Appendix

Association of gestational free and total triiodothyronine with gestational hypertension, preeclampsia, preterm birth and birth weight: an individual-participant data meta-analysis

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Review question [1 change]

What is the association of maternal free and total triiodothyronine with preterm birth? What is the association of maternal free and total triiodothyronine with birth weight? What is the association of maternal free and total triiodothyronine with preeclampsia?

Searches

Databases: Embase, MEDLINE (Ovid), Web of Science, Cochrane and Google Scholar. The search strategy includes only terms relating to or describing the exposure and/or intervention with 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 In order to obtain unpublished data we have: Selected from the search, and contact authors that have published studies on thyroid function during pregnancy with different outcomes. Used our personal network. Published an invitation to join our research consortium (The Consortium on Thyroid and Pregnancy) in various journals (European Thyroid Journal and Obstetrics & Gynecology). Announced our consortium and IPD meta-analysis at various conferences (ETA, ATA, ICE-CSE). Advertised our consortium via social media (twitter, Researchgate). Additional details about the search strategy can be found in the attached PDF document (link provided below).

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

Gestational thyroid function. Pregnancy outcomes.

Participants/population [1 change]

- Non-selected or population-based prospective cohorts.

- Serum free and/or total triiodothyronine 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) [1 change]

Triiodothyronine (T3) is the main bioactive thyroid hormone that is predominantly produced by the intracellular conversion of T4 by deiodinase enzymes in peripheral tissues. Experimental studies suggest that T3 regulates normal placentation, but it remains unknown whether T3 is transferred through the placenta from the mother to the fetus. Both preterm birth and low birth weight are major risk factors for neonatal mortality and morbidity and are associated with a higher risk of non-communicable diseases in later life. However, there is lack of studies investigating the association of free and total T3 concentrations with clinical pregnancy outcomes. Therefore, the clinical relevance of T3 measurements during pregnancy remains unknown. On the other hand, the association of maternal TSH and FT4 concentrations or TPOAb positivity with adverse pregnancy outcomes such as preterm birth and low birth weight has already been established.

Investigating the association of free and total T3, as a reflection of thyroid hormone availability at tissue level (i.e. in the placenta and for the fetus), with pregnancy outcomes will provide novel insights into the mechanism of how maternal thyroid hormone availability can affect fetal growth and maintenance of pregnancy.

Comparator(s)/control
Not applicable

Main outcome(s) [1 change]

1. Preterm birth (earlier than 37 weeks).

2. Very preterm birth (earlier than 32 weeks).

3. Small for gestational age: defined as cohort-specific standardized birth weight (according to gestational age at birth and sex) less than 10th percentile of the population.

4. Large for gestational age: defined as cohort-specific standardized birth weight (according to gestational age at birth and sex) more than 90th percentile of the population.

5. Birth weight (grams), continuously.

6. Preeclampsia.

Measures of effect
Effects measures for main outcomes 1-4 and 6 will be odds ratios and risk difference. Effect measure for main outcome 5 (birth weight) will be mean difference.

Additional outcome(s) [1 change]

1. Gestational age at birth (weeks), continuously.

2. Low birth weight (birth weight <2500 grams).

3. Macrosomia (Birth weight >4000 grams).

4. Pregnancy-induced hypertension.

Measures of effect
Effect measure for additional outcome 1 will be mean difference. Effects measures for additional outcomes 2-4 will be odds ratios and risk difference.

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 AD) 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 AD). 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

(AD).

Risk of bias (quality) assessment

Study quality and risk of bias will be assessed using the Newcastle-Ottawa scale. Randomness of missing data and lost to follow-up will be checked per cohort. Any discrepancies or unusual patterns will be checked with the study investigator.

Strategy for data synthesis [1 change]

Free and total T3 SD scores will be calculated per population and studied in order to retain inter-individual differences. We will study the association of free and total T3 SD scores with the primary and secondary outcomes by performing an individual participant data meta-analysis (combining raw data). We will use both a one-step and two-step approach. For the one step, association of free and total T3 concentrations (SD scores) with the outcomes will be analyzed utilizing generalized linear mixed models with random intercepts and slopes per cohort (*based on statistical power differences, we no longer aimed to identify percentile cut-offs for risk differences). For the two-step approach, association of free and total T3 SD scores with pregnancy outcomes will be analyzed using logistic or linear regression models per cohort and the effect estimates will be meta-analyzed with cohort as random effect to assess heterogeneity with I^2 statistics and asses publication bias utilizing funnel plots and Egger's test.

Analysis of subgroups or subsets [1 change]

1. Effects of free and total T3 on the outcomes according to (interaction and if needed stratified):

a. Gestational age at the time of sampling;

b. Prevalent gestational diabetes;

c. Maternal age;

d. Maternal BMI;

e. Maternal smoking status.

2. Additional adjustment with TPOAb positivity.

Contact details for further information

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Organisational affiliation of the review

Erasmus MC

Review team members and their organisational affiliations [1 change]

Dr Arash Derakhshan. Erasmus University Medical Center
Dr Tim Korevaar. Erasmus University Medical Center
Professor Robin Peeters. Erasmus University Medical Center

Type and method of review

Individual patient data (IPD) meta-analysis, Systematic review

Anticipated or actual start date

01 June 2016

Anticipated completion date [1 change]

30 June 2021

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

Conflicts of interest

Language
English

Country
Netherlands

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Female; Humans; Pregnancy; Pregnancy Outcome; Triiodothyronine

Date of registration in PROSPERO
16 December 2019

Date of first submission
21 August 2019

Details of any existing review of the same topic by the same authors [1 change]

Stage of review at time of this submission [1 change]

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

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

16 December 2019
05 January 2021

Deviations from the protocol

1. We considered gestational hypertension (mentioned as pregnancy induced hypertension in the protocol) as a primary outcome while it was considered a secondary outcome in the protocol.
2. We did not investigate the association of TT3 and FT3 with the adverse obstetric outcomes according to TPOAb status of the mothers due to lack of biological plausibility.
3. We did not investigate the association of TT3 and FT3 with the adverse obstetric outcomes according to prevalent gestational diabetes status of the mothers.
4. We performed extra sensitivity analyses, using the lowest and highest 5^{th} percentiles of TT3 and FT3 as exposures (compared to the middle 50 percentiles) to study the outskirts of the distributions while optimizing statistical power.

Search terms

Embase.com

('thyroid function'/exp OR 'thyroid function test'/de 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 'liothyronine'/exp/dd_ec OR ((thyroid* NEAR/3 (function* OR dysfunction* 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 OR triiodothyronin*):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 ('cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort OR longitudinal* OR prospectiv* OR retrospectiv*):ab,ti OR (((00? 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NEXT/6 (patients OR patient OR subjects OR individuals OR cases OR persons OR men OR women OR males OR females OR participant* OR people OR children OR adolescent* OR boys OR girls OR teens OR teenagers OR infants OR newborns OR elderly OR survivor* OR specimen* OR sample* OR episode* OR isolate* OR pediatric OR paediatric OR adult* OR mothers OR pregnancies)) OR ((hundred OR thousand OR million) NEXT/5 (patients OR patient OR subjects OR individuals OR cases OR persons OR men OR women OR participants OR people OR children OR adolescent* OR boys OR girls OR teens OR teenagers OR infants OR newborns OR elderly OR survivor* OR specimen* OR sample* OR episode* OR isolate* OR pediatric OR paediatric OR adult* OR mothers OR pregnancies)) OR ((n OR included OR recruited OR randomized OR randomized OR assigned OR a-total-of) NEXT/2 (00? OR 01? OR 02? OR 03? OR 04? OR 05? OR 06? OR 07? OR 08? OR 09? OR 10? OR 11? OR 12? OR 13? OR 14? OR 15? OR 16? OR 17? OR 18? OR 19? OR 20? OR 21? OR 22? 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Medline Ovid

("Thyroid Function Tests"/ OR "Thyrotropin"/ OR exp "Thyroid Hormones"/ OR Triiodothyronine/ OR ((thyroid* ADJ3 (function* OR dysfunction* 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 OR triiodothyronin*).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 Cohort Studies/ OR (cohort OR longitudinal* OR prospectiv* OR retrospectiv*).ab,ti. OR (((0## OR 1## OR 2## OR 3## OR 4## OR 5## OR 6## OR 7## OR 8## OR 9## OR 1### OR 2### OR 3### OR 4### OR 5### OR 6### OR 7### OR 8### OR 9###) ADJ6 (patients OR patient OR subjects OR individuals OR cases OR persons OR men OR women OR males OR females OR participant* OR people OR children OR adolescent* OR boys OR girls OR teens OR teenagers OR infants OR newborns OR elderly OR survivor* OR specimen* OR sample* OR episode* OR isolate* OR pediatric OR paediatric OR adult* OR mothers OR pregnancies)) OR ((hundred OR thousand OR million) ADJ5 (patients OR patient OR subjects OR individuals OR cases OR persons OR men OR women OR participants OR people OR children OR adolescent* OR boys OR girls OR teens OR teenagers OR infants OR newborns OR elderly OR survivor* OR specimen* OR sample* OR episode* OR isolate* OR pediatric OR paediatric OR adult* OR mothers OR pregnancies)) OR ((n OR included OR recruited OR randomized OR randomized OR assigned OR a-total-of) ADJ2 (0## OR 1## OR 2## OR 3## OR 4## OR 5## OR 6## OR 7## OR 8## OR 9## OR 1### OR 2### OR 3### OR 4### OR 5### OR 6### OR 7### OR 8### OR 9###))).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. NOT (Therapeutics/ OR Drug Therapy/ OR Thyroxine/ OR (therap* OR drug OR levothyroxin* OR treat*).ab,ti.)

