute risk differences and corresponding 95% CIs were calculated according to Newcombe and Bender, taking into account baseline risk imprecision calculated using the Wilson score method.[8]

eMethods 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.
7.   Selvin, Steve. Statistical analysis of epidemiologic data. Vol. 35. Oxford University Press, 2004.
8.   Newcombe, Robert G., and Ralf Bender. "Implementing GRADE: calculating the risk difference from the baseline risk and the relative risk." BMJ Evidence-Based Medicine 19.1 (2014): 6-8.

eTable 1A. Maternal demographics per cohort (see eTable 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)	2337 (57.6)	1264 (31.2)	335 (8.3)	121 (3.0)	3667 (90.4)	386 (9.5)	2426 (59.8)	1631 (40.2)
ALSPAC (United Kingdom)	28 (4.8)	11 (6-34)	22.9 (3.7)	2182 (42.5)	1662 (32.4)	690 (13.4)	598 (11.7)	3692 (71.9)	1176 (22.9)	5132 (100)	-
Bliddal et al. (Denmark)	31 (4.2)	11.3 (8.9-13.4)	22.8 (4.4)	486 (49.3)	292 (29.6)	85 (8.6)	0	886 (89.9)	60 (6.1)	985 (100)	-
Chen et al. (China)	27 (4.3)	31.1 (6.6-41.0)	NA	7167 (83.1)	1381 (16)	62 (0.7)	10 (0.1)	8603 (99.8)	17 (0.2)	8620 (100)	-
EFSOCH (United Kingdom)	30 (5.2)	28 (28-28)	27.9 (4.6)	474 (48.9)	343 (35.8)	101 (10.5)	38 (4.0)	923 (96.2)	2 (0.2)	959 (100)	-
Generation R (Netherlands)	31 (5.0)	13.2 (9.6-17.6)	24.5 (4.4)	3429 (56.9)	1782 (26.9)	553 (9.2)	207 (3.4)	4348 (72.2)	1007 (16.7)	3281 (54.5)	2742 (45.5)
Ghafoor et al. (Pakistan)	27 (6.4)	19 (15-31)	NA	624 (34.3)	481 (26.4)	391 (21.5)	324 (17.8)	NA	NA	1821 (100)	-
GIRONA 1 (Spain)	31 (5.0)	26.7 (21.6-28.9)	26.8 (4.3)	192 (51.9)	132 (35.7)	0	0	161 (49.2)	52 (15.9)	327 (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 (83.8)	52 (15.9)	370 (100)	-
HAPPY (Netherlands)	30 (3.7)	12 (12-12)	23.8 (3.9)	1021 (48.9)	801 (38.3)	200 (9.6)	29 (1.4)	1732 (82.9)	136 (6.5)	2089 (100)	-
Hisada et al. (Japan)	34 (4.7)	11 (7-15)	20.6 (2.7)	87 (48.1)	76 (42.0)	16 (8.8)	1 (0.6)	159 (87.8)	15 (8.3)	181 (100)	-
INMA (Spain)	31 (4.3)	13 (11-20)	23.5 (4.2)	1246 (56.4)	811 (36.7)	133 (6.0)	18 (0.8)	1479 (66.9)	685 (31.0)	2210 (100)	-
Mosso et al. (Chile)	25 (6.5)	8.4 (5-14)	26.0 (5.0)	308 (54.1)	154 (27.1)	107 (18.8)	0	501 (88.0)	68 (12.0)	569 (100)	-
NFBC (Finland)	27 (5.4)	10 (6-20)	22.2 (3.4)	1961 (33.7)	1954 (33.5)	1056 (18.1)	835 (14.3)	5586 (95.9)	148 (2.5)	5827 (100)	-
PIP Study (United Kingdom)	30 (6.0)	13 (10-17)	26.1 (5.4)	1531 (45.1)	1202 (35.4)	425 (12.5)	228 (6.7)	2903 (85.6)	489 (14.4)	3125 (92.1)	267 (7.9)
Popova et al. (Russia)	29 (4.6)	11 (6-14)	23.8 (4.9)	279 (61.3)	138 (30.3)	34 (7.5)	4 (0.9)	345 (75.8)	110 (24.2)	455 (100)	-
Rhea (Greece)	29 (4.9)	13 (9-23)	25.0 (4.6)	339 (38.1)	341 (38.3)	143 (16.1)	36 (4.0)	683 (76.7)	141 (15.8)	890 (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 (79.7)	147 (19.8)	595 (80.3)	146 (19.7)
Western Australia	31 (5.2)	11.1 (9.7-13.4)	NA	NA	-	-	-	2163 (90.2)	234 (9.8)	2397 (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.

eTable 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)	4034	1.34 (0.84-2.0)	4056	9.48 (8.65-10.41)	3812 (94.0)	245 (6.0)	NA	NA
ALSPAC (United Kingdom)	4968	1.02 (0.65-1.49)	5009	16.1 (14.7-17.7)	4416 (87.7)	620 (12.3)	NA	NA
Bliddal et al. (Denmark)	982	1.37 (0.90-2.08)	979	14.4 (13.2-15.7)	834 (84.8)	150 (15.2)	893 (90.8)	91 (9.2)
Chen et al. (China)	8620	1.74 (1.16-2.59)	8620	9.04 (7.99-10.2)	8057 (94.8)	439 (5.2)	8161 (95.8)	359 (4.2)
EFSOCH (United Kingdom)	956	1.86 (1.37-2.51)	958	12.0 (11.1-13.0)	886 (92.9)	68 (7.1)	NA	NA
Generation R (Netherlands)	5631	1.34 (0.84-2.0)	5670	12.0 (10.6-13.6)	5299 (94.4)	315 (5.6)	NA	NA
Ghafoor et al. (Pakistan)	1821	1.69 (1.26-2.21)	1821	17.4 (15.3-19.2)	1657 (91.0)	164 (9.0)	NA	NA
GIRONA 1 (Spain)	327	1.85 (1.31-1.47)	327	11.4 (10.4-12.3)	287 (89.4)	34 (10.6)	NA	NA
GIRONA 2 (Spain)	370	2.18 (1.58-2.86)	370	12.2 (11.3-13.2)	299 (92.0)	26 (8.0)	NA	NA
HAPPY (Netherlands)	2089	1.45 (0.97-2.10)	2089	14.3 (13.2-15.3)	1923 (92.1)	166 (7.9)	NA	NA
Hisada et al. (Japan)	181	1.10 (0.59-1.80)	NA	-	NA	NA	NA	NA
INMA (Spain)	2210	1.26 (0.82- 1.83)	2210	10.4 (9.51-11.5)	NA	NA	NA	NA
Mosso et al. (Chile)	569	2.02 (1.27-2.98)	569	14.5 (13.2-15.8)	511 (89.8)	58 (10.2)	NA	NA
NFBC (Finland)	5803	1.21 (0.74-1.84)	5747	15.0 (13.7-16.6)	5542 (95.3)	275 (4.7)	5479 (95.2)	278 (4.8)
PIP Study (United Kingdom)	3386	1.30 (0.84-1.89)	3391	14.2 (13.1-15.5)	NA	NA	NA	NA
Popova et al. (Russia)	455	1.35 (0.75-2.05)	448	14.7 (13.4-16.3)	400 (89.3)	48 (10.7)	NA	NA
Rhea (Greece)	890	1.10 (0.69-1.61)	889	15.4 (14.0-17.1)	808 (90.8)	82 (9.2)	842 (94.6)	48 (5.4)
VIVA (United States)	732	1.20 (0.70-1.87)	741	2.09 (1.89-2.29)**	639 (86.2)	102 (13.8)	NA	NA
Western Australia	2397	0.79 (0.49-1.19)	2397	13.0 (12.0-15.0)	2146 (89.5)	251 (10.5)	2093 (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).

