

Supplementary Online Content

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

eMethods. Measurements of Covariates

Information on participants' age at enrollment (year), country of birth (country of the cohort, foreign country), marital status (single, yes/no), tobacco smoke use (never, yes/no), and parity (nulliparous, one, two or more) were collected by self-reported questionnaires or in face-to-face interviews during the first prenatal visit or throughout pregnancy. In ABCD, alcohol intake was asked as the number of glass for alcoholic beverages per week during pregnancy. In Generation R, women were asked during each trimester of pregnancy if they had used any alcoholic drinks during the three months prior to the date of visit. In Rhea, the food-frequency questionnaire (FFQ) was used during the second trimester to assess alcohol intake (gram/day) and then categorized into drinks per week directly. In INMA, weekly alcohol intake was asked by type in categories at enrollment. Project Viva obtained data on consumption of alcoholic beverages from the FFQ that expectant mothers completed in early and mid-pregnancy. Maternal height and weight were measured (Generation R, INMA, and Rhea) or self-reported (ABCD, Project Viva) at enrollment and used to estimate pre-pregnancy body mass index (BMI, kg/m²). Maternal education was the highest completed schooling. Cohort-specific categories for elementary, secondary, and higher levels of education were: ABCD (<6 years /6–10 years/ >10 years); Generation R (primary/secondary/university degree or higher); Rhea (compulsory education up to 9 years/3–5 additional years/university degree or higher); INMA (<11 years /12–15 years/ ≥16 years of education); and Project Viva (high school or less, some college, and college graduate or graduate degree). Social class was described using information on household income or on occupation obtained from self-administered questionnaires. Social class was classified as low income/social class, medium income/social class, and high income/social class according to the International Standard Classification of Occupations (except for Project Viva in which annual household income was used only). Gestational age at the time of thyroid measurement (week) was based on ultrasound data and, if unavailable, on the first day of last menstrual period.

eTable 1. Immunoassays Used for Measurement of Thyroid Parameters in 5 Participating Cohorts

Cohort	Assay
ABCD	Thyroid hormones: Access immunoanalyzer of Beckman Coulter, Inc. Thyroid peroxidase antibody: Elisa ELIZEN TG Ab (E-CK-96), Zentech, Luik, Belgium (TPOAb positive if >80 kIU/L). Interassay coefficients of variation for free T ₄ : 3.1-5.0%. Interassay coefficients of variation for TSH: 5.0%. Interassay coefficient variation for TPOAb: 13.4%.
Generation R	Thyroid hormones: chemiluminescence assays (Vitros ECI; Ortho Clinical Diagnostics, Rochester, NY, USA). Thyroid peroxidase antibody: Phadia 250 immunoassay (Phadia AB, Uppsala, Sweden) (TPOAb positive if >60 IU/ml). Interassay and intra-assay coefficients of variation for free T ₄ : 4.7-5.4% and 1.4-2.7%. Interassay and intra-assay coefficients of variation for TSH: 2.5-4.1% and 1.0-1.2%. Interassay and intra-assay coefficients for TPOAb: 2.5-4.8% and 4.1-4.7%.
INMA	Thyroid hormones: AutoDEL-FIA (PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) and a lanthanide metal europium (Eu) label. Interassay and intra-assay coefficients of variation for free T ₄ : 4.0-6.1% and 3.0-3.7%. Interassay and intra-assay coefficients of variation for TSH: 2.6-3.0% and 1.7-7.7%.
Rhea	Thyroid hormones and thyroid peroxidase antibody: IMMULITE 2000 immunoassay system (Siemens Healthcare Diagnostics, ILL 60015-0778, USA) (TPOAb positive if ≥35 IU/mL). Interassay and intra-assay coefficients of variation <12.5% and < 12.5% for TSH. Interassay and intra-assay coefficients of variation <7.1% and <7.8% for free T ₄ . Interassay and intra-assay coefficients of variation <7.2% and 7.4% for TPOAb.
Project Viva	Thyroid hormones: Chemiluminescence assays (Centaur; Bayer, Fernwald, Germany). Thyroid peroxidase antibody: the Nichols Advantage assay (Nichols Institute Diagnostics) (TPOAb positive if >2.0 IU/ml). Interassay and intra-assay coefficients of variation <4.7% and < 2.9% for TSH.

eTable 2. Cohort-Specific Cutoffs for Free Thyroxine (T₄) and Thyrotropin (TSH) in 5 Cohorts