Web of science

TS=((((thyroid* NEAR/2 (function* OR dysfunction* 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 OR triiodothyronin*)) AND ((pregnan* OR mother* OR prenatal* OR maternal*)) AND ((cohort OR longitudinal* OR prospectiv* OR retrospectiv*)) NOT (therap* OR drug OR levothyroxin* OR treat*)) AND DT=(article)

List of identified studies with search updated on June 21st 2022 that could have been invited to participate:

1. Monaghan AM, Mulhern MS, Mc Sorley EM, et al. Associations between maternal thyroid function in pregnancy and child neurodevelopmental outcomes at 20 months in the Seychelles Child Development Study, Nutrition Cohort 2 (SCDS NC2). *J Nutr Sci*. 2021;10:e71. Published 2021 Aug 31. doi:10.1017/jns.2021.66
2. Liang JW, Chen MX, Hu XA, et al. Potential Biomarkers in Early Pregnancy for Predicting Gestational Diabetes Mellitus and Adverse Pregnancy Outcomes. Clinical Laboratory. 2021 Aug;67(8). DOI: 10.7754/clin.lab.2021.201022.
3. Li Juxiao, J. Hu, C. Bao et al. Preconceptional and the first trimester exposure to PM2. 5 and offspring neurodevelopment at 24 months of age: Examining mediation by maternal thyroid hormones in a birth cohort study. Environmental Pollution 284 (2021): 117133. DOI: 10.1016/j.envpol.2021.117133
4. He, X., Yan, Q., Liu, C., Wang, Z., Liao, P., Liu, T., Shi, Z., Song, Q., Cui, X., Wang, W., & Zang, J. (2022). Association of maternal thyroid dysfunction and autoimmunity with adverse birth outcomes, Endocrine Connections, 11(4), e210599. DOI: 10.1530/EC-21-0599

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
Aminorroaya et al. (Iran)	28.9 (4.9)	9.6 (5-14.3)	25.2 (4.1)	156 (38.8)	196 (48.8)	34 (8.5)	16 (4)	NA	NA	402 (100)	0 (0)
Ashoor et al. (United Kingdom)	31.7 (5.8)	12.4 (11-15.6)	25.7 (4.9)	2338 (47.6)	2576 (52.4)	0 (0)	0 (0)	4465 (90.9)	449 (9.1)	3412 (69.4)	0 (0)
Bliddal et al. (Denmark)	30.7 (4.2)	11.3 (6-20.1)	22.8 (4.3)	0 (0)	483 (56.7)	285 (33.5)	84 (9.9)	884 (93.6)	60 (6.4)	945 (95.9)	40 (4.1)
Chen et al. (China)	27 (4.3)	30.9 (2.1-43.9)	NA	7213 (83.1)	1393 (16.1)	63 (0.7)	10 (0.1)	8662 (99.8)	17 (0.2)	8679 (100)	0 (0)
EFSOCH (United Kingdom)	30.4 (5.2)	28 (28-28)	27.9 (4.6)	475 (49.6)	345 (36)	100 (10.4)	38 (4)	925 (99.8)	2 (0.2)	961 (100)	0 (0)
GIRONA 1 (Spain)	30.4 (5)	26.4 (13.6-34.6)	26.7 (4.3)	123 (52.3)	112 (47.7)	0 (0)	0 (0)	124 (75.2)	41 (24.8)	271 (100)	0 (0)
GIRONA 2 (Spain)	30.9 (4.7)	25.9 (22.6-30.9)	26.4 (3.9)	189 (51.8)	131 (35.9)	45 (12.3)	0 (0)	305 (84.5)	56 (15.5)	365 (100)	0 (0)
Hokkaido study (Japan)	31.2 (4.4)	11 (6-39)	21 (3)	207 (30.1)	346 (50.3)	115 (16.7)	20 (2.9)	800 (92.2)	68 (7.8)	917 (100)	0 (0)
INMA (Spain)	31.4 (4.3)	13 (6.6-33.4)	23.5 (4.2)	1254 (56.4)	814 (36.6)	135 (6.1)	19 (0.9)	1488 (68.3)	690 (31.7)	2224 (100)	0 (0)
MABC (China)	26.6 (3.7)	10 (4-16)	20.8 (2.8)	2855 (89.8)	305 (9.6)	18 (0.6)	0 (0)	3168 (99.7)	10 (0.3)	3178 (100)	0 (0)
NFBC (Finland)	27.8 (5.5)	10 (2-40)	22.3 (3.5)	1928 (33.3)	1956 (33.8)	1051 (18.1)	860 (14.8)	5571 (97.5)	145 (2.5)	5822 (100)	0 (0)
Popova et al. (Russia)	29 (4.5)	11 (5-15)	23.8 (4.9)	222 (62.2)	108 (30.3)	24 (6.7)	3 (0.8)	273 (76.5)	84 (23.5)	357 (100)	0 (0)
Project VIVA (United States)	32.5 (4.7)	9.6 (5.6-20.9)	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)	0 (0)
Rhea (Greece)	28.8 (4.9)	13 (4-27)	25 (4.6)	341 (39.7)	341 (39.7)	142 (16.5)	36 (4.2)	681 (82.8)	141 (17.2)	891 (100)	0 (0)
Western Australia	31 (5.2)	11.1 (9-13.9)	NA	NA	NA	NA	NA	2175 (90.2)	236 (9.8)	2411 (100)	0 (0)

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

EFSOCH: The Exeter Family Study of Childhood Health; INMA: Infancia y Medio Ambiente; MABC: Ma'anshan Birth Cohort study; NFBC: Northern Finland Birth Cohort.

*Gestational age at the time of blood sampling.

Supplemental Table 1B. Maternal free and total triiodothyronine concentrations per cohort.

Cohort (country)	FT3 (pmol/L)		TT3 (nmol/L)		TPOAb status*, N (%)	
	N	Median (95% range)	N	Median (95% range)	Negative	Positive
Aminorroaya et al. (Iran)	402	4.5 (3.5-5.8)	NA	NA	332 (82.6)	70 (17.4)
Ashoor et al. (United Kingdom)	4914	4.6 (3.9-6)	NA	NA	4446 (90.5)	468 (9.5)
Bliddal et al. (Denmark)	985	4.3 (3.4-5.6)	985	2.0 (1.4-3)	834 (84.8)	150 (15.2)
Chen et al. (China)	8679	4.2 (3.3-5.4)	8679	1.4 (0.9-1.9)	8110 (94.8)	443 (5.2)
EFSOCH (United Kingdom)	961	4.2 (3.4-5.4)	NA	NA	887 (92.9)	68 (7.1)
GIRONA 1 (Spain)	271	2.8 (2-3.5)	NA	NA	245 (91.8)	22 (8.2)
GIRONA 2 (Spain)	365	2.7 (2.2-3.5)	NA	NA	297 (92)	26 (8)
Hokkaido study (Japan)	917	4.7 (3.5-7.9)	NA	NA	602 (90.9)	60 (9.1)
INMA (Spain)	NA	NA	2224	2.5 (1.8-3.5)	0 (NaN)	0 (NaN)
MABC (China)	NA	NA	3178	2.4 (1.5-3.6)	2767 (87.1)	409 (12.9)
NFBC (Finland)	5822	5.2 (3.6-7)	NA	NA	3785 (95.6)	173 (4.4)
Popova et al. (Russia)	357	5 (4-6.4)	357	2.6 (1.9-3.8)	316 (89.3)	38 (10.7)
Project VIVA (United States)	NA	NA	741	3.21 (2.2-4.4)	639 (86.2)	102 (13.8)
Rhea (Greece)	891	3.3 (1.9-5.4)	NA	NA	810 (90.9)	81 (9.1)
Western Australia	2411	4.3 (3.3-5.7)	NA	NA	2159 (89.5)	252 (10.5)

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

EFSOCH: The Exeter Family Study of Childhood Health; INMA: Infancia y Medio Ambiente; MABC: Ma'anshan Birth Cohort study; NFBC: Northern Finland Birth Cohort.

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

Supplemental Table 1C. Description of obstetric outcomes per cohort.

Cohort (Country)	N	Preeclampsia, N (%)	N	Gestational hypertension, N (%)	N	Gestational age at birth (weeks)	Preterm birth, N (%)	Very preterm birth, N (%)	N	Birth weight (grams)
Aminorroaya et al. (Iran)	402	14 (3.8)	NA	NA	399	38.6 (10-41)	57 (14.3)	33 (8.3)	360	3151.6 (481.5)
Ashoor et al. (United Kingdom)	4914	94 (1.9)	NA	NA	4892	39.9 (21.3-42)	503 (10.3)	248 (5.1)	4760	3336.9 (646.9)
Bliddal et al. (Denmark)	985	27 (2.7)	985	8 (0.8)	985	40.1 (36-42.1)	41 (4.2)	6 (0.6)	860	3537.7 (548.2)
Chen et al. (China)	8679	76 (0.9)	8679	77 (0.9)	8645	39.6 (36.3-41.4)	343 (4)	38 (0.4)	8628	3335.1 (441.6)
EFSOCH (United Kingdom)	NA	NA	NA	NA	959	40 (36.1-42.1)	44 (4.6)	3 (0.3)	960	3453.8 (522.3)
GIRONA 1 (Spain)	271	4 (2.4)	159	13 (8.2)	269	40 (36-42)	8 (3)	0 (0)	270	3276.4 (468.2)
GIRONA 2 (Spain)	365	3 (0.8)	362	3 (0.8)	365	39 (35.1-42)	19 (5.2)	1 (0.3)	365	3295.5 (484.5)
Hokkaido study (Japan)	917	0 (0)	917	0 (0)	917	39 (36-41)	28 (3.1)	0 (0)	906	3059.6 (360.1)
INMA (Spain)	2224	10 (1.5)	2195	55 (2.5)	2209	39.9 (36-42)	95 (4.3)	7 (0.3)	2198	3259.4 (470.3)
MABC (China)	3178	55 (1.7)	3178	131 (4.1)	3168	39 (36-41)	133 (4.2)	6 (0.2)	3163	3365.7 (448.5)
NFBC (Finland)	5822	124 (2.1)	5822	168 (2.9)	5819	40 (36-42)	254 (4.4)	34 (0.6)	5822	3565.4 (547.5)
Popova et al. (Russia)	357	23 (6.4)	335	33 (9.9)	357	40 (34.9-42)	20 (5.6)	5 (1.4)	356	3457.7 (544.2)
Project VIVA (United States)	741	21 (2.9)	726	56 (7.7)	741	39.9 (35.3-41.9)	42 (5.7)	5 (0.7)	741	3519.5 (556.3)
Rhea (Greece)	891	30 (4)	NA	NA	886	38 (35-40)	92 (10.4)	4 (0.5)	855	3191.6 (451.9)
Western Australia	2411	70 (2.9)	NA	NA	2411	39 (34-41)	148 (6.1)	35 (1.5)	2411	3390.4 (570.1)

Values are mean (SD) or n (valid %). NA: not available. EFSOCH: The Exeter Family Study of Childhood Health; INMA: Infancia y Medio Ambiente; MABC: Ma'anshan Birth Cohort study; NFBC: Northern Finland Birth Cohort.

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

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

Cohort (country)	N	Maternal age	Gestational age at the time of blood sampling	Parity	Smoking	BMI
Aminorroaya et al. (Iran)	402	0	0	0	NA	1 (0.24)
Ashoor et al. (United Kingdom)	4914	0	0	0	0	3 (0.06)
Bliddal et al. (Denmark)	985	0	0	133 (13.5)	41 (4.2)	2 (0.2)
Chen et al. (China)	8679	20 (0.2)	0	0	0	NA
EFSOCH (United Kingdom)	961	0	0	3 (0.3)	34 (3.5)	5 (0.5)
GIRONA 1 (Spain)	271	4 (1.5)	0	36 (13.2)	106 (39.1)	53 (19.5)
GIRONA 2 (Spain)	365	0	2 (0.5)	0	4 (1.1)	1 (0.27)
Hokkaido study (Japan)	917	0	50 (5.5)	229 (24.9)	49 (5.3)	9 (0.98)
INMA (Spain)	2224	1 (0.05)	1 (0.05)	2 (0.09)	46 (2.1)	0
MABC (China)	3178	0	0	0	0	0
NFBC (Finland)	5822	0	229 (3.9)	27 (0.46)	106 (1.8)	149 (2.5)
Popova et al. (Russia)	357	1 (0.3)	0	0	0	0
Rhea (Greece)	891	11 (1.2)	0	31 (3.5)	69 (7.7)	61 (6.8)
VIVA (United States)	741	3 (0.4)	0	0	2 (0.27)	2 (0.27)
Western Australia	2411	0	0	NA	0	NA
Total	33118	40 (0.12)	282 (0.85)	2872 (8.7)	859 (2.6)	11376 (34.3)

Values are n (valid %).

