Supplementary Online Material

Guxens et al. Air pollution during pregnancy and childhood cognitive and psychomotor development: Six European birth cohorts

Methods 1. Description of the air pollution assessment

Air pollution concentrations at the participants' birth home addresses were estimated by Land-use regression models following a standardized procedure described elsewhere.[1-2] Briefly, air pollution monitoring campaigns in the study regions were mostly performed between October 2008 and January 2011, except for French cohort that were done in 2002 and 2005. In all the regions, at least three two-week measurements within one year of nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) were performed at 80 sites (The Netherlands/Belgium and France) or 40 sites (other regions). In addition, in a subgroup of regions, simultaneous measurements of $PM_{2.5}$ absorbance (determined as the reflectance of $PM_{2.5}$ filters) and PM with aerodynamic diameters of less than 10µm (PM_{10}), less than 2.5µm ($PM_{2.5}$), and between 2.5 and 10µm (PM_{coarse}) were performed.[3-4] Results from the three measurements were then averaged, adjusting for temporal trends using data from a centrally located background monitoring site in each region. Predictor variables on nearby traffic intensity, population/household density, and land use were derived from Geographic Information Systems, and were evaluated to explain spatial variation of annual average concentrations using land-use regression. Land-use regression models were developed for each pollutant metric using all measurement sites, and in addition for background NO_2, using only rural and urban background sites. Land-use regression models were then used to estimate ambient air pollution concentration at the participants' birth home addresses, for which the same Geographic Information Systems predictor variables were collected. Moreover, we used a back-extrapolation procedure to estimate the concentrations back in time during each pregnancy of each woman[5-6] in order to assess if pregnancy period is a relevant exposure period. The estimated yearly concentrations ($C_{yearly,i}$) at each home address i were combined with time-specific measurements from one centrally located background monitoring station by averaging the daily concentrations during 1) the year corresponding to the LUR yearly concentration (C_{yearly}) and 2) each pregnancy p_i considered (C_{p_i}). The ratio C_{p_i}/C_{yearly} constituted the temporal component of the model. For each pollutant, the concentration ($C_{p_i, i}$) estimated at the home address i during pregnancy for woman i was estimated as the product of the temporal (C_{p_i}/C_{yearly}) and spatial ($C_{yearly, i}$) components. If the monitoring station was in function for less than 75% of the pregnancy, we considered C_{p_i} as missing. In some cases, when air quality monitoring data from background station was unavailable for a given pollutant, we used measurements for another pollutant during the same time period as a replacement; the choice of that pollutant used to back-extrapolate another pollutant was based on an extensive study of temporal correlations between pollutants simultaneously available in each region (i.e. NO_X was used when $PM_{2.5}$ absorbance was missing, PM_{10} was used when $PM_{2.5}$ was missing, $PM_{2.5}$ was used when PM_{10} was missing, NO_2 when PM_{10} was missing, and total suspended particles were used for temporal adjustment using a conversion factor for the German cohort). For the Greek cohort, non-back-extrapolated NO_2 and NO_x levels were used since not enough data on routine background monitoring network sites for these pollutants was available. We accounted for change of home address during pregnancy when the date of moving and new address was available in estimation of exposure (Dutch and French cohorts). In addition to predicted concentrations, some regions were able to collect traffic intensity on the nearest road and total traffic load (intensity*length) on all major roads within a 100m buffer.

Methods 2. Description of the cognitive and psychomotor development tests

GENERATION R, the Dutch cohort

MacArthur Communicative Development Inventory (MCDI)

At 1.5 years (range 1.4-1.7), language development was assessed using mother report on the Dutch version of the MacArthur Short Form Vocabulary Checklist (MCDI),[7] a list of 112 monomorphemic root words derived from the complete Dutch version of the MCDI: Words and Sentences.[8] The MCDI is appropriate for measuring the expressive and receptive vocabulary of children aged 16-30 months. The MCDI has excellent internal consistency and test-retest reliability, and concurrent validity.[7]

Minessota Infant Development Inventory (MIDI)

A Dutch translation of the Minnesota Infant Development Inventory (MIDI) was used to assess fine and gross psychomotor developmental milestone attainment of 1-year-old infants (range 0.8-3.4) by maternal report.[9] A total of 24 age-appropriate items for children aged 6-18 months according to the MINI manual's instruction were used.[9] Mothers were asked to indicate the milestones their child is able to perform. By totaling the yes-responses, sum score were obtained for the global psychomotor development.

DUISBURG, the German cohort

Bayley Scales of Infant Development II-second edition (BSID II)

Children's cognitive and psychomotor development was assessed at around 1 year (range 0.9-1.2 years) and 2 years (range 2.0-2.1) using the Bayley Scales of Infant Development second edition (BSID II).[10] The mental development scale consists of 178 items that assess age-appropriate cognitive development, including performance abilities, memory, and early language skills and was defined as general cognitive development scale. The psychomotor development scale consists of 116 items that assess fine and gross psychomotor development as was defined as global psychomotor development scale. All testing was done in the infant's home, usually in the presence of the mother, by 2 specially trained psychologists. For visits of Turkish families a Turkish-speaking co-worker was present and the test instructions were given in Turkish. Psychologists were not aware of any exposure information.

EDEN, the French cohort

McArthur Communicative Development Inventory (MCDI)

At 2 years (range 1.8-2.5), language development was assessed using mother report on the French version of the MacArthur Short Form Vocabulary Checklist (MCDI),[11] a list of 100 monomorphemic root words derived from the complete French version of the MCDI. The MCDI is appropriate for measuring the expressive and receptive vocabulary of children aged 16-30 months.

Ages and Stages Questionnaire (ASQ)

Child psychomotor development was assessed at around 3.2 years (range 2.8-3.9). Fine psychomotor and gross psychomotor development were assessed with the "Ages and Stages Questionnaire",[12] a parent completed questionnaire which contains items grouped by developmental areas. It was developed as a development screening tool filled by parents for child from 4 to 60 months. For each item, there is a choice of three responses: yes-sometimes- not yet to represent the children's ability to perform a task with scores of 10, 5 and 0 awarded to each answer respectively. Domain scores are obtained by the sum of items per domain. There are 6 items for gross psychomotor and 6 items for fine psychomotor development. The global psychomotor development was the sum of fine and gross psychomotor development. ASQ was a part of the postal questionnaire sent at 3 years of age to parents of children of the EDEN cohort.

GASPII, the Italian cohort

Denver Developmental Screening Test II (DDST II)

At 1.3 years (range 1.1-1.7) and the 4years (range 3.3-5.1) Denver Developmental Screening Test II (DDST II) was used to assess the neurodevelopment of the children.[13] It is a test designed for use by the clinician, teacher, or other early childhood professional to monitor the development of infants and preschool-aged children. The tests consists of 125 items covering four general functions: personal-social (such as smiling), fine psychomotor-adaptive (such as grasping and drawing), language (such as combining words), and gross psychomotor (such as walking). Ages covered by the tests range from birth to six years.

RHEA, the Greek cohort

Bayley Scales of Infant Development III-third edition (BSID III)

Children’s cognitive and psychomotor development was assessed at around 1.5 years (range 1.4–1.7 years) using the Bayley Scales of Infant Development third edition (BSID III).[14] The BSID III includes 5 scales: cognitive scale of 91 items, receptive communication scale of 49 items, expressive communication scale of 29 items, fine psychomotor scale of 66 items, and gross psychomotor scale of 72 items. For this study the cognitive scale, the receptive communication scale, and the expressive communication scale were combined and defined as general cognitive development. The receptive communication scale and the expressive communication scale were combined and defined as language development. The fine psychomotor scale and gross psychomotor scale were combined and defined as global psychomotor development. All testing was done in the hospital in the presence of the mother, by 3 specially trained psychologists. Psychologists were not aware of any exposure information.

INMA-Asturias, INMA-Gipuzkoa, INMA-Sabadell, INMA-Valencia, the Spanish cohorts

Bayley Scales of Infant Development I-first edition (BSID I)

Children's cognitive and psychomotor development was assessed at around 1.2 years (range 0.9–1.9 years) using the Bayley Scales of Infant Development first edition (BSID I).[15] The mental development scale consists of 163 items that assess age-appropriate cognitive development, including performance abilities, memory, and early language skills. The psychomotor development scale consists of 81 items that assess fine and gross psychomotor development. All testing was done in the health care center in the presence of the mother, by 12 specially trained psychologists. Psychologists were not aware of any exposure information.