	Free T ₄ (pmol/L)		TSH (mIU/L)	
	5 th	95 th	5 th	95 th
ABCD	7.46	12.09	0.26	2.65
Generation R	11.00	20.42	0.25	4.18
INMA	8.35	13.10	0.27	3.05
Rhea	12.16	19.03	0.24	2.60
Project Viva ^a	1.60	2.70	0.13	2.93

^a In Project Viva, free T₄ index was calculated from total T₄ × triiodothyronine resin uptake

Values were calculated in participants with no thyroid disease or thyroid medication use who were thyroid peroxidase antibody negative.

eTable 3. Participants' Characteristics in Pregnant Women Included in the Analysis and Those Women Excluded Because of Missing Data in Exposure and/or Outcome

	ABCD (NL)			Generation R (NL)			INMA (ES)			Rhea (GR)			Project Viva (US)		
	N Incl. n=4399	Incl. n=3867	p	N Incl. n=6004	Incl. n=2605	p	N Incl. n=263	Incl. n=2239	p	N Incl. n=355	Incl. n=483	p	N Incl. n=1298	Incl. n=737	p
Age at enrollment, y	33.5 (4.5)	33.2 (4.9)	<0.001	29.1 (5.5)	30.8 (4.7)	<0.001	31.7 (5.2)	31.4 (4.2)	0.47	31.7 (5.2)	31.4 (4.2)	0.20	31.3 (5.4)	35.5 (4.8)	<0.001
Educational levels, %															
Elementary	28.5	17.8	<0.001	31.8	17.2	<0.001	31.6	24.4	<0.001	22.4	20.1	0.22	4.1	1.2	<0.001
Secondary	28.0	27.6		31.3	30.4		46.2	41.2		46.9	53.0		36.9	24.3	
Higher	43.5	54.6		36.9	52.4		22.2	34.4		30.7	26.9		59.0	74.5	
Nulliparous, %	55.7	60.5	0.33	53.6	60.7	<0.001	55.4	56.6	<0.001	43.6	40.4	0.57	46.8	49.7	0.46
Country of birth, foreign, %	45.3	31.3	<0.001	58.7	42.8	<0.001	12.4	8.4	0.04	11.9	8.9	0.16	24.2	16.2	<0.001
Marital status, single, %	9.3	7.1	<0.001	16.7	11.0	<0.001	1.8	1.7	0.79	10.5	13.0	0.29	10.7	5.4	<0.001
History of smoking, never, %	92.2	93.8	0.13	71.3	75.6	<0.001	60.4	68.2	0.01	66.2	66.7	0.57	68.1	69.5	0.05
Alcohol intake in pregnancy, %	17.1	24.1	<0.001	35.5	46.7	<0.001	12.3	9.6	0.27	34.7	25.1	0.01	60.2	73.6	<0.001
Social class, low, %	16.1	12.0	<0.001	5.2	3.4	<0.001	54.4	53.1	0.54	6.4	8.3	0.17	6.8	1.4	<0.001
Pre-pregnancy BMI, kg/m ²	22.8 (3.7)	22.6 (3.4)	0.30	23.7 (4.4)	23.5 (4.2)	0.11	23.7 (4.1)	23.5 (4.2)	0.39	23.7 (4.1)	23.5 (4.2)	0.66	25.0 (5.7)	24.5 (5.1)	0.03

BMI: Body mass index; Incl.: Included in the analysis; N Inc.: Not included in the analysis because of missing data in exposure and outcome.

Numbers are mean (SD) for continuous variables (age and pre-pregnancy BMI) and percentages for categorical variables.

eTable 4. Variables Used in Forward Selection Logistic Regression Model to Calculate Inverse Probability of Attrition Weights

Variables	Cohorts											
	ABCD		Generation R		INMA		Rhea		Project Viva			
	Explored	Include d	Explore d	Include d	Explore d	Include d	Explore d	Include d	Explore d	Include d		
Age of pregnant women at enrollment	X		X	X	X	X	X	X	X	X		X
Gestational age at thyroid measurement	X	X	X	X	X	X	X	X	X			
Educational levels	X		X		X	X	X	X	X	X		X
Marital status	X		X		X	X	X	X	X	X		
Country of birth	X	X	X	X	X	X	X	X	X	X		X
History of smoking	X	X	X	X	X		X		X			
Alcohol intake during pregnancy	X		X	X	X	X	X	X	X	X		X
Socioeconomic status	X		X		X	X	X		X	X		X
Pre-pregnancy body mass index	X		X		X	X	X		X			
Parity	X		X	X	X	X	X		X			
Second hand smoking	X		X	X	X		X	X	X			
Intelligence Quotient (IQ)			X	X	X		X		X			
Psychiatric symptoms	X		X		X		X		X			
Urinary iodine during pregnancy			X		X		X		X			
Urinary creatinine during pregnancy			X		X		X		X			
Iodine from diet (µg/day)					X	X	X		X			
Gestational age at iodine assessment			X		X	X	X	X	X			