EFSOCH: The Exeter Family Study of Childhood Health; INMA: Infancia y Medio Ambiente; MABC: Ma'anshan Birth Cohort study; NFBC: Northern Finland Birth Cohort.

NA: not available (100% missing).

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

Cohort	Date	Place
Aminorroaya et al.	from September 2015 to January 2017	Isfahan, Iran
Ashoor et al.	between January 2003 and March 2004	Amsterdam, The Netherlands
Bliddal et al.	throughout 2008	Copenhagen, Denmark
Chen et al.	February 2009 until February 2012	Wenzhou, China
EFSOCH	throughout 2006	Exeter, UK
GIRONA 1&2	May 2008 until May 2010	Girona, Catalonia, Spain
Hokkaido study	between July 2002 and July 2005	Hokkaido, Japan
INMA	between 2003 and 2008	Valencia, Sabadell (Catalonia), Asturias, and Gipuzkoa (Basque Country), Spain
MABC	between May 2013 and September 2014	Ma'anshan city, the Anhui province, China
NFBC	July 1, 1985, until June 30, 1986	northernmost provinces of Finland
Popova et al.	January 2012 to December 2016	St. Petersburg, Russia
Project VIVA	between 1999 and 2002	Eastern Massachusetts, USA
Rhea	starting February 2007	Heraklion, Crete, Greece
Western Australia	October 2006 until February 2007	Western Australia, Australia

EFSOCH: The Exeter Family Study of Childhood Health; INMA: Infancia y Medio Ambiente; MABC: Ma'anshan Birth Cohort study; NFBC: Northern Finland Birth Cohort.

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

	Aminorroaya et al.	Ashoor et al.	Chen et al.	EFSOCH	GIRONA 1	GIRONA 2	Hokkaido study
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 for maternal 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**

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

	INMA	MABC	NFBC	Popova et al.	Project VIVA	Rhea	Western Australia
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 for maternal 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**

Supplemental Table 4. P values for the interaction terms of TT3 or FT3 with relevant variables in association with adverse obstetric outcomes.

	BW		**Preterm birth**		**Preeclampsia**		**Gestational HTN**	
	TT3	FT3	TT3	FT3	TT3	FT3	TT3	FT3
Gestational age*	0.66	0.85	0.95	0.91	0.52	0.43	0.84	0.64
Fetal sex	0.97	0.95	0.50	0.32	-	-	-	-
Maternal age	0.79	0.42	0.82	0.11	0.48	0.31	0.38	**0.063**
BMI	0.53	0.25	0.64	0.60	0.72	0.50	0.96	0.12
Smoking	0.81	0.62	0.41	0.39	0.50	0.98	0.84	0.62

Table shows P values for product interaction terms of free and total T3 with gestational age at the time of sampling, fetal sex, maternal age, maternal BMI and smoking status in association with adverse obstetric outcomes in multivariable regression models.

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

Supplemental Table 5. Association of upper and lower 5th percentiles of total and free T3 concentrations with preeclampsia, gestational hypertension or the composite outcome as hypertensive disorders of pregnancy.

	Preeclampsia		Gestational hypertension		Hypertensive disorders of pregnancy	
N	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
<5th percentile						
TT3	0.89 (0.46 to 1.72)	0.73	0.71 (0.39 to 1.30)	0.27	0.81 (0.51 to 1.29)	0.38
FT3	1.36 (0.91 to 2.02)	0.12	1.33 (0.81 to 2.22)	0.25	1.41 (0.96 to 2.03)	0.072
>95th percentile						
TT3	0.91 (0.49 to 1.68)	0.76	1.43 (0.94 to 2.19)	0.09	1.14 (0.77 to 1.68)	0.49
FT3	1.84 (1.27 to 2.67)	0.0011	1.37 (0.82 to 2.26)	0.21	1.28 (0.86 to 1.91)	0.22

Table shows the association of maternal TT3 and FT3 lowest and highest 2.5th percentiles with preeclampsia, gestational hypertension or the composite outcome as hypertensive disorders of pregnancy. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity and gestational age at blood sampling.

Supplemental Table 6. Association of upper and lower 5th percentiles of total and free T3 concentrations with preterm birth and gestational age at birth.

	Preterm birth		**Very preterm birth**		**Gestational ag at birth**	
N	OR (95% CI)	*P* value	OR (95% CI)	*P* value	Beta (95% CI)	*P* value
<5th percentile						
TT3	1.03 (0.71 to 1.50)	0.85	1.86 (0.54 to 6.38)	0.32	-0.005 (-0.11 to 0.10)	0.92
FT3	1.23 (0.96 to 1.58)	0.09	1.07 (0.51 to 2.25)	0.85	-0.05 (-0.14 to 0.03)	0.24
>95th percentile						
TT3	0.84 (0.57 to 1.24)	0.39	*	*	0.04 (-0.06 to 0.14)	0.43
FT3	0.94 (0.71 to 1.23)	0.66	0.72 (0.32 to 1.58)	0.41	-0.02 (-0.11 to 0.06)	0.56

Table shows the association of total and free T3 lowest and highest 5th percentiles with preterm birth (<37 weeks), very preterm birth (<32 weeks) and continuous gestational age at birth (weeks). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

* There were too few outcomes to conduct a reliable analysis.

Supplemental Table 7. Association of upper and lower 5th percentiles of total and free T3 concentrations with birth weight outcomes.

	Small for Gestational Age		Large for Gestational Age		Birth weight (grams)	
N	OR (95% CI)	*P* value	OR (95% CI)	*P* value	Beta (95% CI)	*P* value
<5th percentile						
TT3	1.15 (0.90 to 1.46)	0.24	0.96 (0.74 to 1.24)	0.77	-21.5 (-51 to 8.2)	0.15
FT3	0.92 (0.7 to 1.12)	0.43	0.96 (0.79 to 1.17)	0.73	-2.84 (-26 to 21)	0.81
>95th percentile						
TT3	0.91 (0.71 to 1.17)	0.49	1.13 (0.89 to 1.44)	0.28	26.2 (-3.1 to 55)	0.081
FT3	1.11 (0.92 to 1.34)	0.24	1.03 (0.71 to 1.50)	0.65	-2.27 (-26 to 22)	0.85

Table shows the association of maternal TT3 and FT3 lowest and highest 5th percentiles 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 (for birth weight only).

Supplemental Table 8. Association of total and free T3 concentrations with preterm birth with gestational age at the time of blood sampling preceding the outcome.

	Preterm birth with time of blood sampling limited to <37 weeks		**Very preterm birth with time of blood sampling limited to <32 weeks**	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Z-scores				
TT3	0.97 (0.90 to 1.05)	0.53	0.64 (0.49 to 0.85)	0.0019
FT3	0.97 (0.92 to 1.04)	0.49	0.87 (0.74 to 1.01)	0.083
Within the normal range				
TT3	1.02 (0.93 to 1.13)	0.59	0.61 (0.44 to 0.84)	0.0029
FT3	1.01 (0.94 to 1.09)	0.70	0.86 (0.71 to 1.04)	0.12

Table shows the association of maternal TT3 and FT3 (Z-scores) in full or within the normal range (2.5^{th}-97.5^{th} percentiles) with preterm birth (<37 weeks) and very preterm birth (<32 weeks) while cases were limited to the gestational age before the occurrence of the outcome. All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

Supplemental Table 9. The association of total and free T3 Z-scores with preterm birth and gestational age at birth.

		Gestational ag at birth	
	N total	Beta (95% CI)	*P* value
Z-scores			
TT3	16,046	-0.006 (-0.034 to 0.02)	0.55
FT3	26,510	0.007 (-0.01 to 0.03)	0.51
Within the normal range			
TT3	15,279	-0.016 (-0.04 to 0.01)	0.25
FT3	25,287	-0.007 (-0.03 to 0.02)	0.58

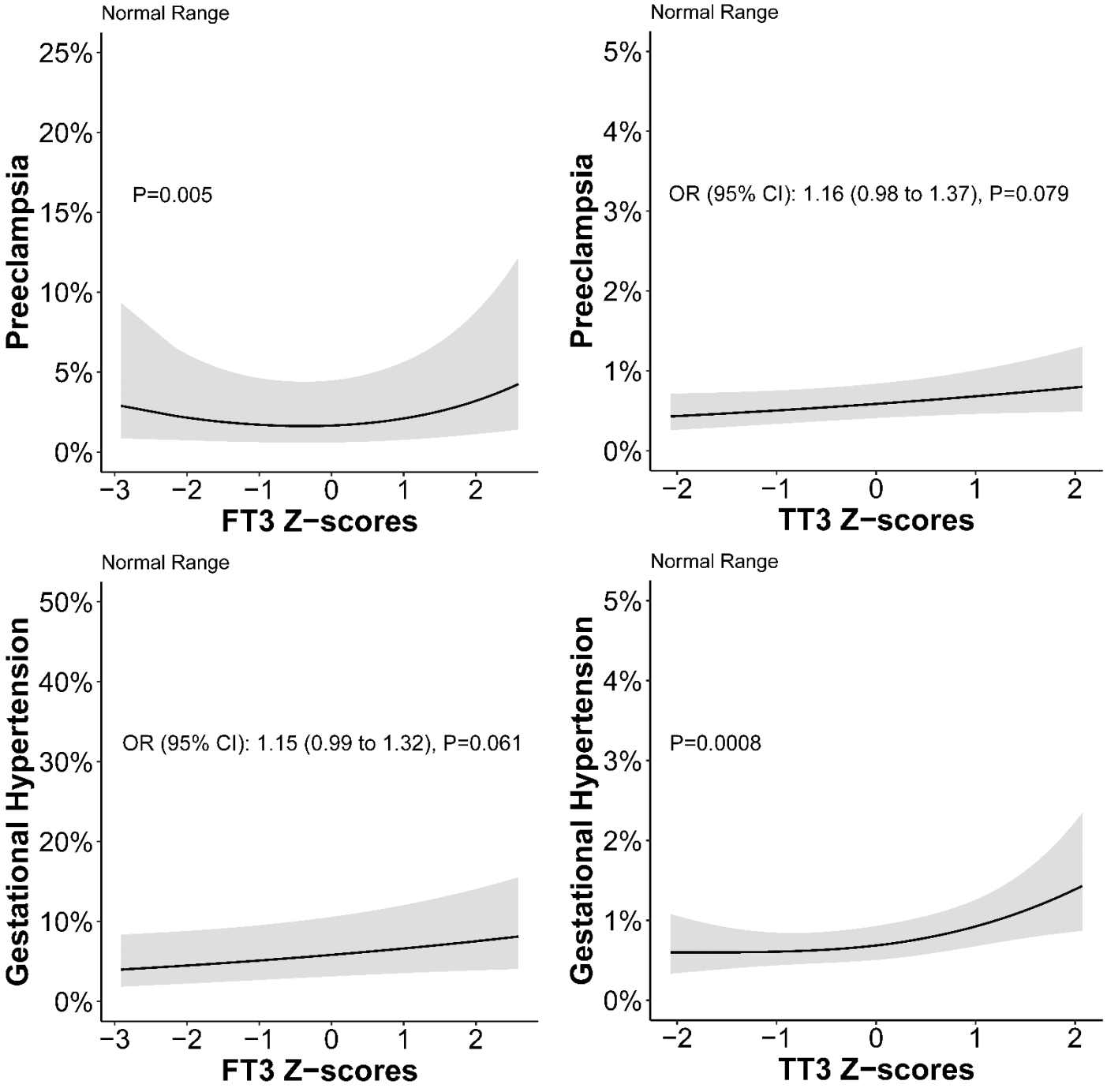
Table shows the association of maternal total and free T3 (TT3 and FT3) in full or within the normal range (2.5^{th}-97.5^{th} percentiles) with preterm birth (<37 weeks), very preterm birth (<32 weeks) and continuous gestational age at birth (weeks). All analyses were adjusted for maternal age, BMI, ethnicity, smoking, parity, gestational age at blood sampling and fetal sex.