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

Cohort (country)	Euthyroid, N (%)	Subclinical hypothyroidism, N (%)	Subclinical hyperthyroidism, N (%)	Hyperthyroidism, N (%)	Hypothyroxinemia, N (%)	Hypothyroidism, N (%)
ABCD (Netherlands)	3698 (91.7)	131 (3.24)	56 (1.38)	45 (1.11)	83 (2.05)	21 (0.52)
ALSPAC (United Kingdom)	4431 (91.1)	185 (3.80)	69 (1.41)	42 (0.86)	102 (2.1)	33 (0.67)
Bliddal et al. (Denmark)	901 (91.5)	28 (2.8)	12 (1.2)	9 (0.9)	24 (2.4)	5 (0.5)
Chen et al. (China)	7995 (92.7)	210 (2.4)	146 (1.7)	61 (0.7)	196 (2.3)	12 (0.1)
EFSOCH (United Kingdom)	878 (91.9)	30 (3.1)	18 (1.9)	5 (0.5)	22 (2.3)	2 (0.2)
Generation R (Netherlands)	5125 (91.7)	177 (3.2)	80 (1.4)	54 (1.0)	140 (2.5)	15 (0.3)
Ghafoor et al. (Pakistan)	1706 (93.7)	29 (1.6)	33 (1.8)	9 (0.5)	39 (2.1)	5 (0.3)
GIRONA 1 (Spain)	300 (91.7)	8 (2.4)	7 (2.1)	1 (0.3)	10 (3.1)	1 (0.3)
GIRONA 2 (Spain)	370 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HAPPY (Netherlands)	1920 (91.9)	67 (3.2)	29 (1.4)	17 (0.8)	51 (2.4)	5 (0.2)
Hisada et al. (Japan)*	NA	NA	NA	NA	NA	NA
INMA (Spain)*	NA	NA	NA	NA	NA	NA
Mosso et al. (Chile)	518 (91.0)	19 (3.3)	4 (0.7)	9 (1.6)	13 (2.3)	6 (1.1)
NFBC (Finland)	5248 (91.5)	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
Popova et al. (Russia)	413 (92.2)	12 (2.7)	8 (1.8)	3 (0.7)	10 (2.2)	2 (0.4)
Rhea (Greece)	822 (92.5)	27 (3.0)	9 (1.0)	11 (1.2)	20 (2.2)	0 (0)
VIVA (United States)	674 (92.1)	31 (4.2)	7 (1.0)	7 (1.0)	10 (1.0)	3 (0.4)
Western Australia	2203 (91.9)	92 (3.8)	9 (0.4)	24 (1.0)	56 (2.3)	13 (0.5)
Total	37,202	1234	594	328	904	157

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

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

eTable 1D. Description of pregnancy characteristics per cohort.

Cohort (Country)	N	Gestational age at birth (weeks)	Preterm birth (<37 weeks), N (%)	Very preterm birth (<32 weeks), N(%)	Child sex, N (%)*	
					Female	Male
ABCD (Netherlands)	4057	40 (34-42)	250 (6.2)	70 (1.7)	2070 (51.0)	1976 (48.7)
ALSPAC (United Kingdom)	5132	40 (35-42)	235 (4.6)	26 (0.5)	2486 (48.4)	2646 (51.6)
Bliddal et al. (Denmark)	985	40.1 (36-42)	40 (4.1)	5 (0.5)	NA	NA
Chen et al. (China)	8620	39.6 (36-41)	328 (3.8)	26 (0.3)	NA	NA
EFSOCH (United Kingdom)	959	40 (36-42)	45 (4.7)	3 (0.3)	465 (48.5)	493 (51.4)
Generation R (Netherlands)	6023	40.1 (35-42)	302 (5.0)	45 (0.7)	2982 (49.5)	3041 (50.5)
Ghafoor et al. (Pakistan)	1821	38 (29-41)	211 (11.6)	58 (3.2)	944 (51.8)	868 (47.7)
GIRONA 1 (Spain)	327	40 (36-42)	10 (3.1)	0 (0.0)	149 (45.6)	177 (54.1)
GIRONA 2 (Spain)	370	39 (35-42)	19 (5.1)	1 (0.3)	185 (50.0)	185 (50.0)
HAPPY (Netherlands)	2089	39.9 (35.3-41.7)	94 (4.5)	25 (1.2)	1052 (49.7)	1021 (48.9)
Hisada et al. (Japan)	181	39 (35-41)	6 (3.3)	1 (0.6)	90 (49.7)	90 (49.7)
INMA (Spain)	2210	39.8 (36-42)	95 (4.3)	7 (0.3)	1063 (48.1)	1146 (51.9)
Mosso et al. (Chile)	569	39 (35-41)	37 (6.5)	2 (0.4)	261 (45.9)	287 (50.4)
NFBC (Finland)	5827	40 (36-42)	232 (4.0)	27 (0.5)	2825 (48.5)	3002 (51.5)
PIP Study (United Kingdom)	3392	40 (36-41)	163 (4.8)	16 (0.5)	1712 (50.6)	1674 (49.4)
Popova et al. (Russia)	455	40 (35-42)	19 (4.2)	4 (0.9)	205 (45.1)	249 (54.7)
Rhea (Greece)	890	38 (35-40)	92 (10.3)	4 (0.4)	433 (48.7)	457 (51.3)
VIVA (United States)	741	40 (35-41)	42 (5.7)	5 (0.7)	361 (48.7)	380 (51.3)
Western Australia	2397	39 (34-41)	137 (5.7)	24 (1.0)	1147 (47.9)	1250 (52.1)