eTable 5. Imputation Modelling

Software used and key settings: STATA 14.0 software (Stata Corporation, College Station, Texas) – Ice command (with 10 cycles)
Number of imputed datasets created: 25
Variables included in the imputation procedure for ABCD: Thyroid stimulating hormone (TSH) in pregnancy (mIU/l), Free thyroxine (T₄) in pregnancy (µg/dl), particulate matter (PM)_{2.5} absorbance - averaged in the first trimester of pregnancy, PM_{2.5-10} - averaged in the first trimester of pregnancy, NO₂ - averaged in the first trimester of pregnancy, pregnant women's characteristics (education levels, country of birth, women's age at enrollment, gestational age at thyroid measurement, history of smoking, alcohol intake during pregnancy, social class, marital status, parity, pre-pregnancy body mass index, and psychiatric symptoms). Variables included in the imputation procedure for Generation R: TSH in pregnancy (mIU/l), free T₄ in pregnancy (µg/dl), PM_{2.5} absorbance - averaged in the first trimester of pregnancy, PM_{2.5-10} - averaged in the first trimester of pregnancy, NO₂ - averaged in the first trimester of pregnancy, pregnant women's characteristics (education level, country of birth of parents, women's age at enrollment, gestational age at thyroid measurement, history of smoking, alcohol intake during pregnancy, social class, marital status, parity, secondhand smoking, IQ, pre-pregnancy body mass index, and psychiatric symptoms, urinary iodine concentrations during pregnancy, urinary creatinine concentrations during pregnancy, and gestational age at iodine assessment). Variables included in the imputation procedure for INMA: TSH in pregnancy (mIU/l), free T₄ in pregnancy (µg/dl), PM_{2.5} absorbance - averaged in the first trimester of pregnancy, PM_{2.5-10} - averaged in the first trimester of pregnancy, NO₂ - averaged in the first trimester of pregnancy, maternal characteristics (education levels, country of birth, women's age at enrollment, gestational age at thyroid measurement, history of smoking, alcohol intake during pregnancy, social class, marital status, parity, secondhand smoking, IQ, pre-pregnancy body mass index, psychopathological symptoms, urinary iodine concentrations during pregnancy, urinary creatinine concentrations during pregnancy, iodine from diet (µg/day) and gestational age at iodine assessment (data on urinary iodine concentrations and gestational age at assessment were not available in the region of Asturias; data on PM was only available in Sabadell). Variables included in the imputation procedure for Rhea: TSH in pregnancy (mIU/l), free T₄ in pregnancy (µg/dl), PM_{2.5} absorbance - averaged in the first trimester of pregnancy, PM_{2.5-10} - averaged in the first trimester of pregnancy, pregnant women's characteristics (education levels, country of birth, women's age at enrollment, gestational age at thyroid measurement, history of smoking, alcohol intake during pregnancy, social class, marital status, parity, secondhand smoking, IQ, pre-pregnancy body mass index, psychopathological symptoms, urinary iodine concentrations during pregnancy, urinary creatinine concentrations during pregnancy, iodine from diet (µg/day) and gestational age at iodine assessment). Variables included in the imputation procedure for Project Viva: TSH in pregnancy (mIU/l), free T₄ index in pregnancy, PM_{2.5} - averaged in the first trimester of pregnancy, Black carbon - averaged in the first trimester, NO₂ - averaged in the second trimester, pregnant women's characteristics (education levels, country of birth, women's age at enrollment, gestational age at thyroid measurement, history of smoking, alcohol intake during pregnancy, social class, marital status, parity, secondhand smoking, IQ, pre-pregnancy body mass index, psychopathological symptoms, urinary iodine concentrations during pregnancy, urinary creatinine concentrations during pregnancy, iodine levels from diet (µg/day), gestational age at iodine assessment).
Treatment of binary/categorical variables: logistic and multinomial models
Statistical interactions included in imputation models: none

eTable 6. Concentrations of Air Pollutants Averaged Over the First Trimester of Pregnancy Based on Residential Addresses in 5 Cohorts