Supplemental Table 10. Association of total and free T3 concentrations with low birth weight or macrosomia.

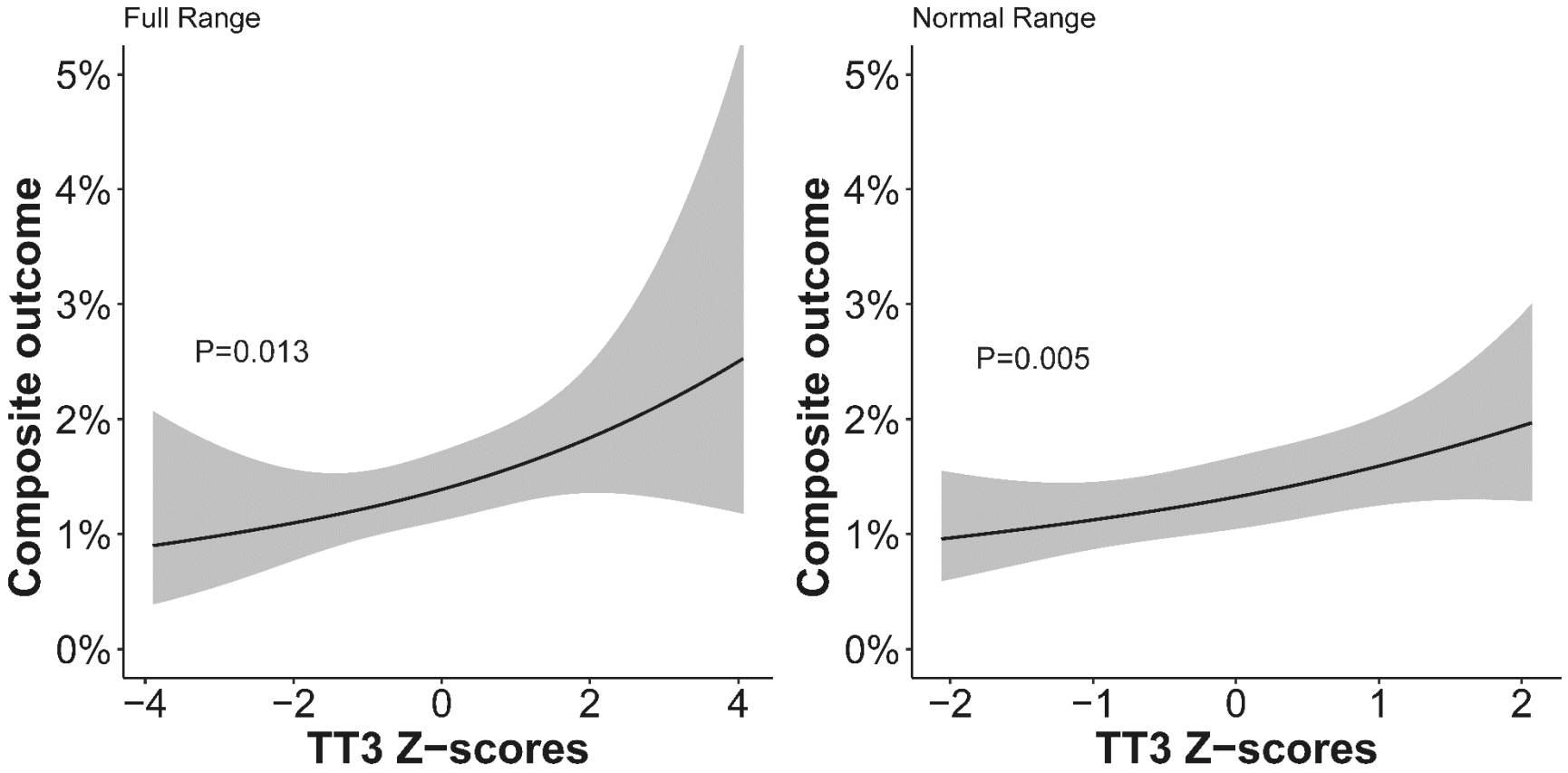
		Low birth weight		**Macrosomia**	
	N	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Z-scores					
TT3	15,848	1.00 (0.89 to 1.12)	0.97	1.05 (0.98 to 1.12)	0.11
FT3	26,269	1.01 (0.92 to 1.10)	0.80	1.03 (0.98 to 1.08)	0.14

Table shows the association of maternal TT3 and FT3 (Z-scores with low birth weight (<2500 grams) or macrosomia (>4000 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 (for birth weight only).

Supplemental figure 1. Association of FT3 and TT3 within the normal range (cohort-specific 2.5th to 97.5th percentiles) with preeclampsia and gestational hypertension.

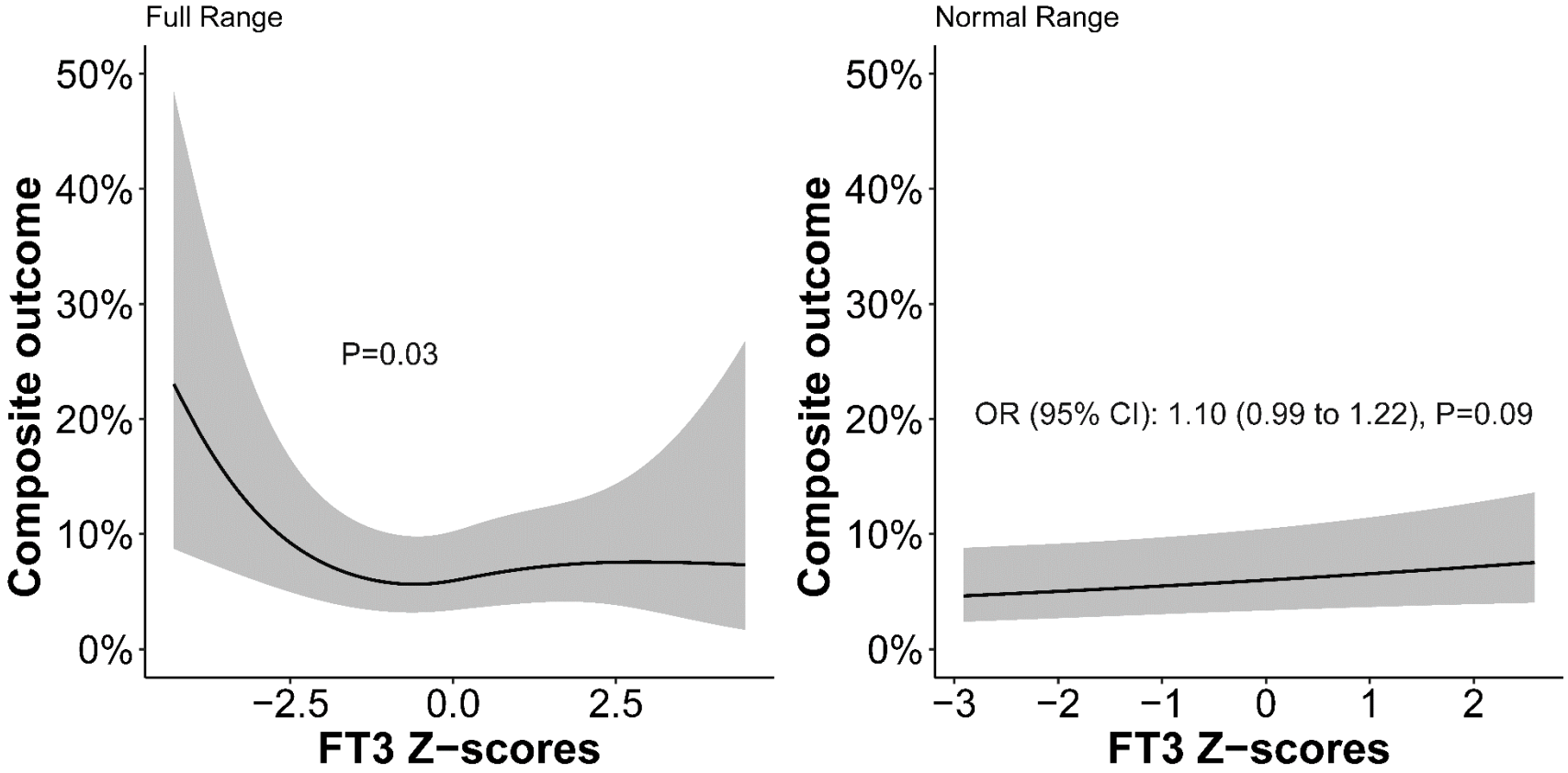


Supplemental Figure 2. Association of TT3 with the composite outcome of hypertensive disorders of pregnancy*.