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

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

eTable 1E. Percentage 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)	4,057	93 (2.3)	19 (0.5)	0	4 (0.1)	930 (22.9)	11 (0.3)
ALSPAC (United Kingdom)	5,132	0	0	0	264 (5.1)	801 (15.6)	0
Bliddal et al. (Denmark)	985	0	0	122 (12.4)	39 (4.0)	42 (4.3)	NA
Chen et al. (China)	8,620	20 (0.2)	0	0	0	NA	NA
EFSOCH (United Kingdom)	959	0	0	3 (0.3)	34 (3.5)	5 (0.5)	1 (0.1)
Generation R (Netherlands)	6,023	0	20 (0.3)	52 (0.9)	668 (11.1)	35 (0.6)	0
Ghafoor et al. (Pakistan)	1,821	4 (0.2)	0	1 (0.1)	NA	NA	9 (0.5)
GIRONA 1 (Spain)	327	6 (1.8)	66 (20.2)	35 (10.7)	114 (34.9)	60 (18.3)	1 (0.3)
GIRONA 2 (Spain)	370	0	2 (0.5)	0	4 (1.1)	2 (0.5)	0
HAPPY (Netherlands)	2,089	0	0	38 (1.8)	221 (10.6)	78 (3.7)	16 (0.8)
Hisada et al. (Japan)	181	2 (1.1)	31 (17.1)	1 (0.6)	7 (3.9)	1 (0.6)	1 (0.6)
INMA (Spain)	2,210	1 (0.0)	1 (0.0)	2 (0.1)	46 (2.1)	0	1 (0.0)
Mosso et al. (Chile)	569	0	0	0	0	1 (0.2)	21 (3.7)
NFBC (Finland)	5,827	0	15 (0.3)	21 (0.4)	93 (1.6)	141 (2.4)	0
PIP Study (United Kingdom)	3,392	11 (0.3)	15 (0.4)	6 (0.2)	0	320 (9.4)	23 (0.7)
Popova et al. (Russia)	455	1 (0.2)	0	0	0	0	1 (0.2)
Rhea (Greece)	890	11 (1.2)	0	31 (3.5)	66 (7.4)	60 (6.7)	0
VIVA (United States)	741	3 (0.4)	0	0	2 (0.3)	2 (0.3)	0
Western Australia	2,397	0	0	NA	0	NA	0
Total	47,045	169 (0.4%)	158 (0.35%)	2709 (5.8%)	3383 (7.2%)	15317 (32.6%)	9690 (20.6%)

Values are n (valid %).

NA: not available (100% missing).

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eTable 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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eTable 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 missingness *	*	*		*		*	*	
c) follow up rate < 85% and those lost show slightly different FT4 and T3								
d) no statement								
Total Score (Stars out of a max. 9)	9	9	9	9	9	9	9	9

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) <u>Representativeness of the exposed cohort</u>											
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) <u>Selection of the non exposed cohort</u>											
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) <u>Ascertainment of exposure</u>											
a) secure record (laboratory measurement) *	*	*	*	*	*	*	*	*	*	*	*
b) structured interview *											
c) written self report											
d) no description											
4) <u>Demonstration that outcome of interest was not present at start of study</u>											
a) yes *	*	*	*	*	*	*	*	*	*	*	*
b) no											
Comparability											
1) <u>Comparability of cohorts on the basis of the design or analysis</u>											
a) study controls for maternal age *	*	*	*	*	*	*	*	*	*	*	*
b) study controls formaternal smoking *	*	*	*	*	*	X	*	*	*	*	*
Outcome											
1) <u>Assessment of outcome</u>											
a) either independent blind assessment * or (combined with) b) record linkage *	*	*	*	*	*	*	*	*	*	*	*
c) self report											
d) no description											
2) <u>Was follow-up long enough for outcomes to occur</u>											
a) yes (select an adequate follow up period for outcome of interest) *	*	*	*	*	*	*	*	*	*	*	*
b) no											
3) <u>Adequacy of follow up of cohorts</u>											
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 missingness *	*	*		*		*	*		*	*	*
c) follow up rate < 85% and those lost show slightly different FT4 and T3, (Bliddal cohort; missing gestational age at birth (N=150) versus non-missing (N=979), for median FT4 14.7 vs 14.4 pmol/L, P=0.039; and for median T3 1.97 vs 2.05 ng/ml, P=0.004).								X			
d) no statement											
Total Score (Stars out of a max. 9)	9	9	9	9	9	8	9	8	9	9	9

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

Cohort	TSH (mU/L)		FT4 (pmol/L)	
	2.5[th] percentile	97.5[th] percentile	2.5[th] percentile	97.5[th] 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).

eTable 5. Comparison of TSH and FT4 concentrations and TPOAb positivity between women with or without data on gestational age at birth.

	GESTB available		GESTB missing		
	N		N		*P* value
TSH (SD)	46,421	0 (0.004)	935	-0.03 (0.03)	0.28[a]
FT4 (SD)	46,291	-0.001 (0.004)	935	0.06 (0.03)	0.05[a]
TPOAb positivity, N (%)	40,559	3043 (7.5)	522	68 (13.0)	<0.001[b]

Data are mean (standard error of mean) and percentage as appropriate. GESTB: gestational age at birth.

[a] Student's t-test

[b] Chi-square test

eTable 6. The association of TSH and FT4 concentrations or TgAb positivity with preterm birth.

	Preterm birth (<37 weeks)				Very preterm birth (<32 weeks)			
	N of events/ Total (%)	Risk Difference (95% CI), %	OR (95% CI)	P value	N of events/ Total (%)	Risk Difference (95% CI), %	OR (95% CI)	P value
Continuous								
TSH	2,324/46,421 (5.0)	0.2 (0.0 to 0.4)	1.04 (1.00 to 1.09)	0.04	346/46,421 (0.7)	0.0 (-0.05 to 0.1)	1.04 (0.93 to 1.16)	0.42
FT4	2,328/46,291 (5.0)	-0.1 (-0.3 to 0.1)	0.98 (0.94 to 1.02)	0.44	346/46,291 (0.7)	-0.1 (-0.2 to -0.01)	0.88 (0.79 to 0.98)	0.03
Thyroglobulin Antibody								
TgAb negative	774/17,468 (4.4)	Ref	Ref		83/17,468 (0.5)	Ref	Ref	Ref
TgAb positive	46/1,080 (4.3)	-0.5 (-1.6 to 0.9)	0.88 (0.64 to 1.20)	0.42	3/1,080 (0.3)	*	*	*

Table shows the association of continuous TSH or FT4 Z-scores as well as thyroglobulin antibody (TgAb) positivity with preterm birth (<37 weeks including < 32 weeks) or very preterm birth (<32 weeks). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

* Denotes too few samples for reliable analysis.

eTable 7. Association of thyroid function test abnormalities, TSH or FT4 concentrations, TPOAb or TgAb positivity with gestational age at birth (weeks).

	N	Gestational age at birth (mean weeks)	
		Beta (95% CI)	P value
Thyroid function test abnormalities			
Euthyroid	37,202	Reference	-
Subclinical Hypothyroidism	1,234	-0.08 (-0.18 to 0.01)	0.09
Subclinical Hyperthyroidism	594	-0.07 (-0.20 to 0.06)	0.36
Overt hyperthyroidism	328	0.004 (-0.19 to 0.20)	0.96
Isolated hypothyroxinemia	904	-0.24 (-0.35 to -0.12)	<0.001
Continuous			
TSH	46,421	-0.002 (-0.01 to 0.01)	0.74
FT4	46,291	0.01 (-0.005 to 0.02)	0.18
Assay manufacturer cut-off			
TPOAb negative	37,516	Reference	-
TPOAb positive	3,043	-0.17 (-0.22 to -0.11)	<0.001
Sensitivity analysis			
TPOAb positivity combined with*			
TSH within normal range	2,615	-0.19 (-0.24 to -0.13)	<0.001
TSH >2.5 mU/L	989	-0.09 (-0.18 to 0.01)	0.10
TSH >4 mU/L	406	-0.08 (-0.25 to 0.10)	0.34

Table shows the association of thyroid function test abnormalities, maternal thyroid function as continuous TSH and FT4 Z-scores as well as TPOAb positivity with gestational age at birth (weeks). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex. Euthyroid was defined as a normal (2.5[th]-97.5[th] cohort-specific percentile) of TSH and FT4; subclinical hypothyroidism as an increased TSH with a normal FT4; subclinical hyperthyroidism as a decreased TSH with a normal FT4; overt hyperthyroidism as a decreased TSH with an increased FT4 and isolated hypothyroxinemia as a normal TSH with a decreased FT4.