ABCD	Median	Interquartile range
NO ₂	41.6	14.7
NO _x	68.7	38.3
PM _{2.5}	20.6	4.5
PM ₁₀	34.6	7.20
PM _{2.5-10}	13.9	3.1
PM _{2.5} absorbance	2.00	1.1
Generation R		
NO ₂	40.7	15.5
NO _x	60.7	34.8
PM _{2.5}	19.7	3.6
PM ₁₀	32.2	6.5
PM _{2.5-10}	12.0	3.0
PM _{2.5} absorbance	1.7	0.7
INMA		
NO ₂	27.2	22.2
NO _x	51.3	45.2
PM _{2.5}	15.0	4.0
PM ₁₀	27.3	7.4
PM _{2.5-10}	12.2	3.9
PM _{2.5} absorbance	2.3	1.6
Rhea		
PM _{2.5}	12.4	2.9
PM ₁₀	31.3	6.7
PM _{2.5-10}	19.0	3.8
PM _{2.5} absorbance	1.5	0.7
Project Viva		
NO ₂	21.6	2.6
PM _{2.5}	11.5	1.6

Nitrogen dioxide: NO₂; Nitrogen oxides: NO_x; Not available: NA; Particulate matter less than 10µm: PM₁₀; Particulate matter less than 2.5µm: PM_{2.5}; Particulate matter between 2.5 and 10µm: PM_{coarse}; Reflectance of PM_{2.5} filters: PM_{2.5} absorbance.

Concentrations are in µg/m³ except for PM_{2.5} absorbance, which is expressed in 10⁻⁵m⁻¹. Data on PM was only available in Sabadell region of INMA

eTable 7. Spearman Correlations Between Concentrations of Traffic-Related Air Pollutants in 5 Cohorts

ABCD	NO ₂	NO _x	PM ₁₀	PM _{2.5}	PM _{2.5-10}
NO _x	0.912				
PM ₁₀	0.427	0.287			
PM _{2.5}	0.314	0.205	0.948		
PM _{2.5-10}	0.496	0.330	0.951	0.819	
PM _{2.5} absorbance	0.868	0.868	0.543	0.498	0.534
Generation R					
NO _x	0.925				
PM ₁₀	0.443	0.378			
PM _{2.5}	0.347	0.241	0.954		
PM _{2.5-10}	0.438	0.380	0.875	0.838	
PM _{2.5} absorbance	0.924	0.912	0.517	0.415	0.457
INMA					
NO _x	0.880				
PM ₁₀	0.839	0.862			
PM _{2.5}	0.796	0.837	0.932		
PM _{2.5-10}	0.780	0.794	0.941	0.766	
PM _{2.5} absorbance	0.793	0.970	0.864	0.868	0.769
Rhea					
PM _{2.5}	NA	NA	0.822		
PM _{2.5-10}	NA	NA	0.936	0.592	
PM _{2.5} absorbance	NA	NA	0.101	0.202	-0.030
Project Viva					
PM _{2.5}	-0.198	NA	NA	NA	NA

Nitrogen dioxide: NO₂; Nitrogen oxides: NO_x; Not available: NA; Particulate matter less than 10µm: PM₁₀; Particulate matter less than 2.5µm: PM_{2.5}; Particulate matter between 2.5 and 10µm: PM_{2.5-10}; Reflectance of PM_{2.5} filters: PM_{2.5} absorbance.

Data on PM was only available in Sabadell region of INMA.

eTable 8. Associations Between Exposure to Ambient Air Pollutants in the First Trimester and Thyroid Function During Pregnancy: Unadjusted Analysis