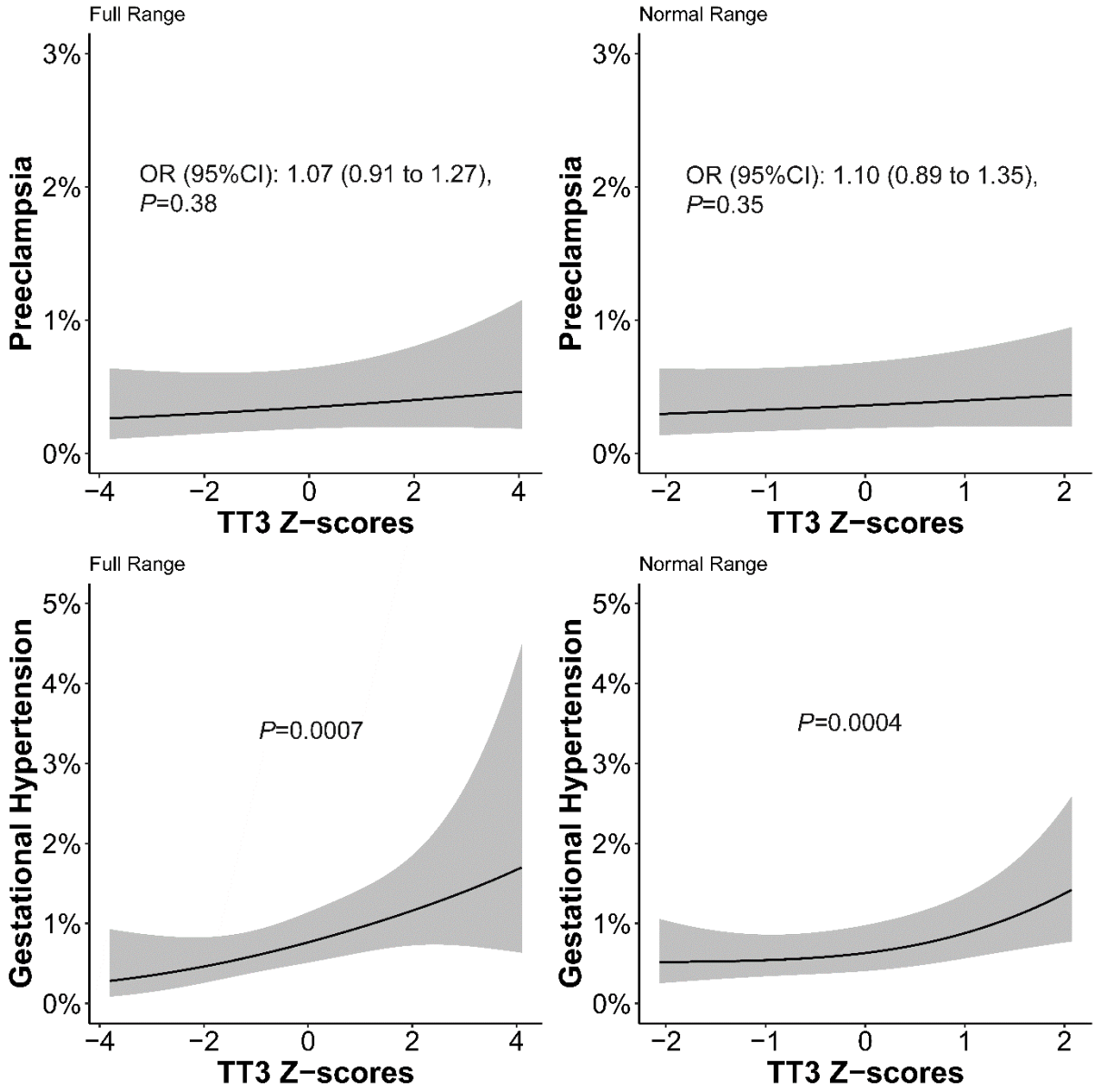
*A composite of preeclampsia and gestational hypertension only in studies with data on both outcomes

Supplemental Figure 3. Association of FT3 with the composite outcome of hypertensive disorders of pregnancy*.

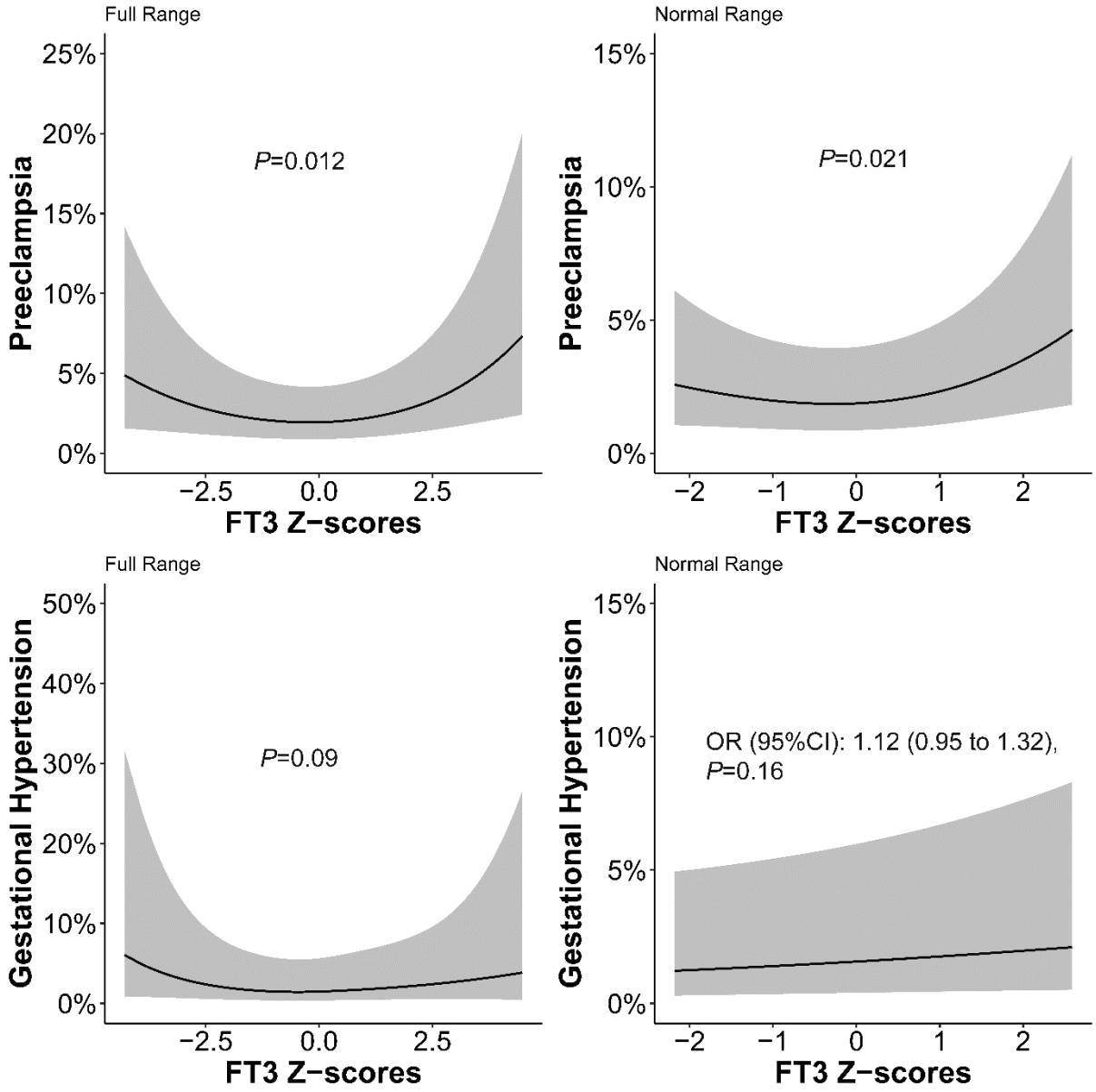


*A composite of preeclampsia and gestational hypertension only in studies with data on both outcomes.

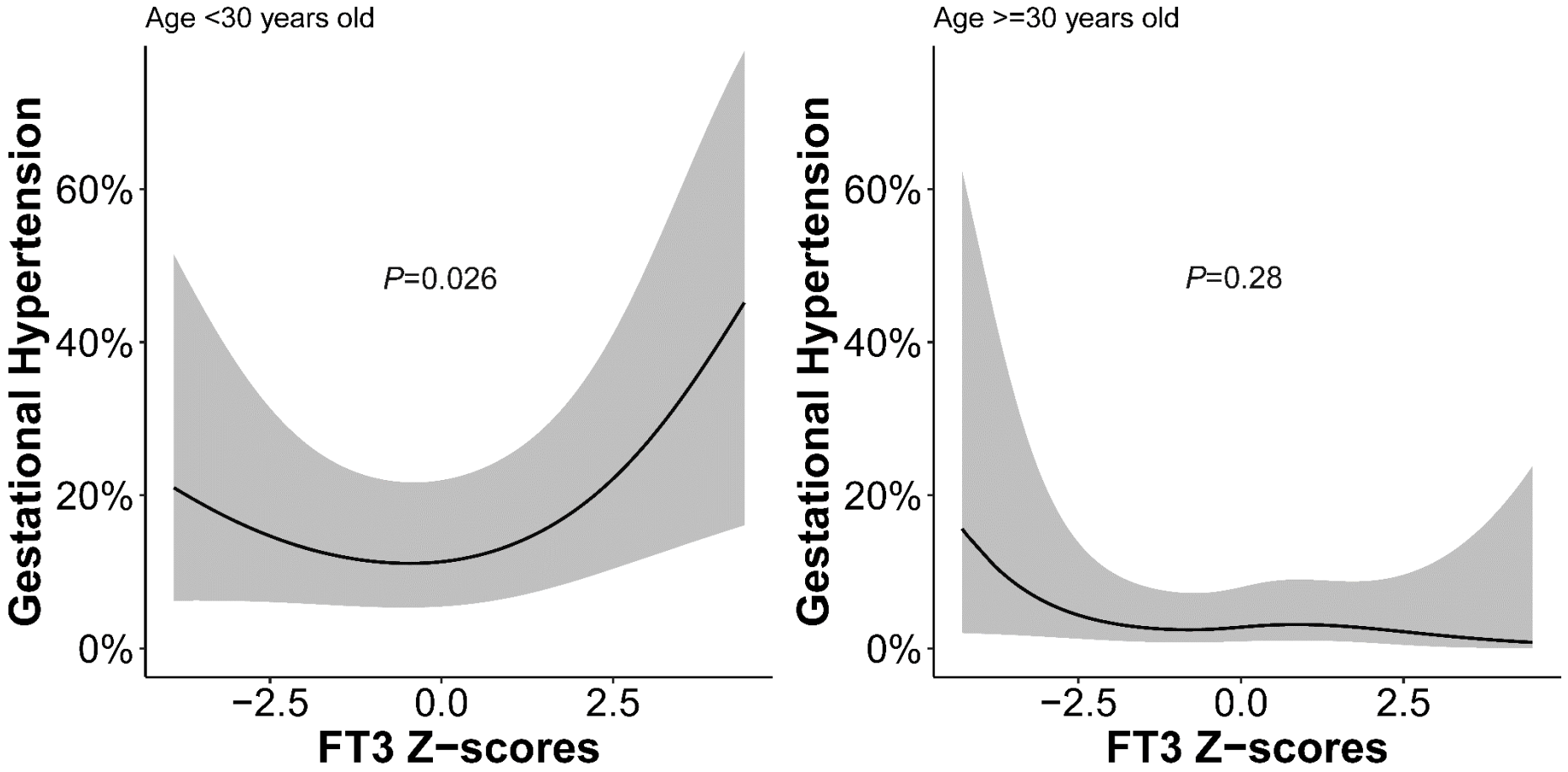
Supplemental Figure 4. Association of TT3 with preeclampsia and gestational hypertension with analyses limited to gestational age of sampling earlier than 24 weeks.