* TPOAb positive women with TSH levels within the normal range or more than 2.5 and 4 mU/L were compared to TPOAb negative women regardless of their TSH levels.

eTable 8. Association of TPOAb positivity with mutual adjustments with TSH and FT4 or subclinical hypothyroidism or hypothyroxinemia with preterm birth.

	Preterm birth (<37 weeks)		Very preterm birth (<32 weeks)		Gestational age at birth (weeks)	
N=39,287	*OR (95% CI)*	*P value*	*OR (95% CI)*	*P value*	*Beta (95% CI)*	*P value*
TPOAb Positivity	1.27 (1.08-1.49)	0.003	2.44 (1.78-3.35)	<0.001	-0.16 (-0.21 to -0.10)	<0.001
TSH	1.05 (1.00-1.10)	0.04	0.96 (0.86-1.08)	0.59	0.004 (-0.01 to 0.02)	0.68
FT4	0.98 (0.94-1.03)	0.62	0.89 (0.78-1.00)	0.05	0.01 (-0.01 to 0.02)	0.13
N=37,806	*OR (95% CI)*	*P value*	*OR (95% CI)*	*P value*	*Beta (95% CI)*	*P value*
Subclinical hypothyroidism	1.20 (0.94-1.54)	0.13	0.74 (0.37-1.47)	0.39	-0.05 (-0.14 to 0.04)	0.34
TPOAb positivity	1.30 (1.11-1.53)	0.001	2.71 (1.97-3.73)	<0.001	-0.16 (-0.21 to -0.10)	<0.001
N=37,655	*OR (95% CI)*	*P value*	*OR (95% CI)*	*P value*	*Beta (95% CI)*	*P value*
Hypothyroxinemia	1.43 (1.10-1.87)	0.007	2.49 (1.50-4.14)	<0.001	-0.22 (-0.33 to -0.10)	<0.001
TPOAb Positivity	1.33 (1.12-1.58)	<0.001	2.95 (2.17-4.02)	<0.001	-0.20 (-0.25 to -0.14)	<0.001

Table shows the association of maternal thyroid antibodies with preterm birth earlier than 37 or 32 weeks as well as gestational age at birth (weeks) while adjusted with Z-scores of TSH and FT4 or subclinical hypothyroidism or hypothyroxinemia status. All analyses were also adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

eTable 9. Sensitivity analyses for the association of TPOAb cut-offs with preterm birth.

			Preterm birth (<37 weeks)			Very preterm birth (<32 weeks)			Gestational age at birth (mean weeks)	
	N exposed	(% cases)	OR (95% CI)	P value	(% cases)	OR (95% CI)	P value	Beta (95% CI)	P value
TPOAb >94th percentile	2,443	(4.5%)	1.21 (1.02-1.44)	0.02	(1.5%)	1.99 (1.40-2.83)	<0.001	-0.13 (-0.18 to -0.07)	<0.001
TPOAb >100 IU/l	1,885	(5.0%)	1.42 (1.18-1.70)	<0.001	(2.3%)	2.76 (1.98-3.85)	<0.001	-0.25 (-0.32 to -0.17)	<0.001
TPOAb >500 IU/l	474	(4.6%)	1.17 (0.80-1.71)	0.41	(1.5%)	*		-0.15 (-0.30 to 0.006)	0.06
TPOAb >2x assay cut-off	2,110	(4.5%)	1.15 (0.95-1.39)	0.14	(1.3%)	1.76 (1.18-2.62)	0.005	-0.09 (-0.16 to -0.01)	0.02
TPOAb >5x assay cut-off	1,273	(4.0%)	0.90 (0.69-1.17)	0.44	-	*		0.001 (-0.09 to 0.09)	0.97

Table shows the association of varying cut-offs for TPOAb positivity with preterm birth <37 weeks (including 32 weeks) or <32 weeks. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

* Denotes too few samples for reliable analysis

eTable 10. P values for the interaction terms between TPOAb, TgAb, TSH or FT4 with BMI, parity or gestational age at the time of blood sampling in association with preterm birth (<37 weeks).

	TPOAb positivity	TgAb positivity	TSH	FT4
BMI	0.56	0.85	0.93	0.07
Parity	0.62	0.40	0.10	0.50
Gestational age at the time of blood sampling	*	*	0.43	0.08

P values are for the product interaction terms in separate multivariable regression models adjusted for maternal age, ethnicity, smoking, fetal sex and BMI, parity and gestational age at blood sampling.

* Analysis was not performed due to a lack of biological plausibility for any effects.
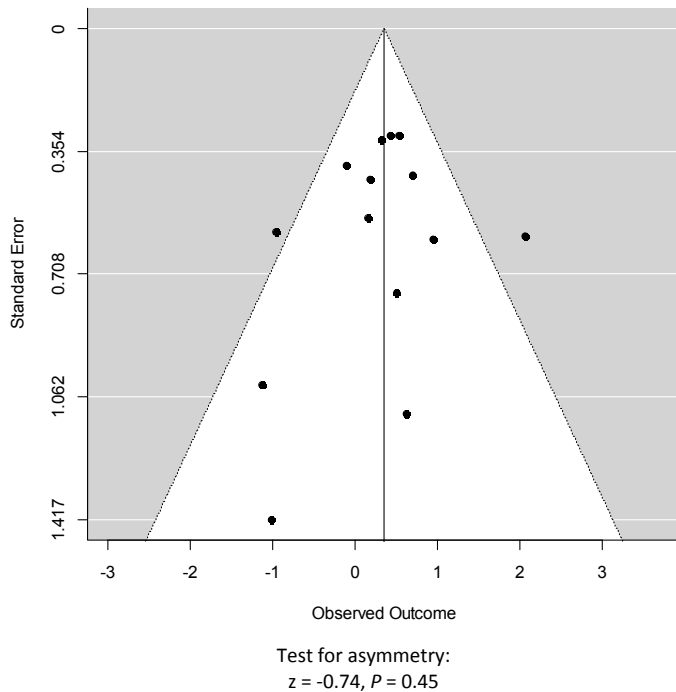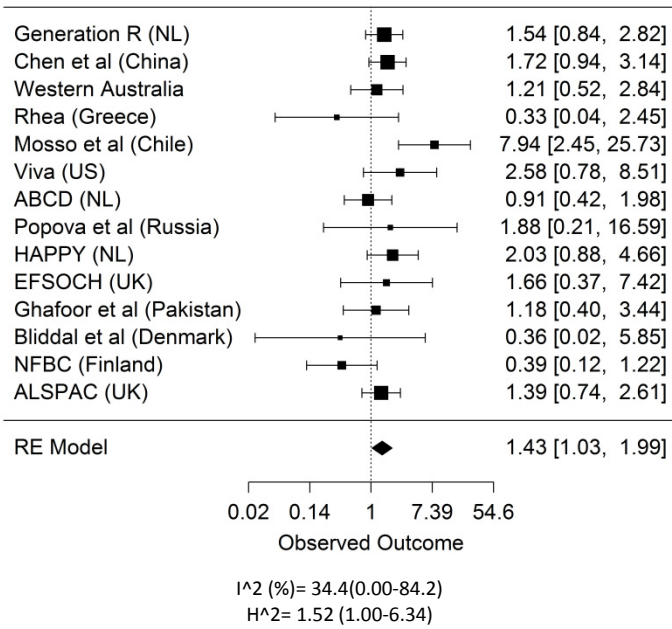
eTable 11. Association of FT4 or TSH with preterm birth (<37 weeks) according to gestational age at the time of blood sampling or BMI or parity.