INMA-Sabadell, INMA-Valencia, INMA-Granada, the Spanish cohorts

McCarthy Scales of Children's Abilities (MSCA)

Cognitive/language and psychomotor development was assessed at around 5 years (range 3.9-6.4) by trained psychologists using the Spanish version of the McCarthy Scales of Children's Abilities (MCSA) that consists of 18 items.[16] The MCSA includes a general cognitive development score and 5 conventional sub-area scores. For this analysis 2 of these sub-areas were used: 1) language development subscale, which refers to those cognitive tasks related to any kind of verbal information processing; and 2) psychomotor development subscale that includes both fine (i.e., drawing) and gross (i.e., playing with a ball) psychomotor skills. All testing was done in the health care center by 5 specially trained psychologists. Psychologists were not aware of any exposure information.

Figure 1. Distribution of general cognition, language, global psychomotor, fine psychomotor, and gross psychomotor development raw scores

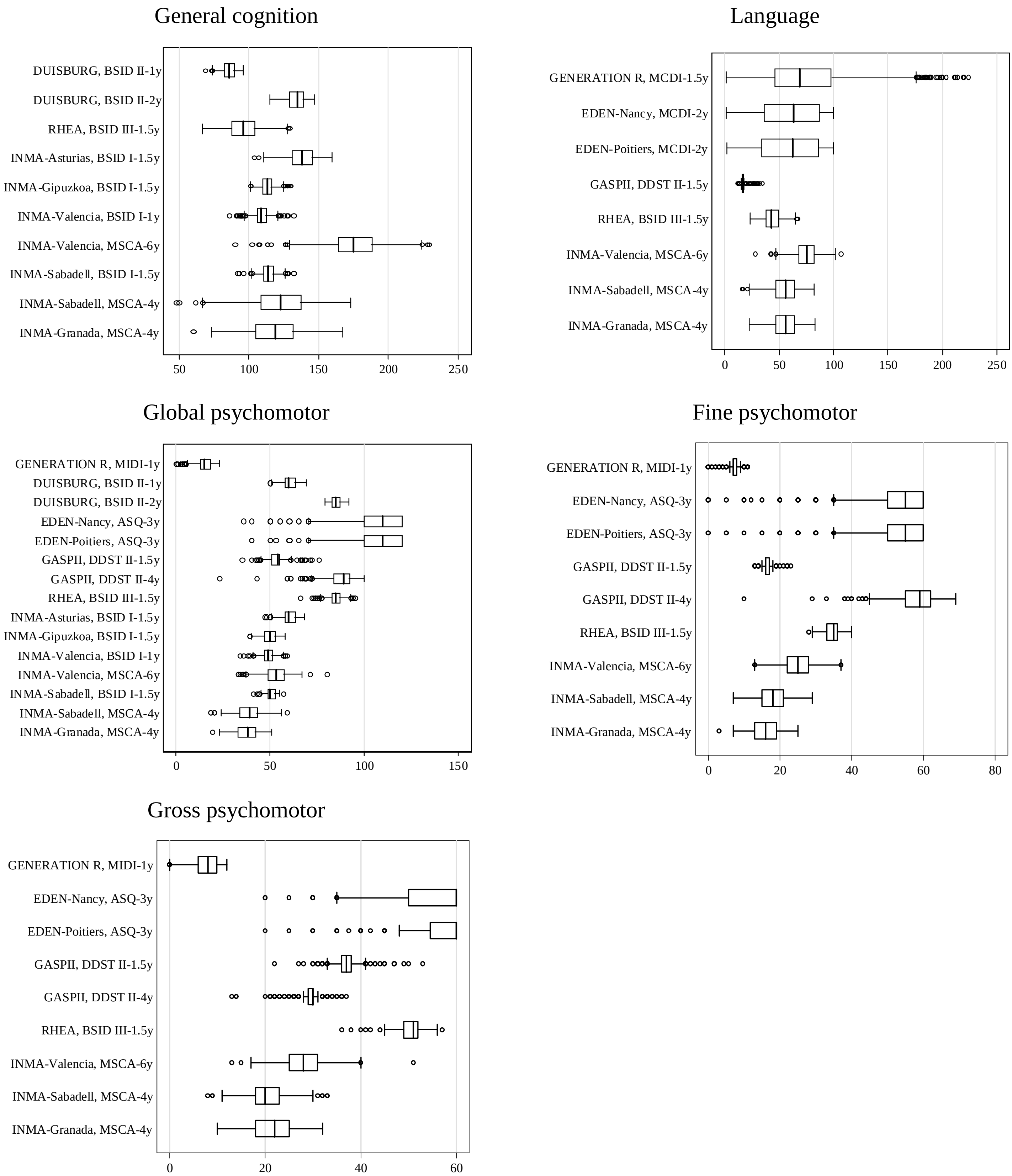


Table 1. Cohorts-specific categories of maternal educational level variable

Cohorts	Country	Cohort-specific categories		
		Low	**Medium**	**High**
GENERATION R	**The Netherlands**	Primary school	Secondary school	University degree or higher
DUISBURG	**Germany**	≤9 years of education	10 years of education	≥11 years of education
EDEN	**France**	≤11 years of education	12 years of education	≥13 years of education
GASPII	**Italy**	Primary school	Secondary school	University degree or higher
RHEA	**Greece**	Compulsory education (up to 9 years)	Lyceum and/or Post-secondary (3-5 additional years)	University degree or higher (≥15 years)
INMA	**Spain**	≤11 years of education	12–15 years of education	≥16 years of education

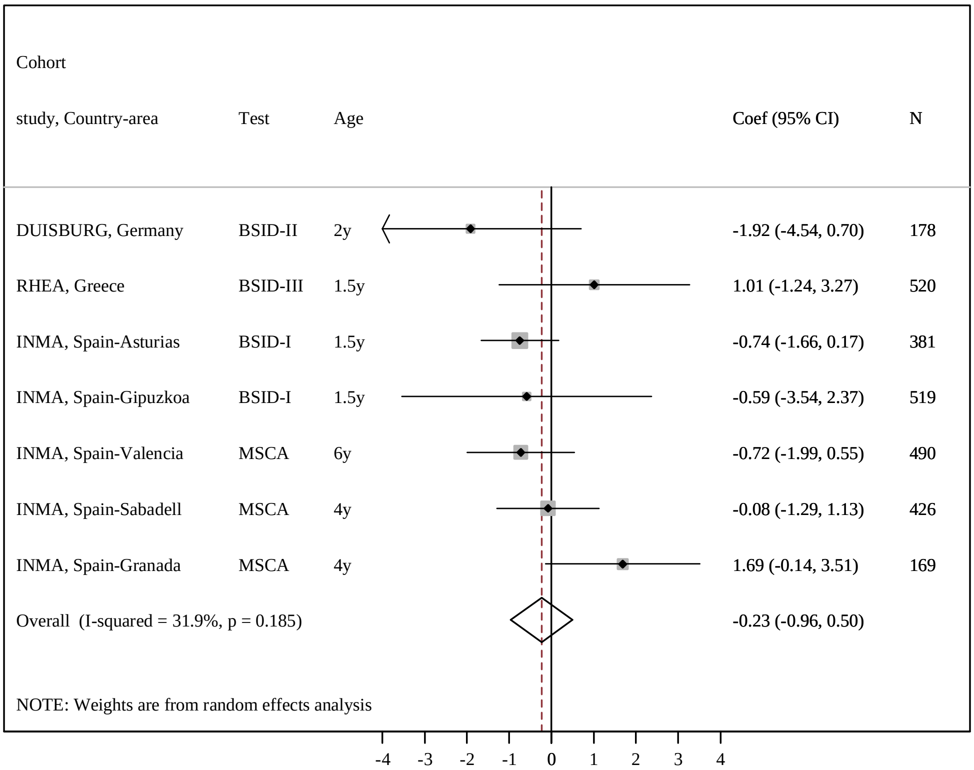
Table 2. Spearman correlations between air pollution levels during pregnancy[a] and traffic indicator variables