	Hypothyroxinemia					High TSH			
	N ^a	OR (95%CI)	P _h	I ²		N ^a	OR (95%CI)	P _h	I ²
NO ₂ (per Δ10 μg/m ³)	4	0.88 (0.69-1.12)	0.01	75.00		4	1.02 (0.94-1.12)	0.78	0.00
NO _x (per Δ 20 μg/m ³)	3	0.91 (0.83-1.00)	0.25	27.74		3	1.00 (0.94-1.06)	0.79	0.00
PM _{2.5} (per Δ 5 μg/m ³)	5	1.11 (0.89-1.39)	0.28	21.48		5	1.16 (0.94-1.45)	0.19	34.39
PM ₁₀ (per Δ 10 μg/m ³)	4	1.02 (0.79-1.31)	0.27	23.68		4	1.16 (0.87-1.55)	0.09	53.67
PM _{2.5-10} (per Δ 5 μg/m ³)	4	0.90 (0.60-1.37)	0.03	66.02		4	1.12 (0.84-1.50)	0.10	52.34
PM _{2.5} absorbance (per Δ 10 ⁻⁵ m ⁻¹)	4	0.97 (0.82-1.14)	0.52	0.00		4	1.10 (0.96-1.26)	0.90	0.00

CI: Confidence interval; OR: Odds ratio; NO₂: Nitrogen dioxide; NO_x: Nitrogen oxides; P_h: P value of heterogeneity; PM₁₀: Particulate matter less than 10μm; PM_{2.5}: Particulate matter less than 2.5μm; PM_{2.5-10}: Particulate matter between 2.5 and 10μm; PM_{2.5}absorbance: Reflectance of PM_{2.5} filters; T₄: Thyroxine; TPOAb: Thyroid peroxidase antibodies; TSH: Thyroid stimulating hormone.

Odds ratios (95%CI) were estimated using random-effects meta-analysis by cohort (ABCD, Generation R, INMA, Rhea, and Project Viva).

We defined hypothyroxinemia as free T₄ below the 5th percentile of cohort distribution despite normal TSH. Higher TSH was defined as values > 95th percentile. I² refers to the percentage of the total variability due to between-areas heterogeneity. P value of heterogeneity was estimated using the Cochran's Q test.

^a Number of cohorts included in the meta-analysis. Data on PM was only available in Sabadell region of INMA.

eTable 9. Associations Between Exposure to Ambient Air Pollutants in the First Trimester and Thyroid Function During Pregnancy: Complete Case Analysis

	Hypothyroxinemia					High TSH			
	N ^a	OR (95%CI)	P _h	I ²		N ^a	OR (95%CI)	P _h	I ²
NO ₂ (per Δ10 μg/m ³)	4	0.97 (0.83-1.12)	0.30	19.30		4	1.01 (0.92-1.11)	0.65	0.00
NO _x (per Δ 20 μg/m ³)	3	0.95 (0.86-1.04)	0.64	0.00		3	0.98 (0.92-1.05)	0.69	0.00
PM _{2.5} (per Δ 5 μg/m ³)	5	1.28 (0.99-1.66)	0.69	0.00		5	1.09 (0.71-1.67)	0.03	65.90
PM ₁₀ (per Δ 10 μg/m ³)	4	1.30 (1.01-1.67)	0.36	8.1		4	1.11 (0.81-1.53)	0.09	50.60
PM _{2.5-10} (per Δ 5 μg/m ³)	4	1.12 (0.84-1.49)	0.56	0.00		4	1.11 (0.74-1.65)	0.07	58.00
PM _{2.5} absorbance (per Δ 10 ⁻⁵ m ⁻¹)	4	1.03 (0.83-1.28)	0.88	0.00		4	1.06 (0.91-1.24)	0.59	0.00

CI: Confidence interval; OR: Odds ratio; NO₂: Nitrogen dioxide; NO_x: Nitrogen oxides; P_h: P value of heterogeneity; PM₁₀: Particulate matter less than 10μm; PM_{2.5}: Particulate matter less than 2.5μm; PM_{2.5-10}: Particulate matter between 2.5 and 10μm; PM_{2.5}absorbance: Reflectance of PM_{2.5} filters; T₄: Thyroxine; TPOAb: Thyroid peroxidase antibodies; TSH: Thyroid stimulating hormone.