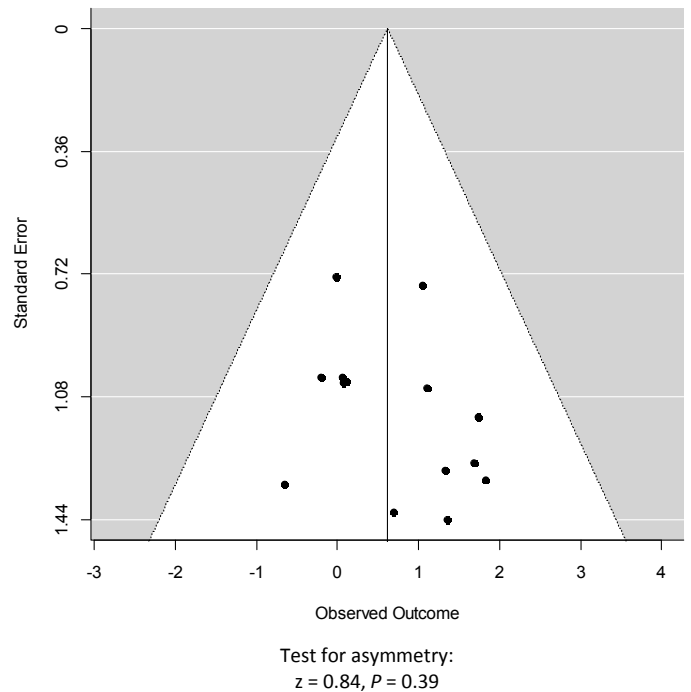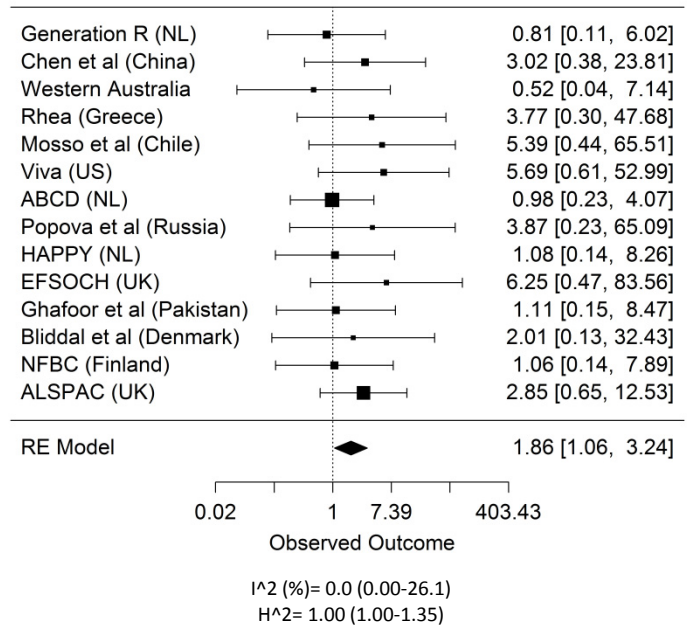|	1st trimester		2nd trimester		3rd trimester		P for interaction
	N of events/total	OR (95% CI)	N of events/total	OR (95% CI)	N of events/total	OR (95% CI)	
FT4	728/14,725	1.02 (0.94 to 1.10)	1,258/23,655	0.98 (0.92 to 1.04)	342/7,911	1.00 (0.89 to 1.13)	0.08
	BMI<25 kg/m^2		25≤BMI<30 kg/m^2		BMI≥30 kg/m^2		
	N of events/total	OR (95% CI)	N of events/total	OR (95% CI)	N of events/total	OR (95% CI)	
FT4	1,462/30,348	1.01 (0.95 to 1.07)	692/12,933	0.93 (0.85 to 1.02)	174/2,836	0.95 (0.82 to 1.11)	0.07
	Parity=0		Parity 1 or 2		Parity≥3		
	N of events/total	OR (95% CI)	N of events/total	OR (95% CI)	N of events/total	OR (95% CI)	
TSH	1,301/25,252	1.06 (1.00 to 1.13)	864/17,667	1.02 (0.94 to 1.11)	159/2,479	1.01 (0.94 to 1.08)	0.10

All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at the time of blood sampling and fetal sex. Trimesters were defined as:
<12 weeks, 12-25 weeks and >25 weeks of pregnancy.