Cohort	Location	NO_2 *vs.* NOx	NO_2 *vs.* $PM_{2.5}$ absorbance	NO_x *vs.* $PM_{2.5}$ absorbance	$PM_{2.5}$ *vs.* $PM_{2.5}$ absorbance	NO_2 *vs.* Traffic density	NO_2 *vs.* Traffic load	$PM_{2.5}$ absorbance *vs.* Traffic density	$PM_{2.5}$ absorbance *vs.* Traffic load
GENERATION R	The Netherlands	0.86[b]	0.80[b]	0.79[b]	0.82[b]	0.25[b]	0.33[b]	0.18[b]	0.29[b]
DUISBURG	Germany	0.94[b]	0.55[b]	0.55[b]	0.45[b]	0.13	0.25[b]	0.28[b]	0.44[b]
EDEN	France-Nancy	na	na	na	na	0.45[b]	0.57[b]	na	na
	France-Poitiers	na	na	na	na	0.53[b]	0.39[b]	na	na
GASPII	Italy	0.70[b]	0.57[b]	0.75[b]	0.63[b]	0.16[b]	0.46[b]	0.43[b]	0.51[b]
RHEA	Greece	0.99[b]	0.50[b]	0.51[b]	0.18[b]	na	na	na	na
INMA	Spain-Asturias	0.99[b]	na	na	na	na	na	na	na
	Spain-Gipuzkoa	0.96[b]	na	na	na	na	na	na	na
	Spain-Sabadell	0.92[b]	0.82[b]	0.96[b]	0.77[b]	na	na	na	na
	Spain-Valencia	0.98[b]	na	na	na	na	na	na	na
	Spain-Granada	0.98[b]	na	na	na	na	na	na	na

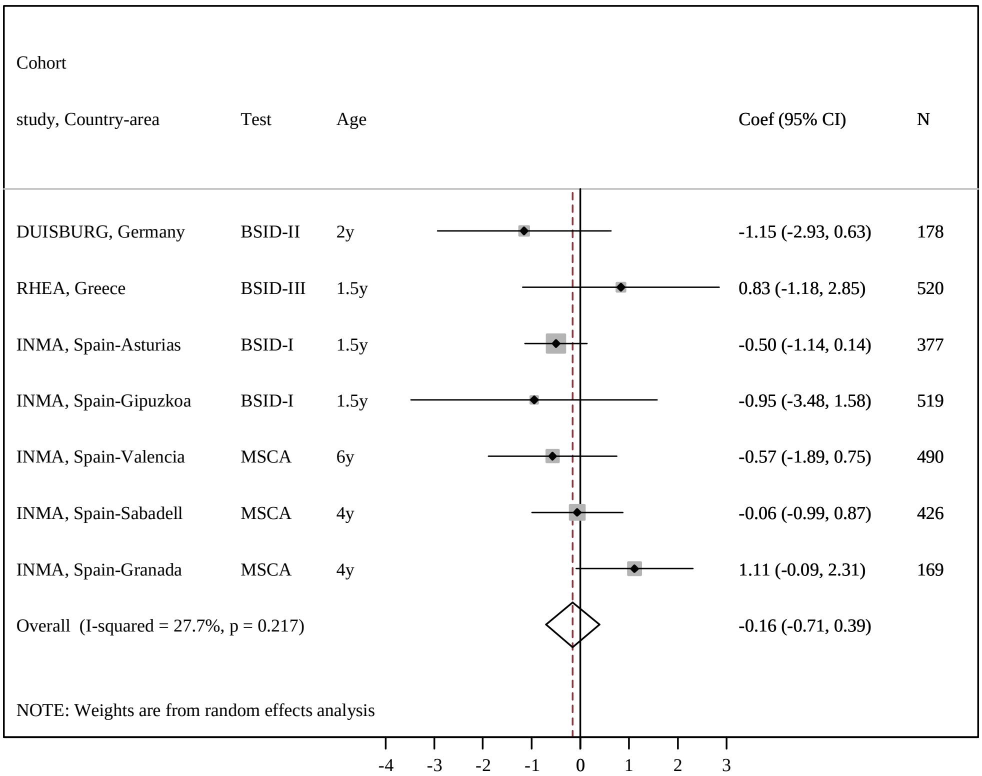
na, data not available
[a]Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohort
[b]p-value <0.05

Figure 2. Fully-adjusted associations[a] between air pollution exposure during pregnancy[b] and general cognition

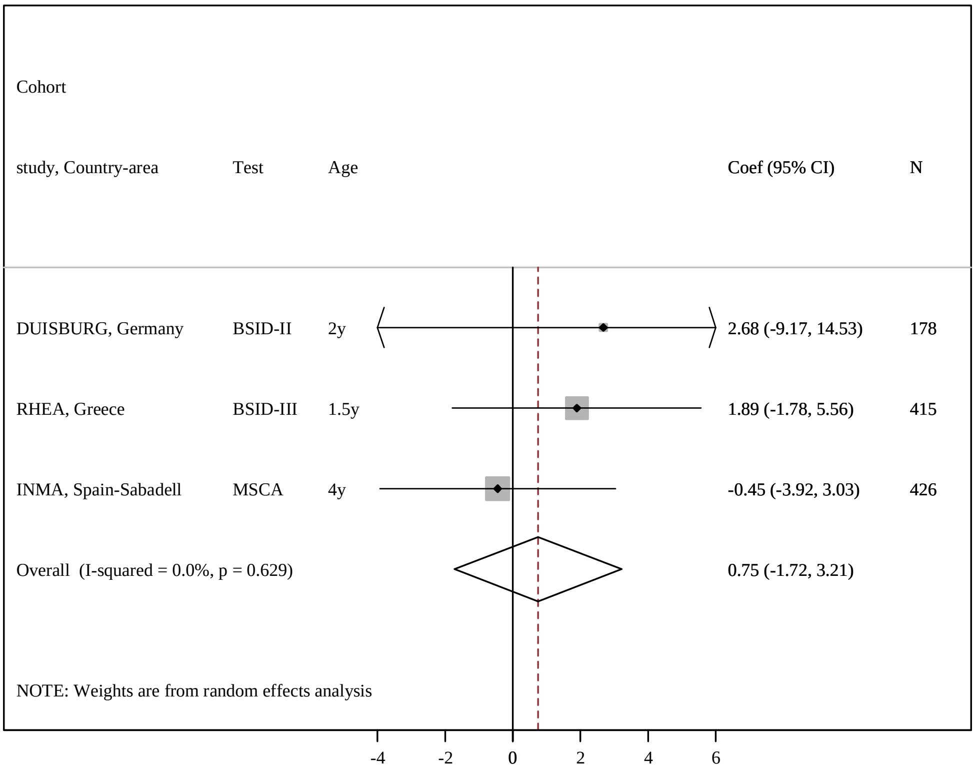
NO_2 (per Δ10 μg/m^3)



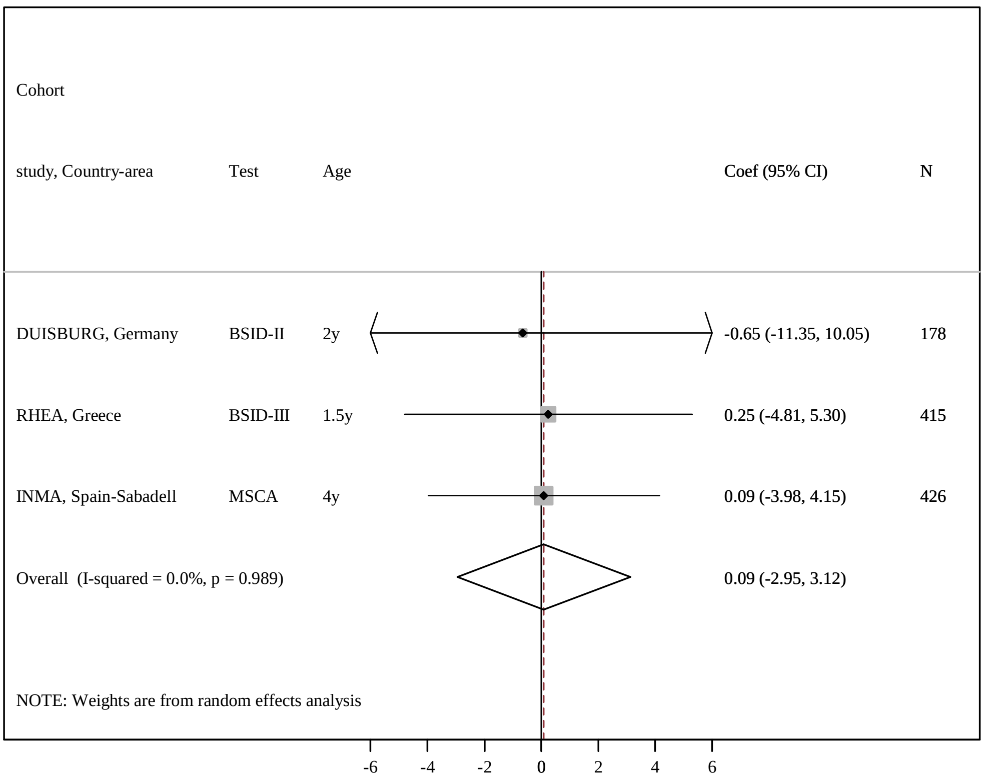
NO_X (per Δ20 μg/m^3)