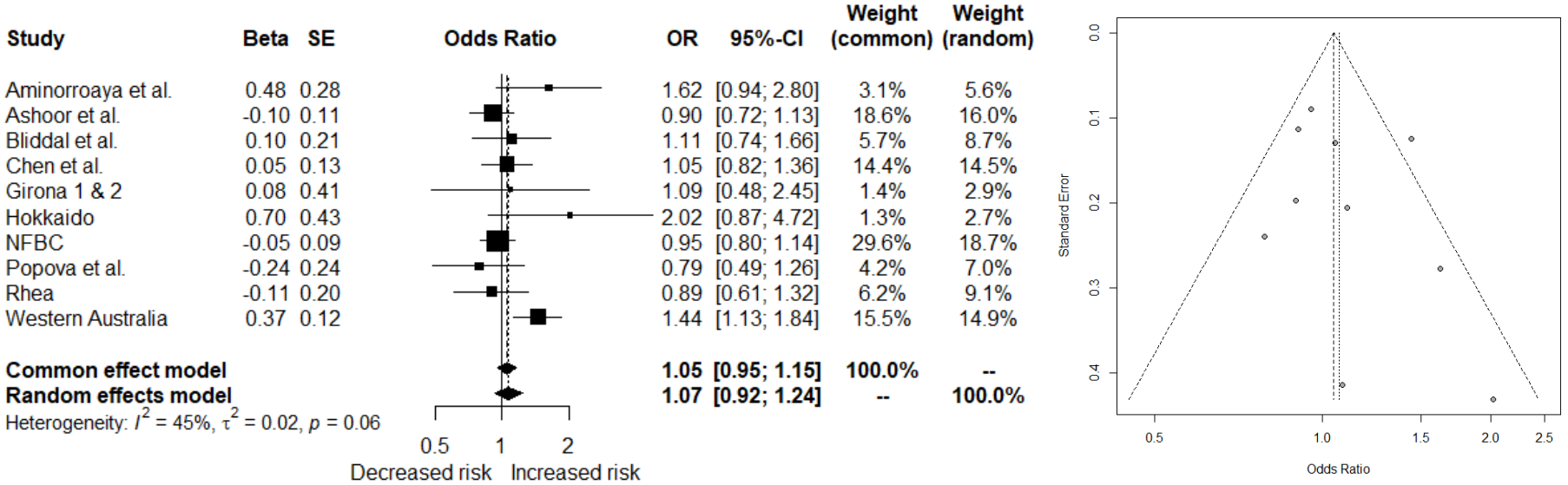
Supplemental Figure 5. Association of FT3 with preeclampsia and gestational hypertension with analyses limited to gestational age of sampling earlier than 24 week.



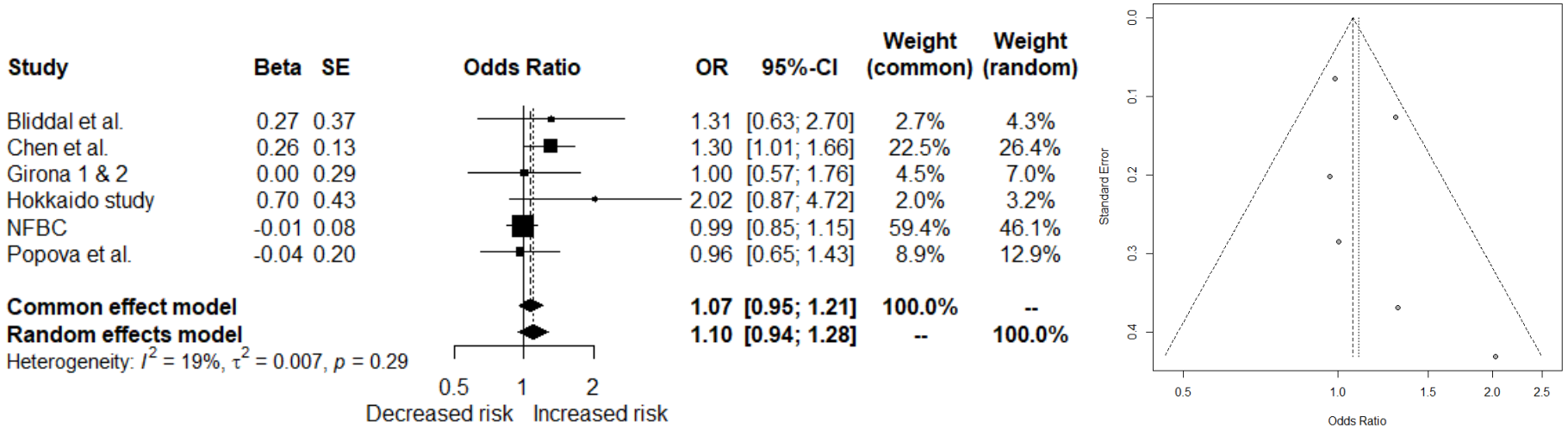
Supplemental Figure 6. Association of FT3 with gestational hypertension according to maternal age.



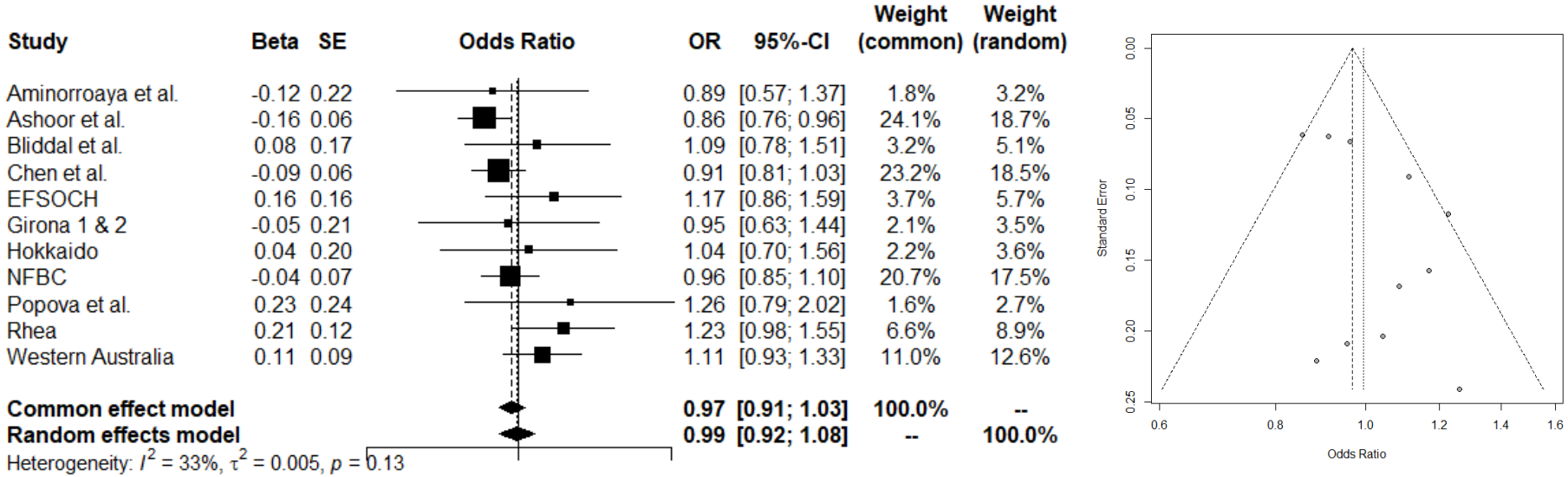
Supplemental Figure 7. Two-step meta-analyses and funnel plots for the association of FT3 with preeclampsia.



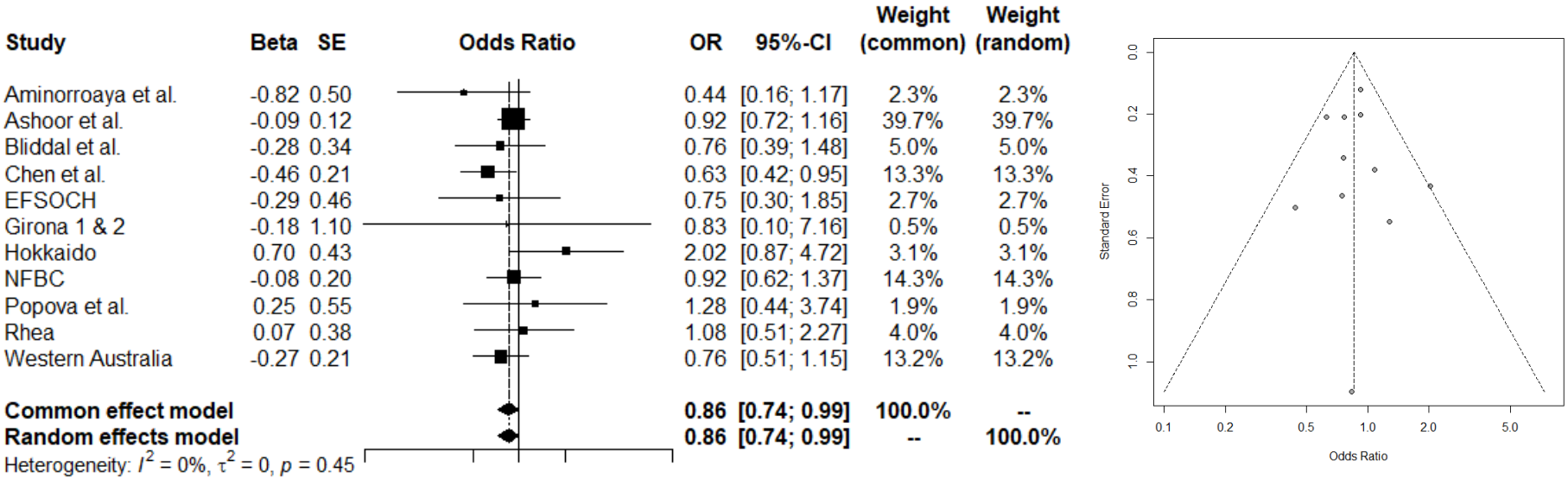
Supplemental Figure 8. Two-step meta-analyses and funnel plots for the association of FT3 with gestational hypertension.



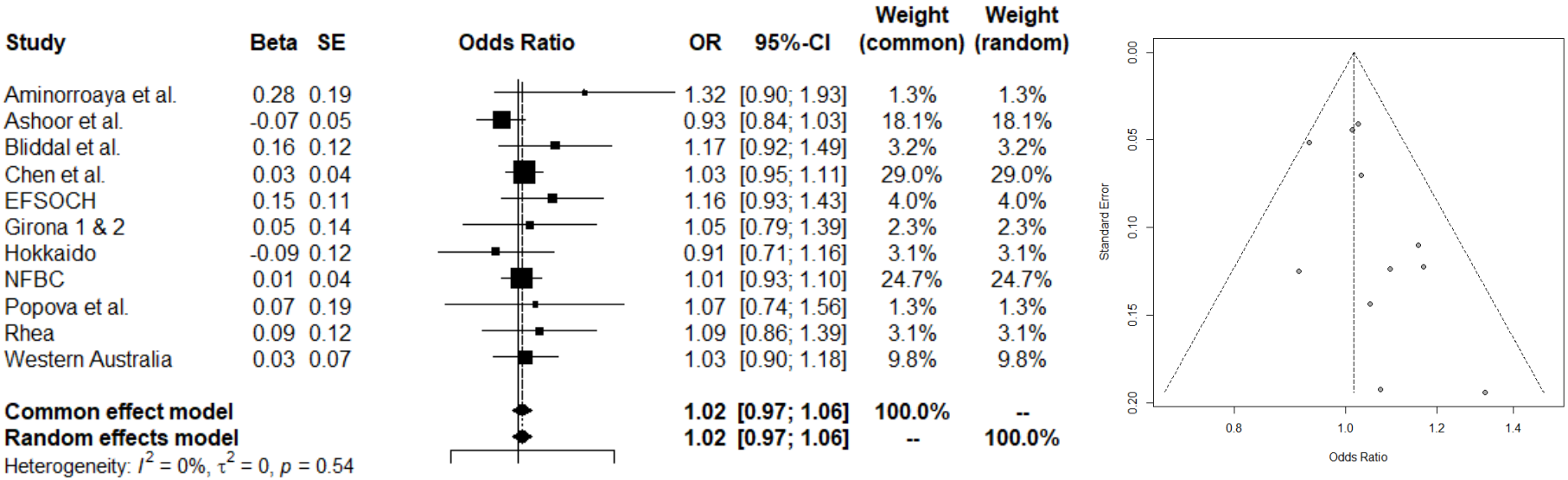
Supplemental Figure 9. Two-step meta-analyses and funnel plots for the association of FT3 with preterm birth.