eFigure 1A. Two-step meta-analyses and funnel plots for the association of subclinical hypothyroidism with preterm and very preterm birth.
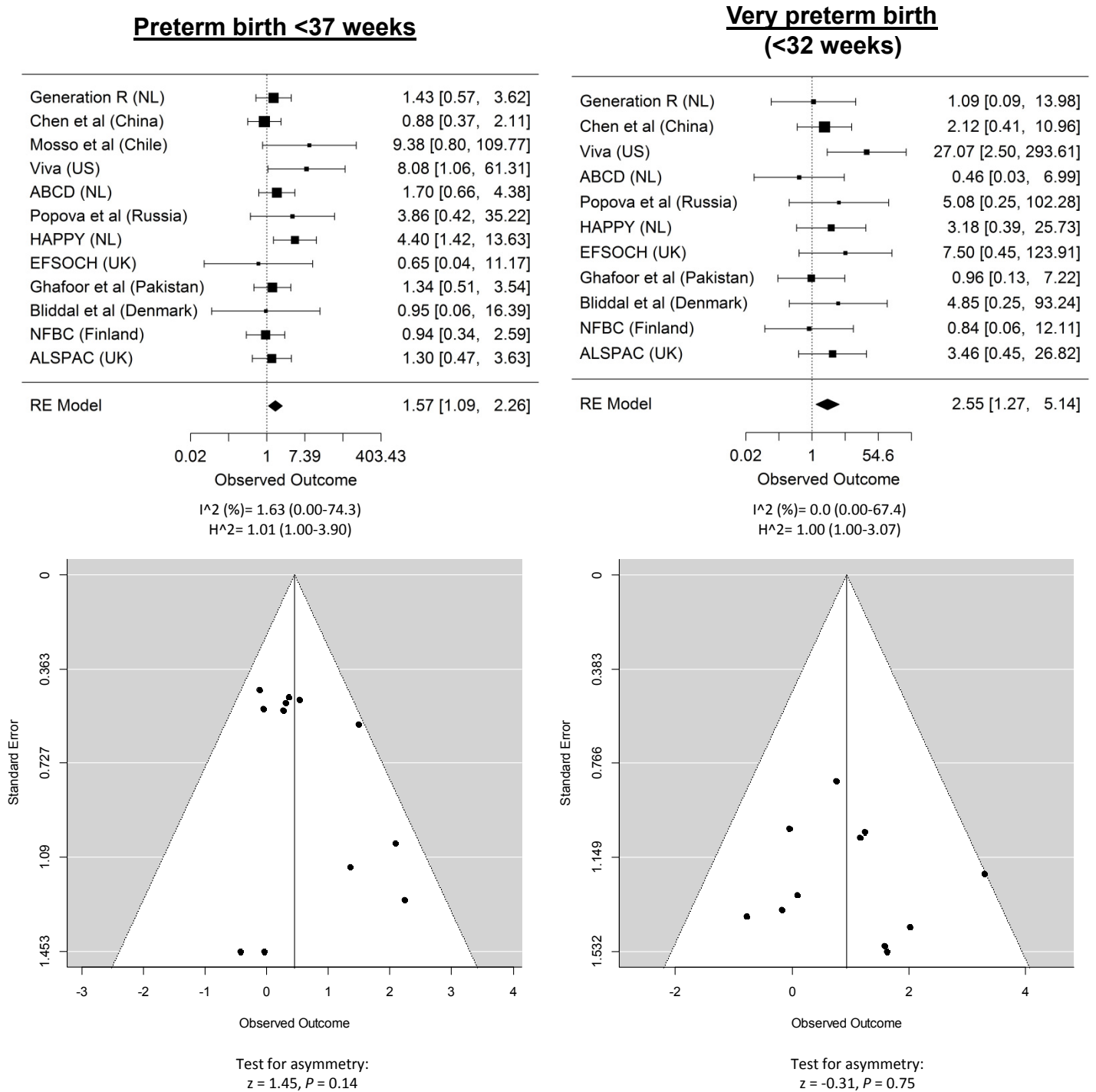
eFigure 1B. Two-step meta-analyses and funnel plots for the association of subclinical hyperthyroidism with preterm and very preterm birth.
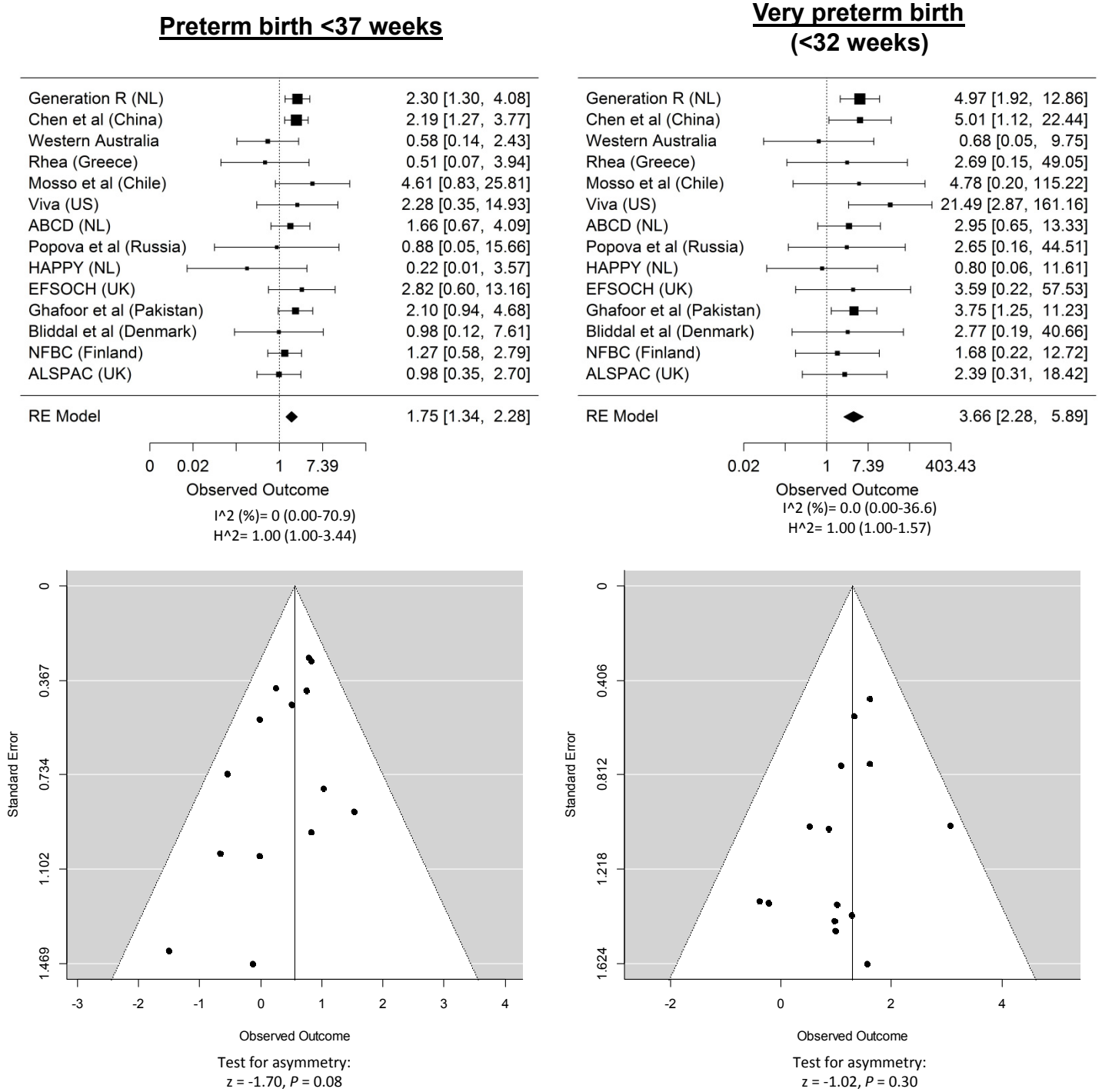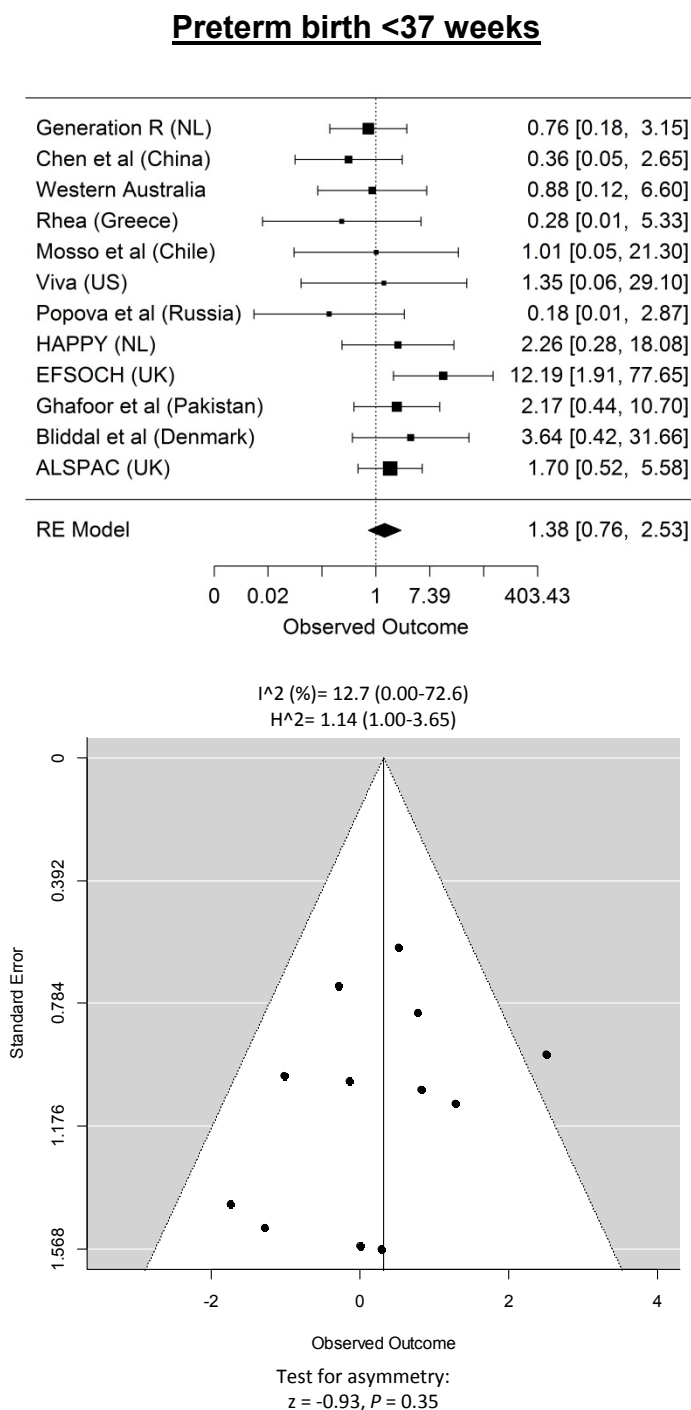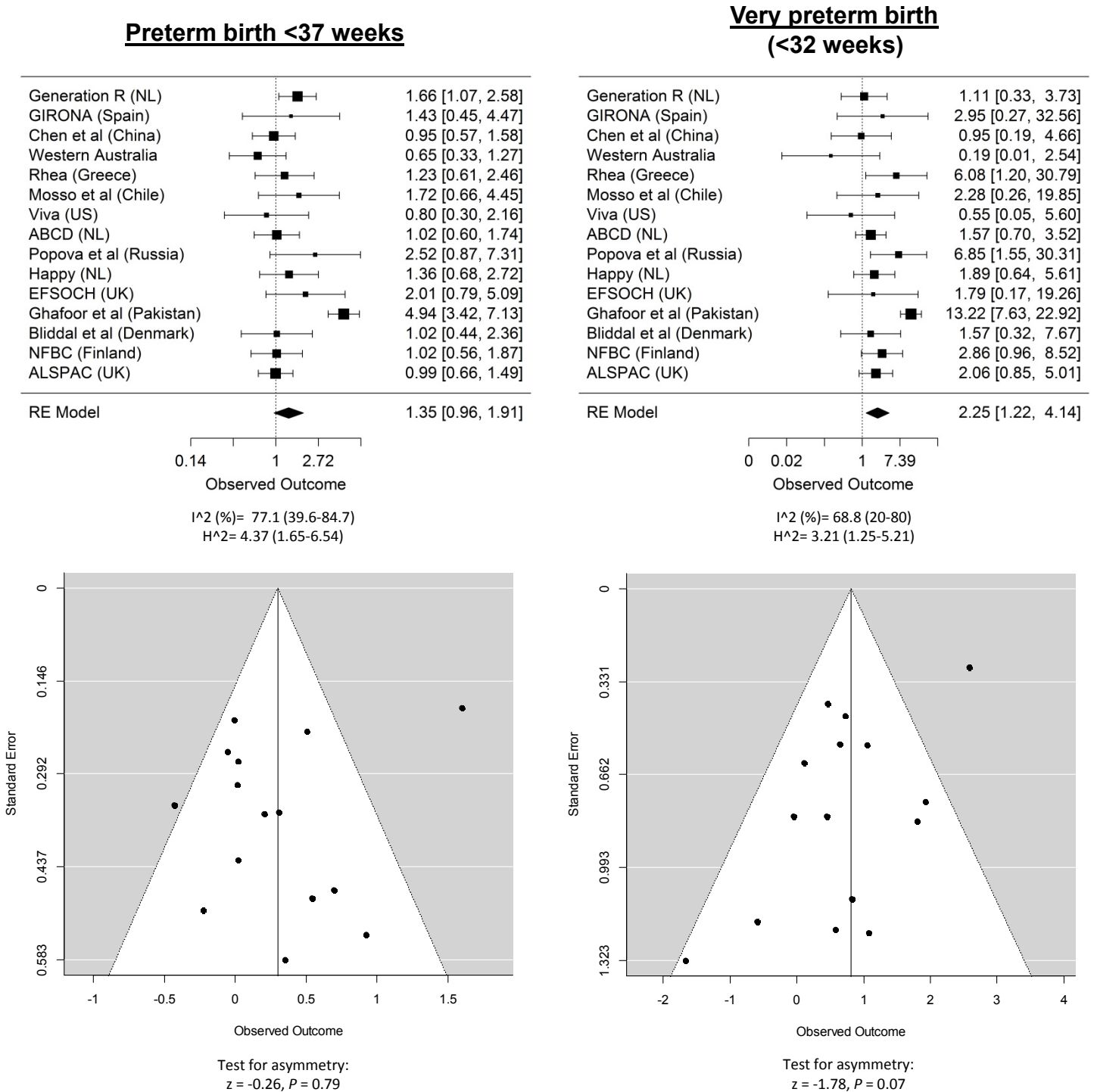