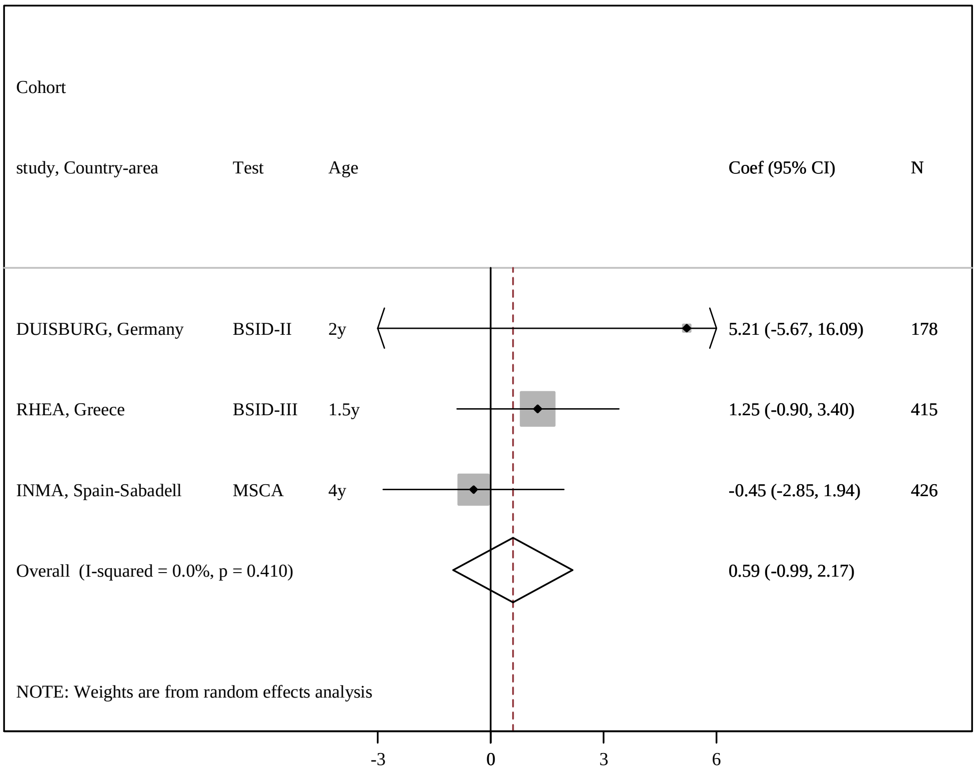
PM_{10} (per $\Delta 10\ \mu g/m^3$)



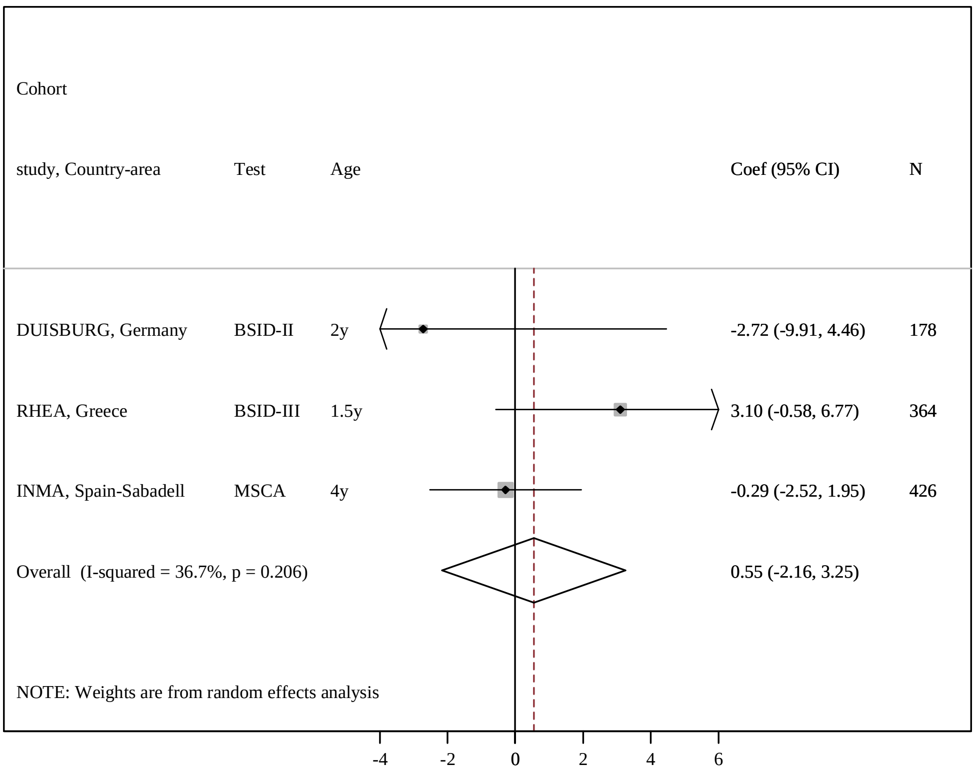
$PM_{2.5}$ (per $\Delta 5\ \mu g/m^3$)



PM_{coarse} (per Δ5 µg/m^3)



$PM_{2.5}$absorbance (per Δ$10^{-5}m^{-1}$)



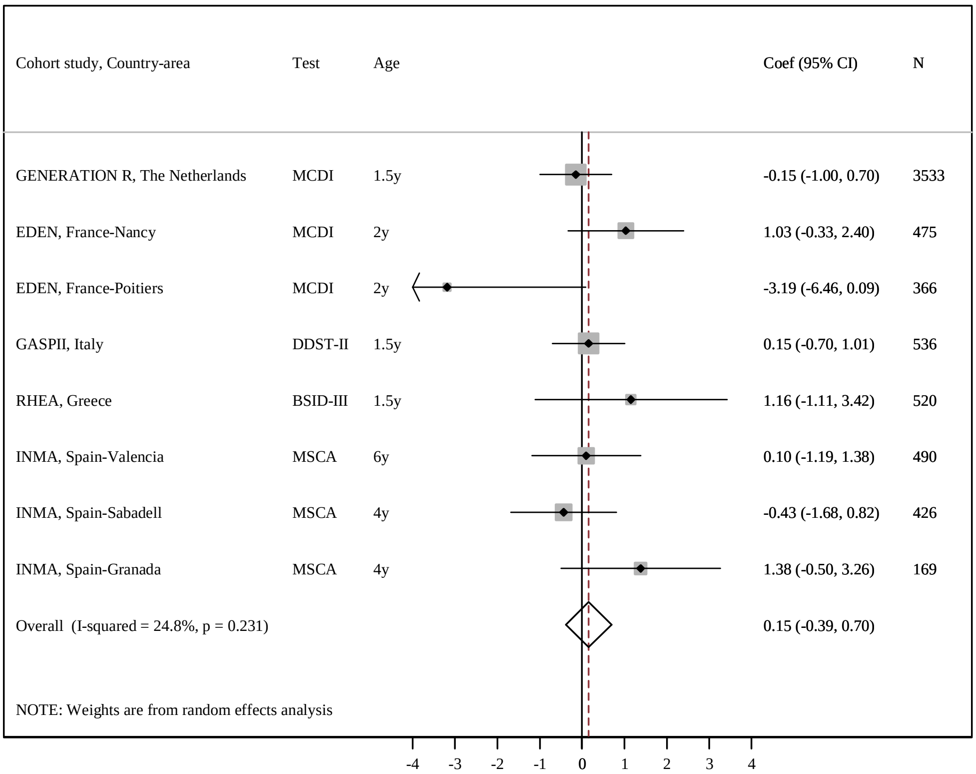
95% CI, 95% Confidence Interval; Coef, Coefficient; NO_2, nitrogen dioxide; NOx, nitrogen oxides; PM_{10}, particle matter less than 10µm; $PM_{2.5}$, particle matter less than 2.5µm; PM_{coarse}, particle matter between 2.5 and 10µm; $PM_{2.5}$absorbance, reflectance of $PM_{2.5}$ filters