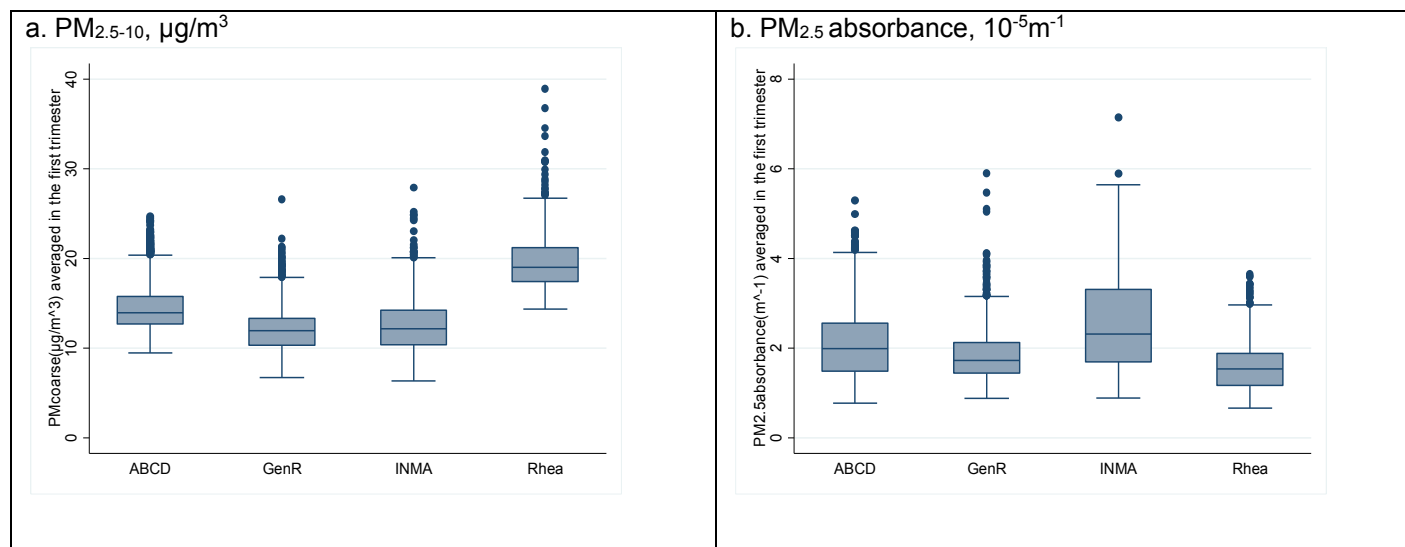
Odds ratios (95%CI) were estimated using random-effects meta-analysis by cohort (ABCD, Generation R, INMA, Rhea, and Project Viva).

We defined hypothyroxinemia as free T₄ below the 5th percentile of cohort distribution despite normal TSH. Higher TSH was defined as values > 95th percentile. I² refers to the percentage of the total variability due to between-areas heterogeneity. P value of heterogeneity was estimated using the Cochran's Q test.

Models were adjusted for pregnant women's age at enrollment, educational level, country of birth, gestational age at thyroid measurement, history of smoking, alcohol intake during pregnancy, socioeconomic status, marital status, parity, and pre-pregnancy body mass index. In addition, analysis in INMA was adjusted for regions (Sabadell, Gipuzkoa, Valencia, and Asturias).

^a Number of cohorts included in the meta-analysis. Data on PM was only available in Sabadell region of INMA.