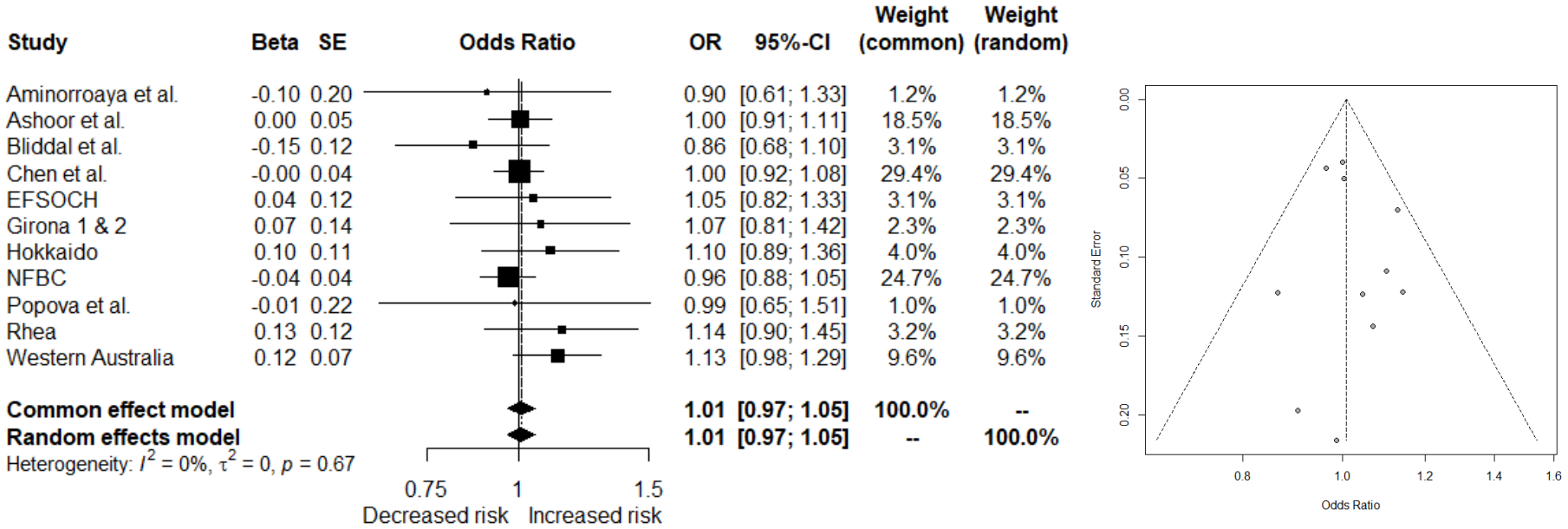
Supplemental Figure 10. Two-step meta-analyses and funnel plots for the association of FT3 with very preterm birth.



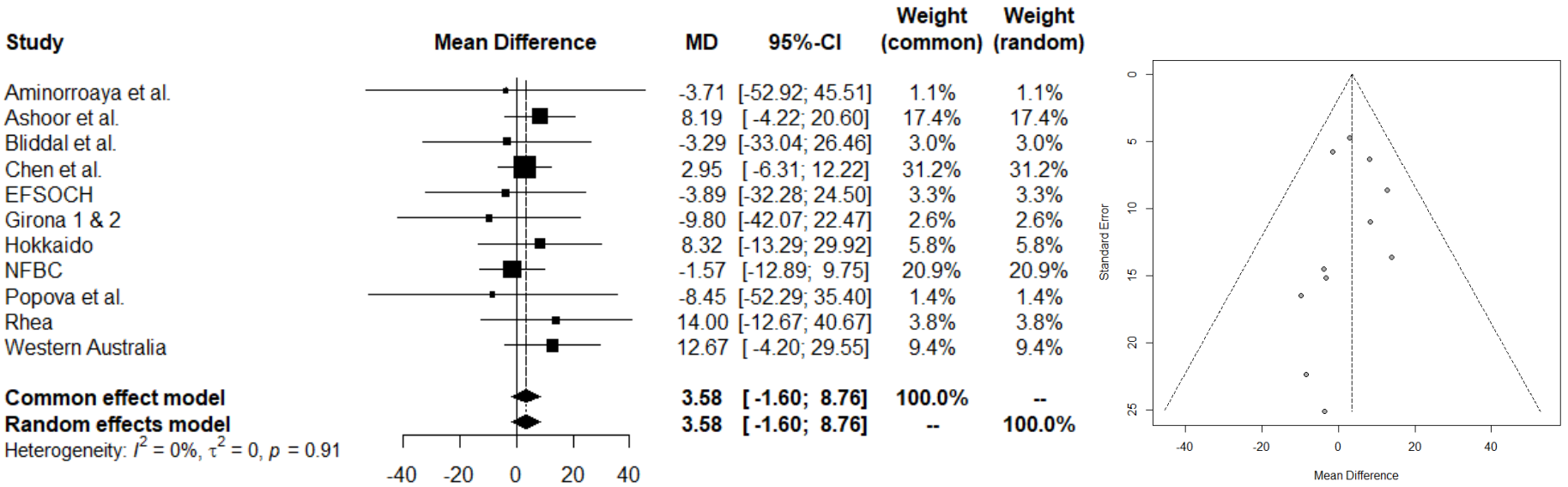
Supplemental Figure 11. Two-step meta-analyses and funnel plots for the association of FT3 with small for gestational age.



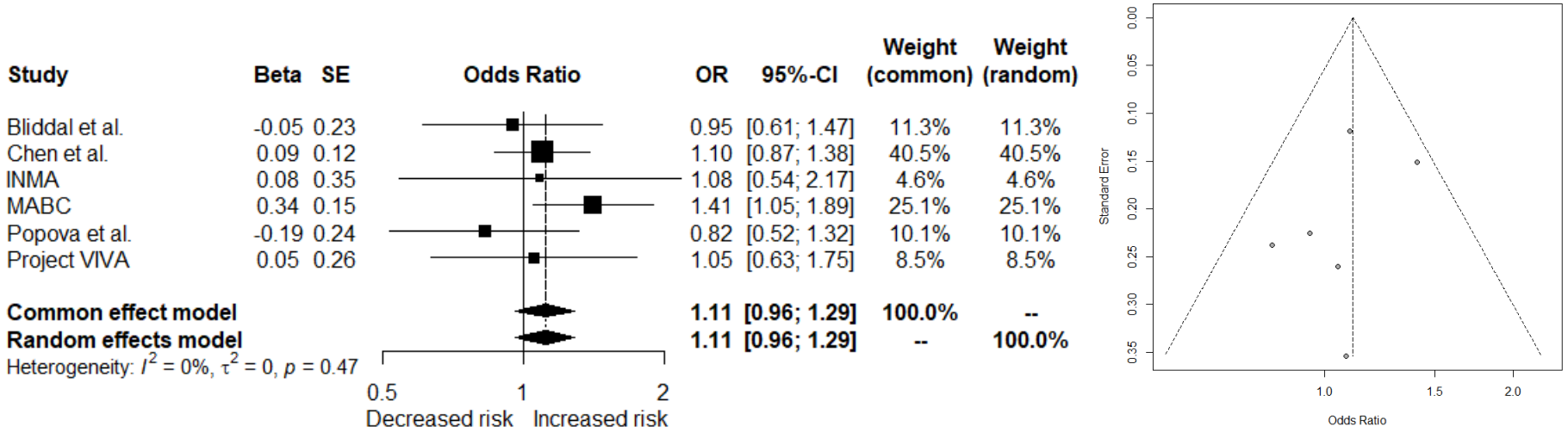
Supplemental Figure 12. Two-step meta-analyses and funnel plots for the association of FT3 with large for gestational age.



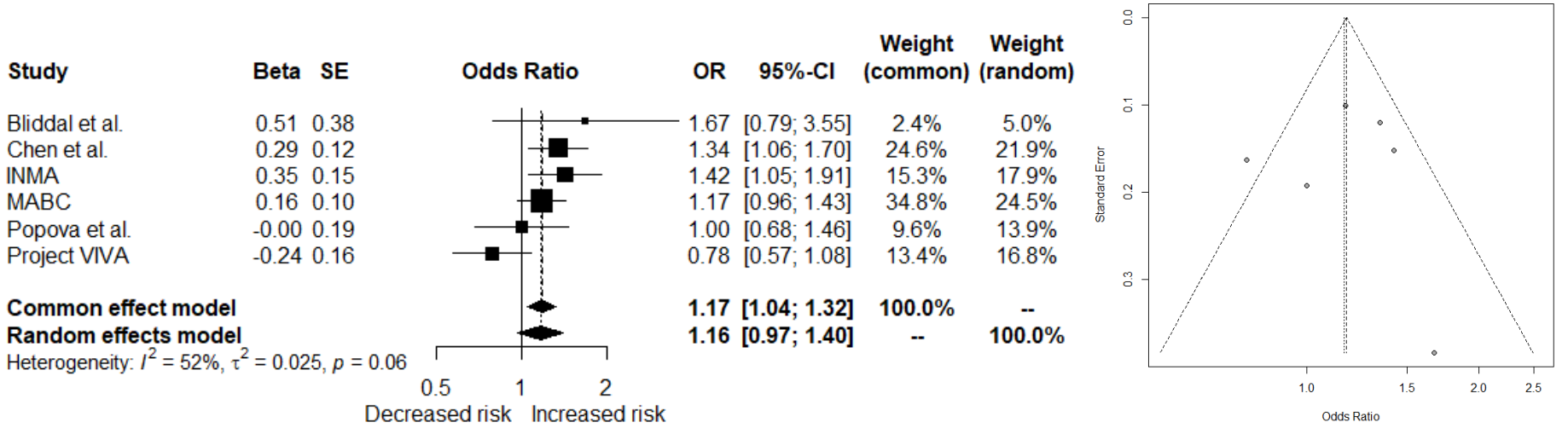
Supplemental Figure 13. Two-step meta-analyses and funnel plots for the association of FT3 with birth weight.