[a] Region-specific and summary risk estimates (Coefficient and 95% CI) for congitive development expressed for an increase of 10µg/m^3 in NO_2 levels (A), 20µg/m^3 in NO_x levels (B), 10µg/m^3 in PM_{10} levels (C), 5µg/m^3 in $PM_{2.5}$ levels (D), 5µg/m^3 in PM_{coarse} levels (E), $10^{-5}m^{-1}$ in $PM_{2.5}$ absorbance levels (F) during pregnancy, adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the general cognition assessment, and evaluator and quality of the general cognition test. Grey squares around region-specific coefficient represent the relative weight that the estimate contributes to the summary coefficient.

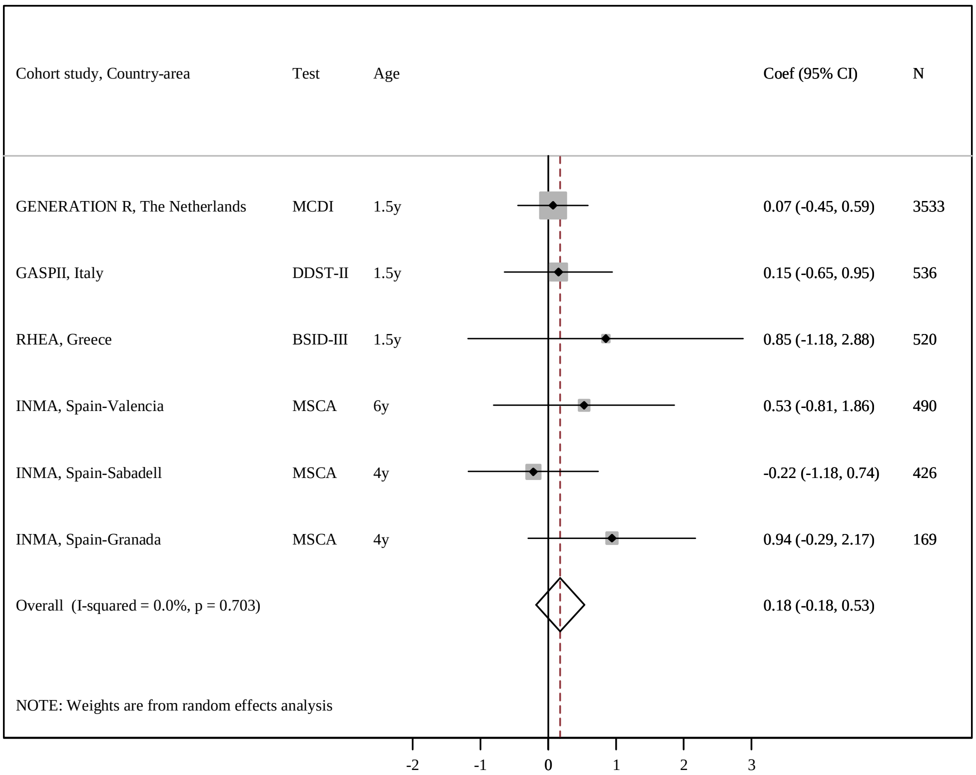
[b] Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohort

Figure 3. Fully-adjusted associations[a] between air pollution exposure during pregnancy[b] and language development

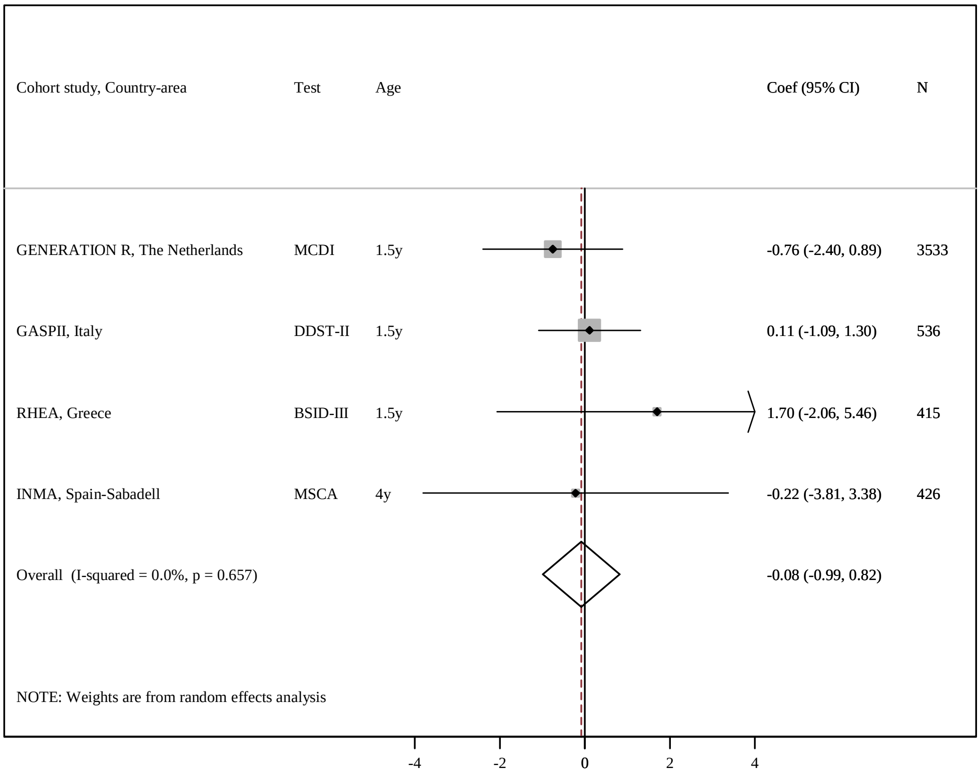
NO_2 (per Δ10 $\mu g/m^3$)



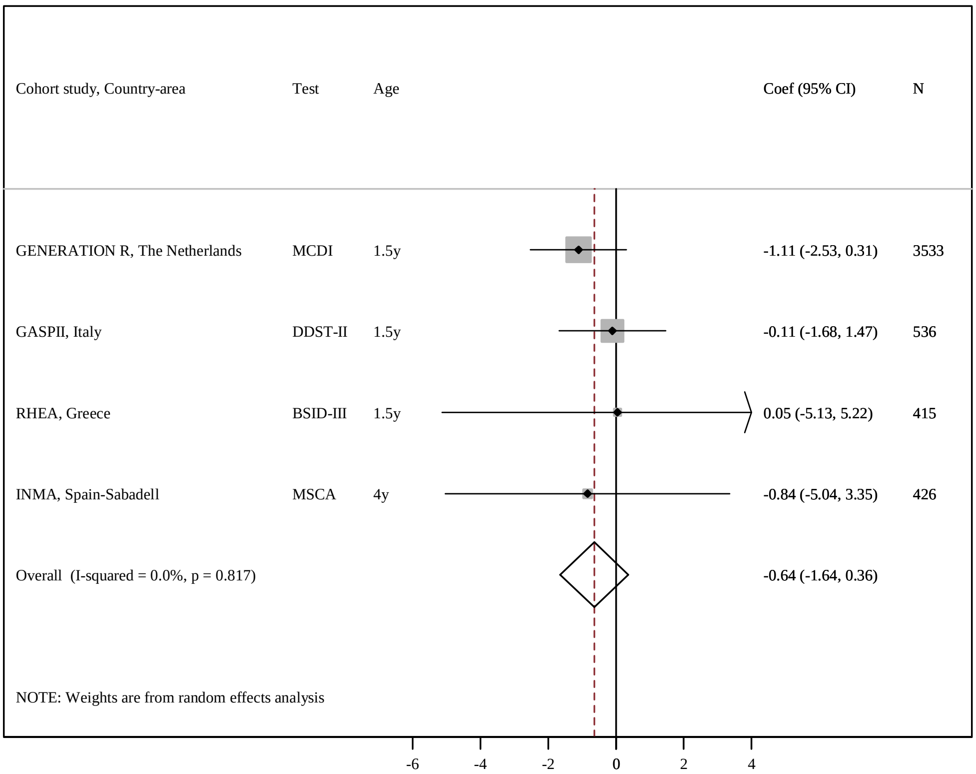
NO_X (per Δ20 $\mu g/m^3$)