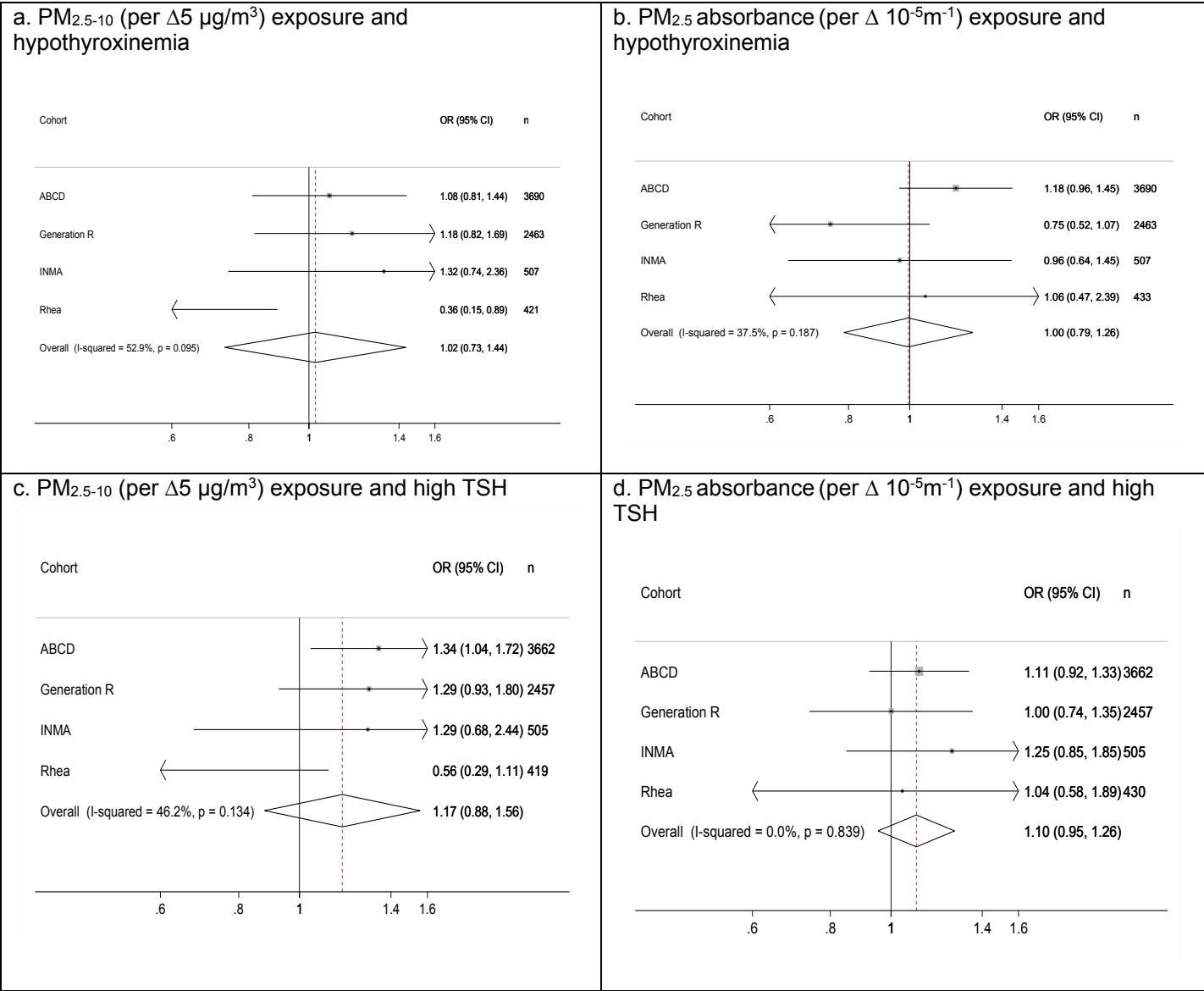
eFigure 1. Distribution of PM_{2.5-10} and PM_{2.5} Absorbance Averaged Across the First Trimester of Pregnancy in 5 Birth Cohorts



ABCD: Amsterdam Born Children and their development; GenR: the Generation R Study; INMA: Infancia y Medio Ambiente; PM_{2.5-10}: Particulate matter between 2.5 and 10µm; PM_{2.5} absorbance: Reflectance of PM_{2.5} filters

Data are presented as available in each cohort. Data on PM were only available in Sabadell sub-cohort of INMA.

eFigure 2. Exposure to $PM_{2.5-10}$ and $PM_{2.5}$ Absorbance in the First Trimester and Thyroid Function During Pregnancy



ABCD: Amsterdam Born Children and their development; CI: Confidence interval; OR: Odds ratio; P: P value of heterogeneity; $PM_{2.5-10}$: Particulate matter between 2.5 and $10\mu m$; $PM_{2.5}$ absorbance: Reflectance of $PM_{2.5}$ filters; T4: Thyroxine; TSH: Thyroid stimulating hormone.

Odds ratios (95%CI) are shown for the associations between $PM_{2.5-10}$ exposure and hypothyroxinemia (a), $PM_{2.5}$ absorbance exposure and hypothyroxinemia (b), $PM_{2.5-10}$ exposure and high TSH (c), and $PM_{2.5}$ absorbance exposure and high TSH (d), estimated using random-effects meta-analysis by cohort (ABCD, Generation R, INMA, Rhea, and Project Viva).

We defined hypothyroxinemia as free T₄ below the 5th percentile of cohort distribution despite normal TSH. High TSH was defined as values > 95th percentile. I² refers to the percentage of the total variability due to between-areas heterogeneity. P value of heterogeneity was estimated using the Cochran's Q test.

Models were adjusted for pregnant women's age at enrollment, educational level, country of birth, gestational age at thyroid measurement, history of smoking, alcohol intake during pregnancy, socioeconomic status, marital status, parity, and pre-pregnancy body mass index. Data on PM were only available in Sabadell region of INMA. Data are presented as available in each cohort.