Preterm birth <37 weeks

Study	Estimate [95% CI]
Generation R (NL)	1.43 [0.57, 3.62]
Chen et al (China)	0.88 [0.37, 2.11]
Mosso et al (Chile)	9.38 [0.80, 109.77]
Viva (US)	8.08 [1.06, 61.31]
ABCD (NL)	1.70 [0.66, 4.38]
Popova et al (Russia)	3.86 [0.42, 35.22]
HAPPY (NL)	4.40 [1.42, 13.63]
EFSOCH (UK)	0.65 [0.04, 11.17]
Ghafoor et al (Pakistan)	1.34 [0.51, 3.54]
Bliddal et al (Denmark)	0.95 [0.06, 16.39]
NFBC (Finland)	0.94 [0.34, 2.59]
ALSPAC (UK)	1.30 [0.47, 3.63]
RE Model	1.57 [1.09, 2.26]

I^2 (%)= 1.63 (0.00-74.3)
H^2= 1.01 (1.00-3.90)

Very preterm birth (<32 weeks)

Study	Estimate [95% CI]
Generation R (NL)	1.09 [0.09, 13.98]
Chen et al (China)	2.12 [0.41, 10.96]
Viva (US)	27.07 [2.50, 293.61]
ABCD (NL)	0.46 [0.03, 6.99]
Popova et al (Russia)	5.08 [0.25, 102.28]
HAPPY (NL)	3.18 [0.39, 25.73]
EFSOCH (UK)	7.50 [0.45, 123.91]
Ghafoor et al (Pakistan)	0.96 [0.13, 7.22]
Bliddal et al (Denmark)	4.85 [0.25, 93.24]
NFBC (Finland)	0.84 [0.06, 12.11]
ALSPAC (UK)	3.46 [0.45, 26.82]
RE Model	2.55 [1.27, 5.14]

I^2 (%)= 0.0 (0.00-67.4)
H^2= 1.00 (1.00-3.07)

Test for asymmetry:
z = 1.45, P = 0.14

Test for asymmetry:
z = -0.31, P = 0.75

eFigure 1C. Two-step meta-analyses and funnel plots for the association of hypothyroxinemia with preterm and very preterm birth.