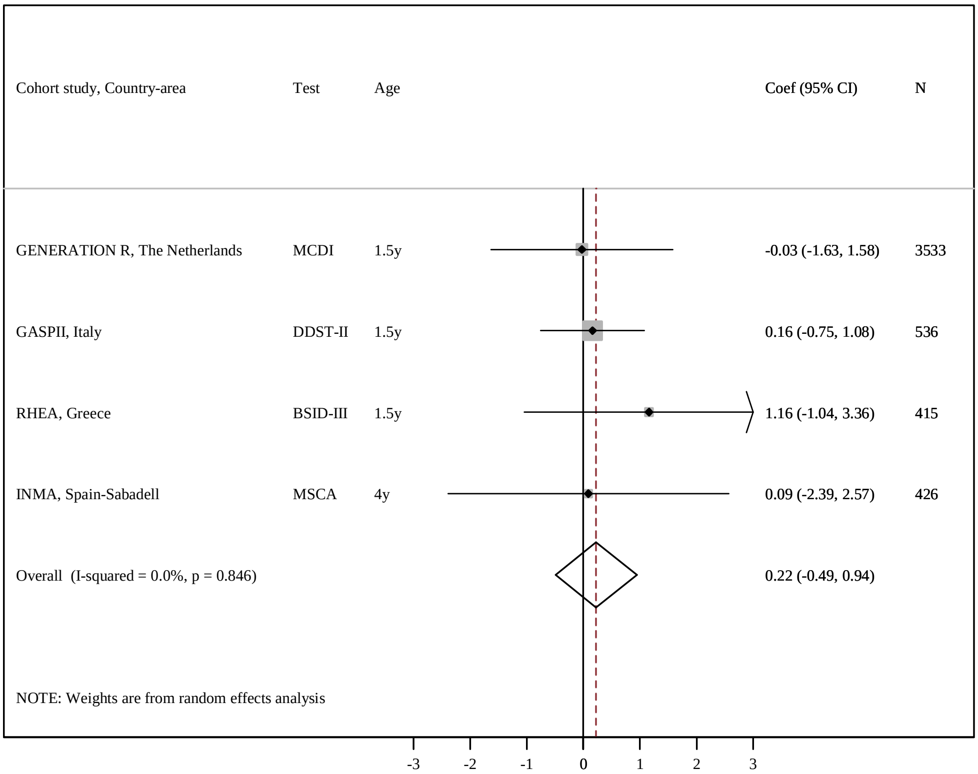
PM$_{10}$ (per Δ10 μg/m^3)



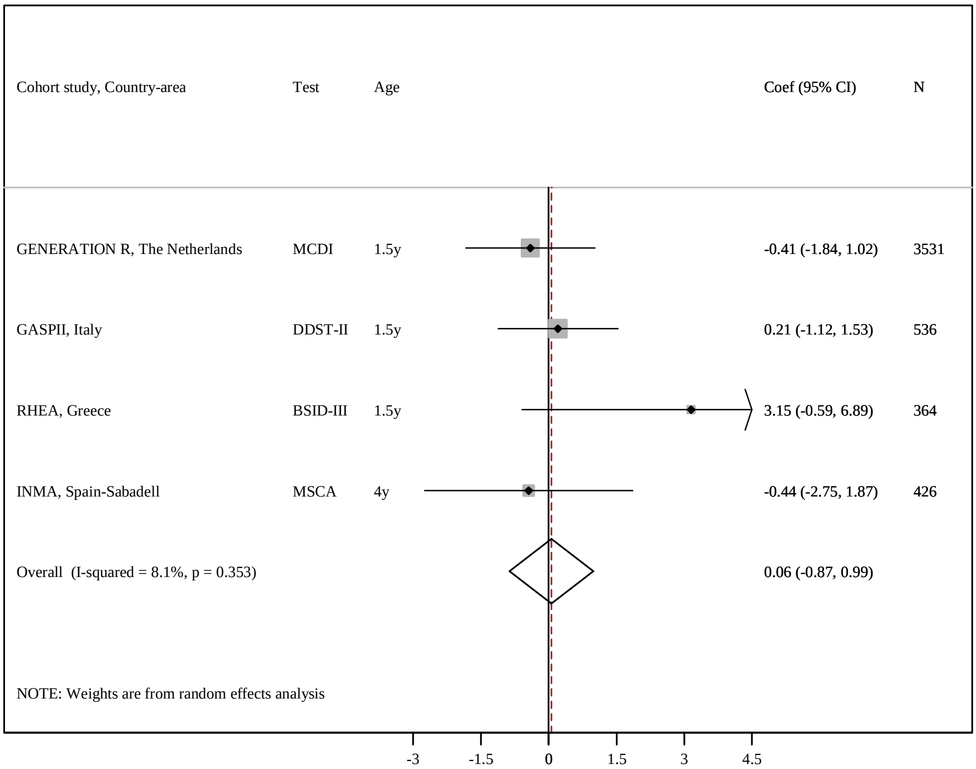
PM$_{2.5}$ (per Δ5 μg/m^3)



PM$_{coarse}$ (per Δ5 μg/m^3)



PM$_{2.5}$absorbance (per Δ10^{-5}m^{-1})



95% CI, 95% Confidence Interval; Coef, Coefficient; NO_2, nitrogen dioxide; NOx, nitrogen oxides; PM$_{10}$, particle matter less than 10µm; PM$_{2.5}$, particle matter less than 2.5µm; PM$_{coarse}$, particle matter between 2.5 and 10µm; PM$_{2.5}$absorbance, reflectance of PM$_{2.5}$ filters

[a] Region-specific and summary risk estimates (Coefficient and 95% CI) for language development expressed for an increase of 10µg/m^3 in NO_2 levels (A), 20µg/m^3 in NO_x levels (B), 10µg/m^3 in PM$_{10}$ levels (C), 5µg/m^3 in PM$_{2.5}$ levels (D), 5µg/m^3 in PM$_{coarse}$ levels (E), 10^{-5}m^{-1} in PM$_{2.5}$ absorbance levels (F) during pregnancy, adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the language development assessment, and evaluator and quality of the language development test. Grey squares around region-specific coefficient represent the relative weight that the estimate contributes to the summary coefficient.

[b]Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohort

Table 3. Minimally-adjusted combined associations[a] between air pollution exposure during pregnancy[b] and general cognition, language and global psychomotor development

	General cognition					Language development					Global psychomotor development				
	N[c]	Coef.	95% CI	p-heter	I^2	N[c]	Coef.	95% CI	p-heter	I^2	N[c]	Coef.	95% CI	p-heter	I^2
NO_2 (per Δ10 µg/m^3)	7	-0.05	-1.01; 0.92	0.022	59.5%	8	0.25	-0.29; 0.79	0.292	17.5%	11	-0.72	-1.45; 0.02	0.004	61.1%
NOx (per Δ20 µg/m^3)	7	0.03	-0.72; 0.77	0.027	57.9%	6	0.31	-0.14; 0.76	0.304	17.1%	9	-0.47	-1.06; 0.13	0.009	61.0%
PM_{10} (per Δ10 µg/m^3)	3	1.27	-1.39; 3.92	0.483	0.0%	4	0.34	-1.21; 1.89	0.191	36.8%	5	-1.10	-2.15; -0.05	0.976	0.0%
$PM_{2.5}$ (per Δ5 µg/m^3)	3	1.83	-1.34; 5.00	0.910	0.0%	4	-0.20	-1.71; 1.31	0.271	23.3%	5	-1.32	-2.38; -0.27	0.455	0.0%
PM_{coarse} (per Δ5 µg/m^3)	3	0.70	-1.83; 3.22	0.189	39.9%	4	0.54	-0.37; 1.44	0.480	0.0%	5	-0.61	-1.47; 0.25	0.995	0.0%
$PM_{2.5}$absorbance (per Δ$10^{-5}m^{-1}$)	3	2.46	-0.89; 5.81	0.120	52.8%	4	0.97	-0.93; 2.87	0.032	65.9%	5	-0.68	-1.83; 0.48	0.283	20.6%