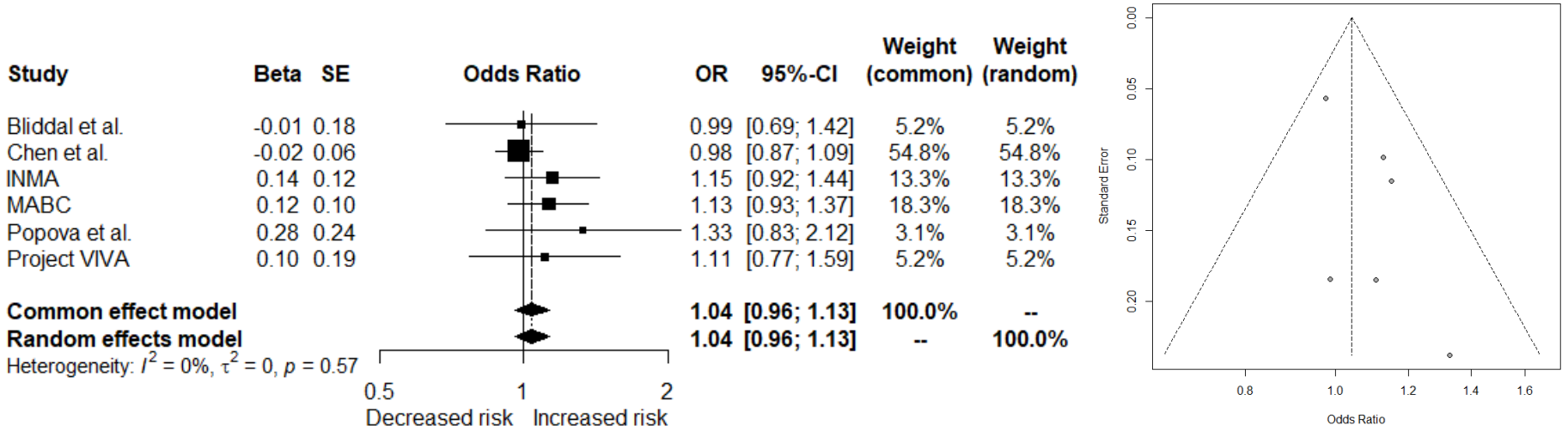
Supplemental Figure 14. Two-step meta-analyses and funnel plots for the association of TT3 with preeclampsia.



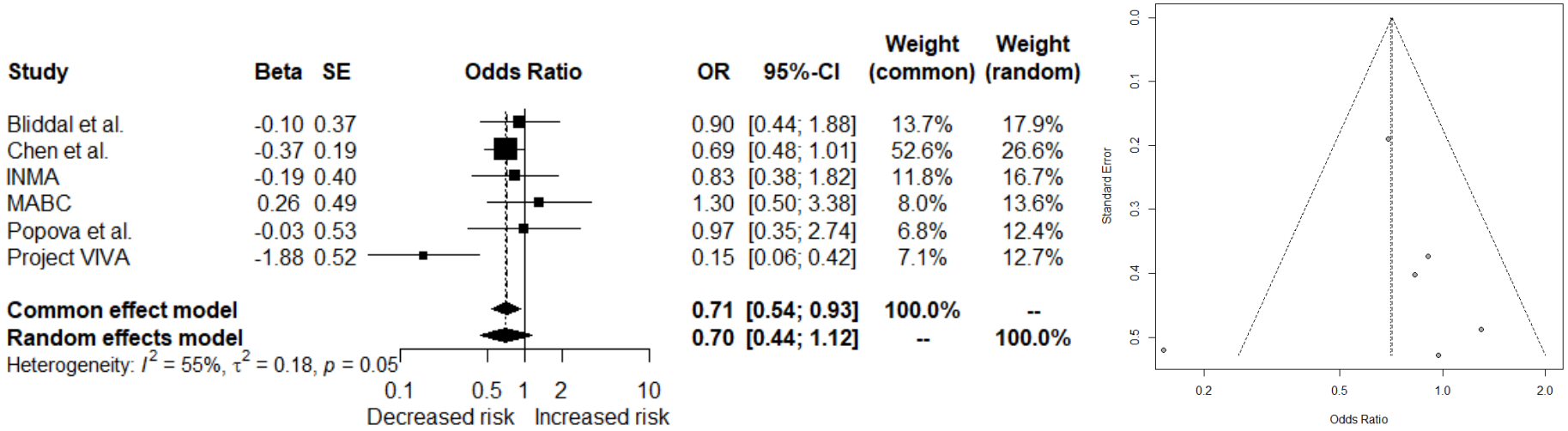
Supplemental Figure 15. Two-step meta-analyses and funnel plots for the association of TT3 with gestational hypertension.



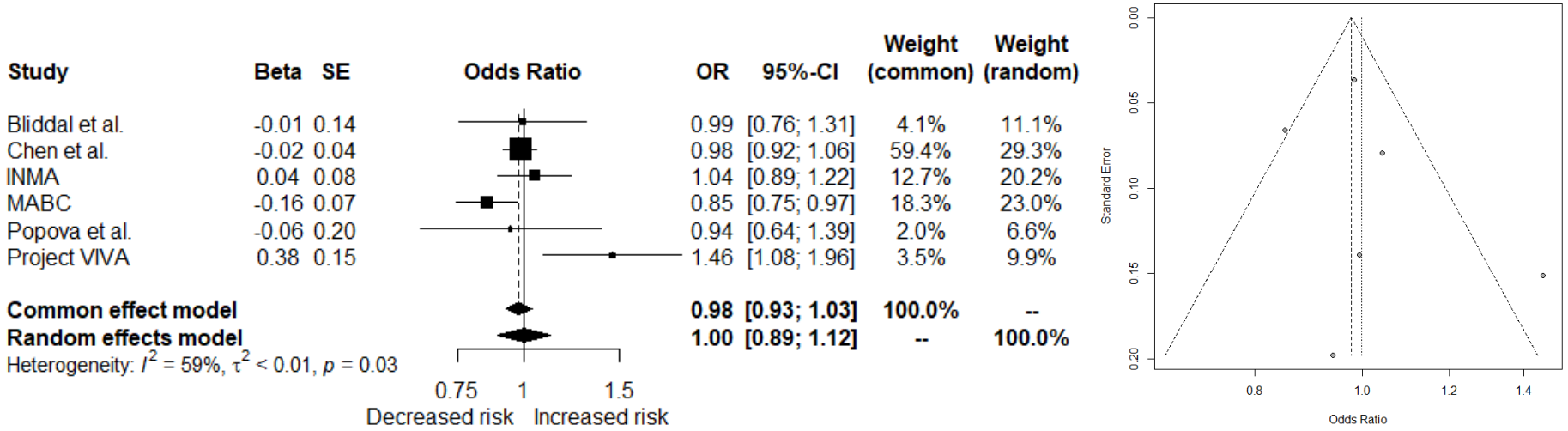
Supplemental Figure 16. Two-step meta-analyses and funnel plots for the association of TT3 with preterm birth.



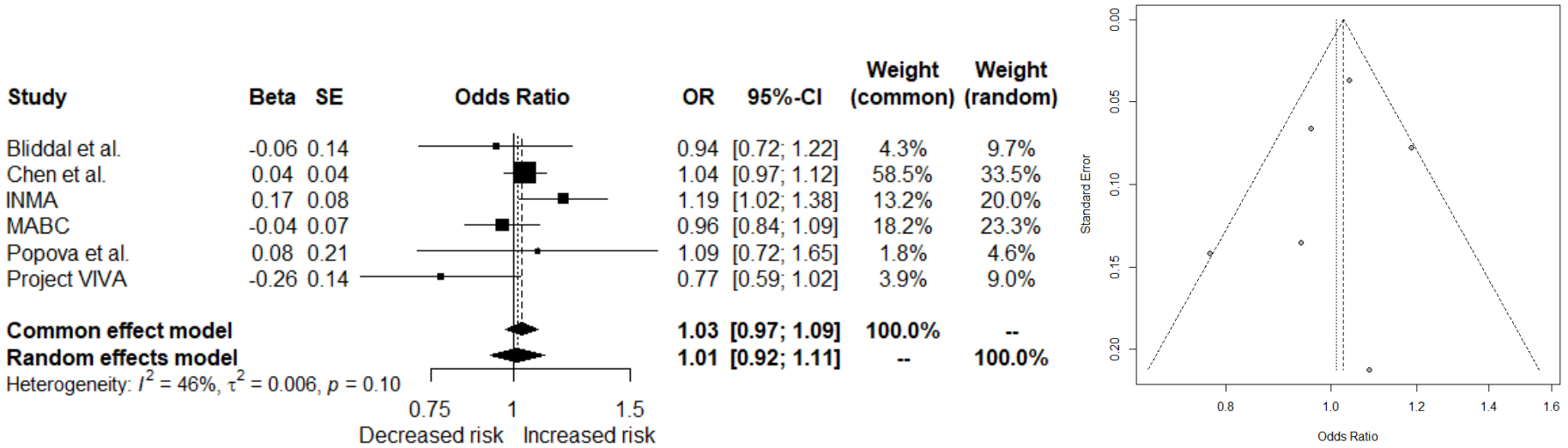
Supplemental Figure 17. Two-step meta-analyses and funnel plots for the association of TT3 with very preterm birth.



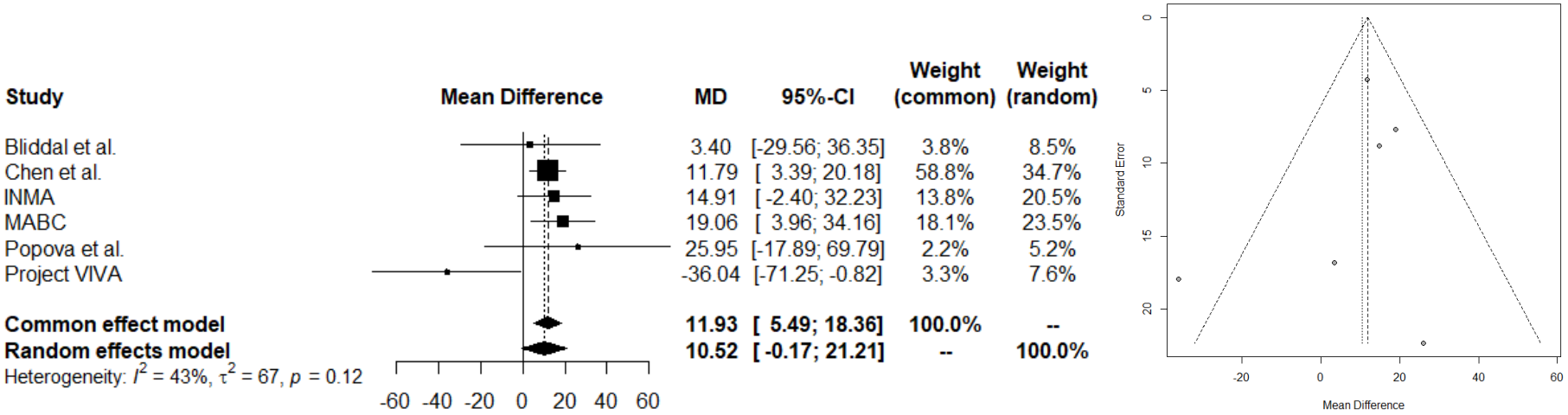
Supplemental Figure 18. Two-step meta-analyses and funnel plots for the association of TT3 with small for gestational age.



Supplemental Figure 19. Two-step meta-analyses and funnel plots for the association of TT3 with large for gestational age.



Supplemental Figure 20. Two-step meta-analyses and funnel plots for the association of TT3 with birth weight.



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