Preterm birth <37 weeks

Study	Observed Outcome
Generation R (NL)	2.30 [1.30, 4.08]
Chen et al (China)	2.19 [1.27, 3.77]
Western Australia	0.58 [0.14, 2.43]
Rhea (Greece)	0.51 [0.07, 3.94]
Mosso et al (Chile)	4.61 [0.83, 25.81]
Viva (US)	2.28 [0.35, 14.93]
ABCD (NL)	1.66 [0.67, 4.09]
Popova et al (Russia)	0.88 [0.05, 15.66]
HAPPY (NL)	0.22 [0.01, 3.57]
EFSOCH (UK)	2.82 [0.60, 13.16]
Ghafoor et al (Pakistan)	2.10 [0.94, 4.68]
Bliddal et al (Denmark)	0.98 [0.12, 7.61]
NFBC (Finland)	1.27 [0.58, 2.79]
ALSPAC (UK)	0.98 [0.35, 2.70]
RE Model	1.75 [1.34, 2.28]

I^2 (%)= 0 (0.00-70.9)
H^2= 1.00 (1.00-3.44)

Very preterm birth (<32 weeks)

Study	Observed Outcome
Generation R (NL)	4.97 [1.92, 12.86]
Chen et al (China)	5.01 [1.12, 22.44]
Western Australia	0.68 [0.05, 9.75]
Rhea (Greece)	2.69 [0.15, 49.05]
Mosso et al (Chile)	4.78 [0.20, 115.22]
Viva (US)	21.49 [2.87, 161.16]
ABCD (NL)	2.95 [0.65, 13.33]
Popova et al (Russia)	2.65 [0.16, 44.51]
HAPPY (NL)	0.80 [0.06, 11.61]
EFSOCH (UK)	3.59 [0.22, 57.53]
Ghafoor et al (Pakistan)	3.75 [1.25, 11.23]
Bliddal et al (Denmark)	2.77 [0.19, 40.66]
NFBC (Finland)	1.68 [0.22, 12.72]
ALSPAC (UK)	2.39 [0.31, 18.42]
RE Model	3.66 [2.28, 5.89]

I^2 (%)= 0.0 (0.00-36.6)
H^2= 1.00 (1.00-1.57)

Test for asymmetry:
z = -1.70, P = 0.08

Test for asymmetry:
z = -1.02, P = 0.30

eFigure 1D. Two-step meta-analyses and funnel plots for the association of overt hyperthyroidism with preterm birth.

Preterm birth <37 weeks

Generation R (NL)		0.76 [0.18, 3.15]
Chen et al (China)		0.36 [0.05, 2.65]
Western Australia		0.88 [0.12, 6.60]
Rhea (Greece)		0.28 [0.01, 5.33]
Mosso et al (Chile)		1.01 [0.05, 21.30]
Viva (US)		1.35 [0.06, 29.10]
Popova et al (Russia)		0.18 [0.01, 2.87]
HAPPY (NL)		2.26 [0.28, 18.08]
EFSOCH (UK)		12.19 [1.91, 77.65]
Ghafoor et al (Pakistan)		2.17 [0.44, 10.70]
Bliddal et al (Denmark)		3.64 [0.42, 31.66]
ALSPAC (UK)		1.70 [0.52, 5.58]
RE Model		1.38 [0.76, 2.53]

0   0.02   1   7.39   403.43
Observed Outcome

I^2 (%)= 12.7 (0.00-72.6)
H^2= 1.14 (1.00-3.65)

Standard Error

Observed Outcome

Test for asymmetry:
z = -0.93, *P* = 0.35

eFigure 2. Two-step meta-analyses and funnel plots for the association of TPOAb positivity with preterm and very preterm birth.

Preterm birth <37 weeks

Generation R (NL)	1.66 [1.07, 2.58]
GIRONA (Spain)	1.43 [0.45, 4.47]
Chen et al (China)	0.95 [0.57, 1.58]
Western Australia	0.65 [0.33, 1.27]
Rhea (Greece)	1.23 [0.61, 2.46]
Mosso et al (Chile)	1.72 [0.66, 4.45]
Viva (US)	0.80 [0.30, 2.16]
ABCD (NL)	1.02 [0.60, 1.74]
Popova et al (Russia)	2.52 [0.87, 7.31]
Happy (NL)	1.36 [0.68, 2.72]
EFSOCH (UK)	2.01 [0.79, 5.09]
Ghafoor et al (Pakistan)	4.94 [3.42, 7.13]
Bliddal et al (Denmark)	1.02 [0.44, 2.36]
NFBC (Finland)	1.02 [0.56, 1.87]
ALSPAC (UK)	0.99 [0.66, 1.49]
RE Model	1.35 [0.96, 1.91]

I^2 (%)= 77.1 (39.6-84.7)
H^2= 4.37 (1.65-6.54)

Very preterm birth (<32 weeks)

Generation R (NL)	1.11 [0.33, 3.73]
GIRONA (Spain)	2.95 [0.27, 32.56]
Chen et al (China)	0.95 [0.19, 4.66]
Western Australia	0.19 [0.01, 2.54]
Rhea (Greece)	6.08 [1.20, 30.79]
Mosso et al (Chile)	2.28 [0.26, 19.85]
Viva (US)	0.55 [0.05, 5.60]
ABCD (NL)	1.57 [0.70, 3.52]
Popova et al (Russia)	6.85 [1.55, 30.31]
Happy (NL)	1.89 [0.64, 5.61]
EFSOCH (UK)	1.79 [0.17, 19.26]
Ghafoor et al (Pakistan)	13.22 [7.63, 22.92]
Bliddal et al (Denmark)	1.57 [0.32, 7.67]
NFBC (Finland)	2.86 [0.96, 8.52]
ALSPAC (UK)	2.06 [0.85, 5.01]
RE Model	2.25 [1.22, 4.14]

I^2 (%)= 68.8 (20-80)
H^2= 3.21 (1.25-5.21)

Test for asymmetry:
z = -0.26, P = 0.79

Test for asymmetry:
z = -1.78, P = 0.07

Supplemental acknowledgements and grant details

ABCD

ALSPAC

Bliddal et al. cohort

Generation R

Ghafoor et al. cohort

GIRONA

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