95% CI, 95% Confidence Interval; Coef, Coefficient; I^2 =Percentage of the total variability due to between-regions heterogeneity; NO_2, nitrogen dioxide; NOx, nitrogen oxides; p-heter, P value of heterogeneity using the Cochran's *Q* test; PM_{10}, particle matter less than 10µm; $PM_{2.5}$, particle matter less than 2.5µm; PM_{coarse}, particle matter between 2.5 and 10µm; $PM_{2.5}$absorbance, reflectance of $PM_{2.5}$ filters

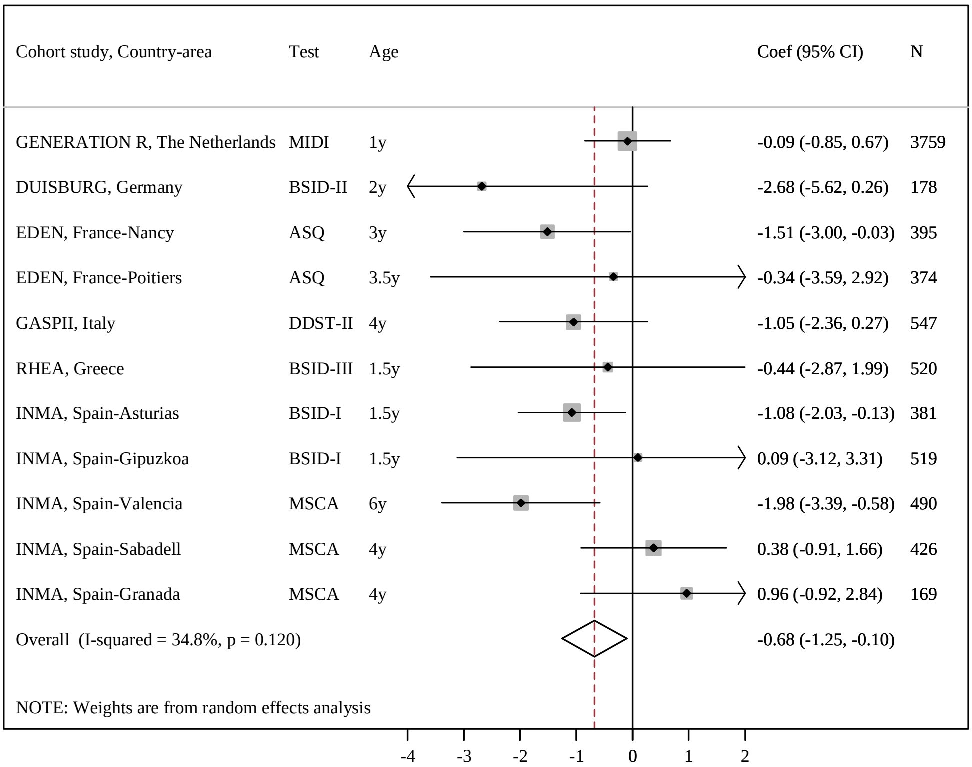
[a]Coefficient and 95% confidence interval estimated by random-effects meta-analysis by region. Models were adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child’s birth date, urbanicity at child’s birth address, child's age at the cognitive or psychomotor development assessment, and evaluator and quality of the cognitive or psychomotor development test

[b]Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohort

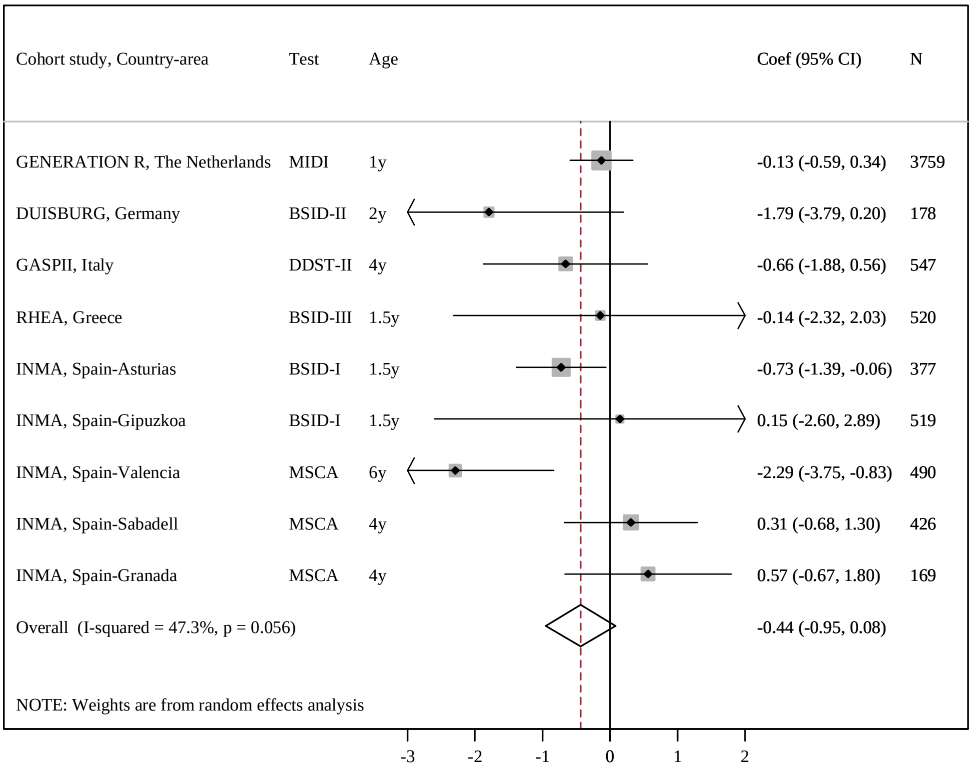
[c]Number of regions included in the meta-analysis

Figure 4. Fully-adjusted associations[a] between air pollution exposure during pregnancy[b] and global psychomotor development

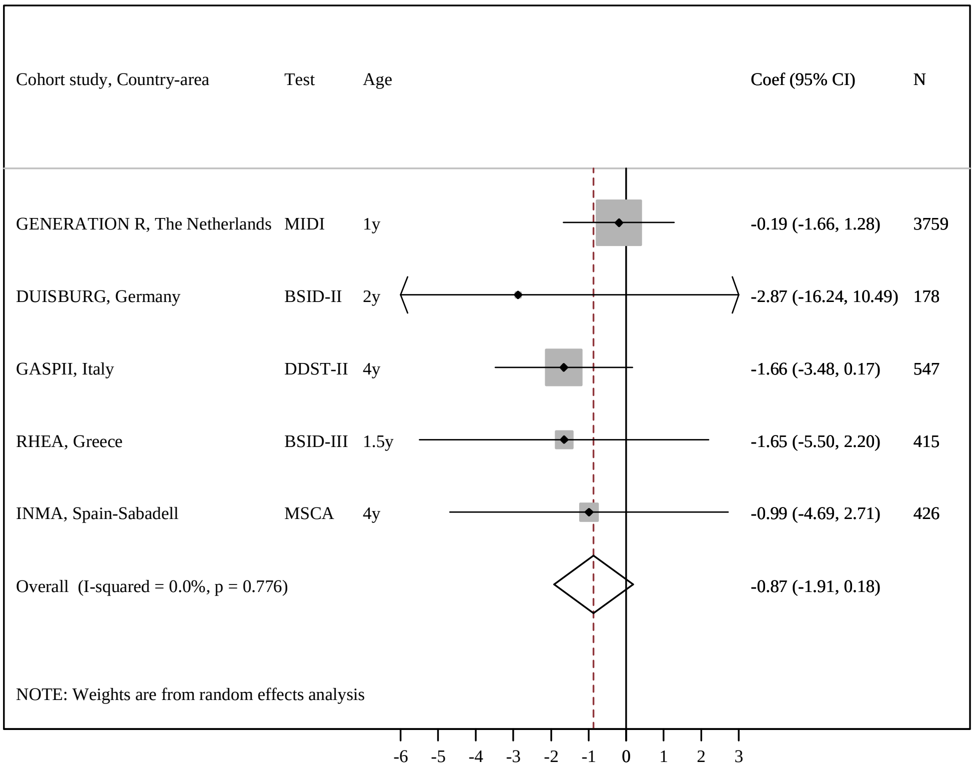
NO_2 (per Δ10 µg/m^3)



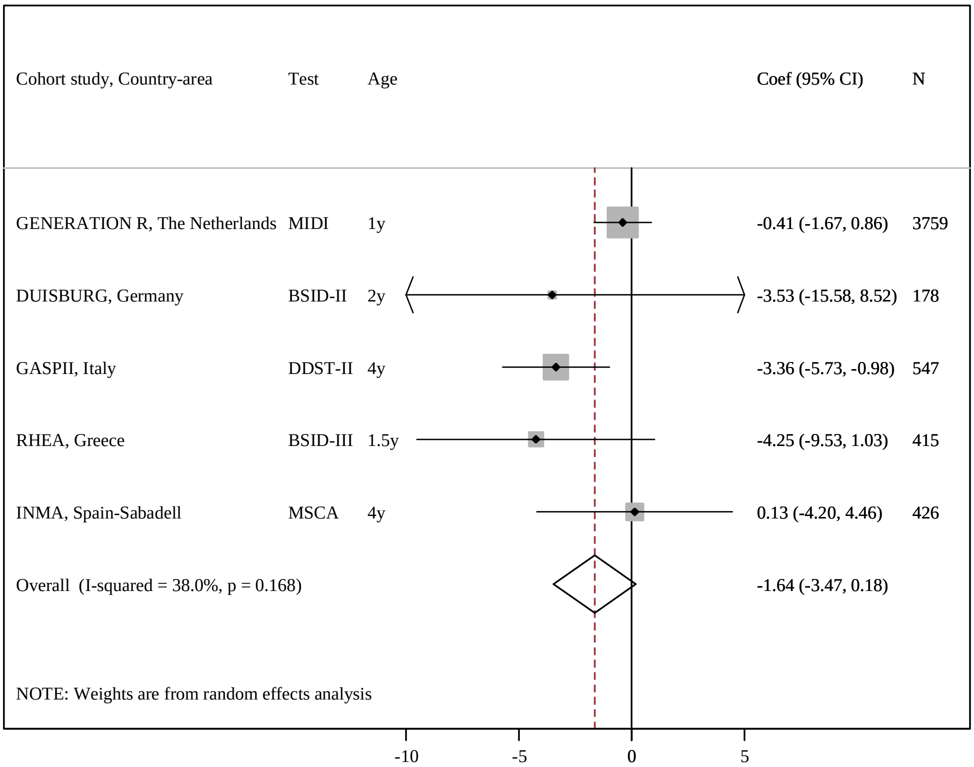
NO_X (per Δ20 µg/m^3)



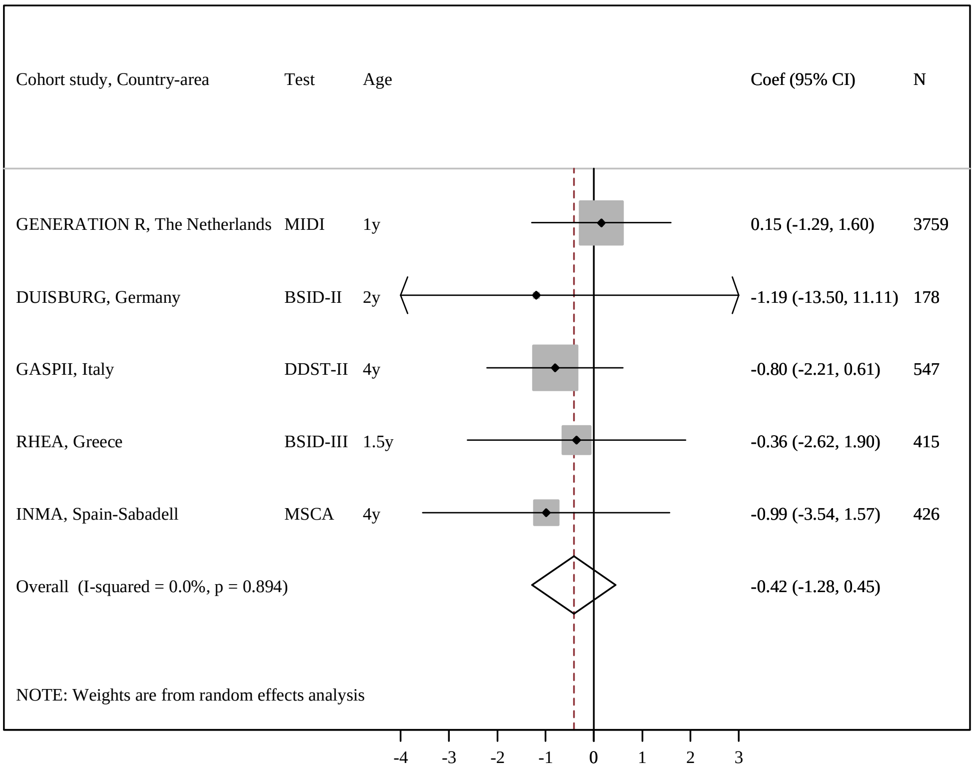
PM_{10} (per Δ10 μg/m^3)



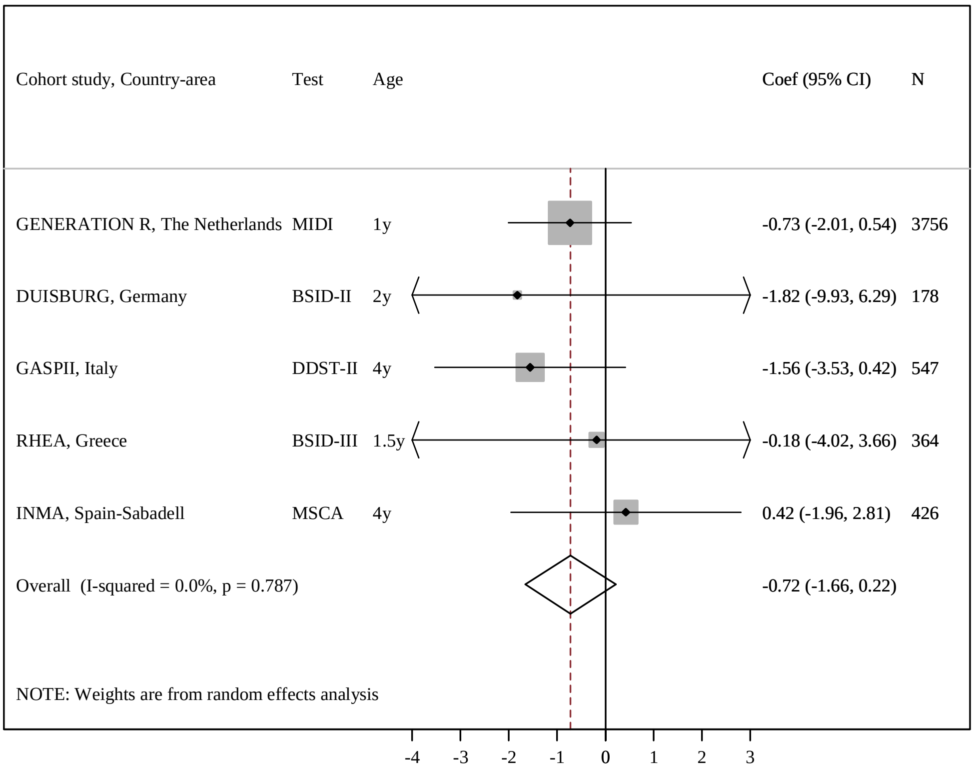
$PM_{2.5}$ (per Δ5 μg/m^3)



PM_{coarse} (per Δ5 µg/m^3)



$PM_{2.5}$absorbance (per Δ10^{-5}m^{-1})



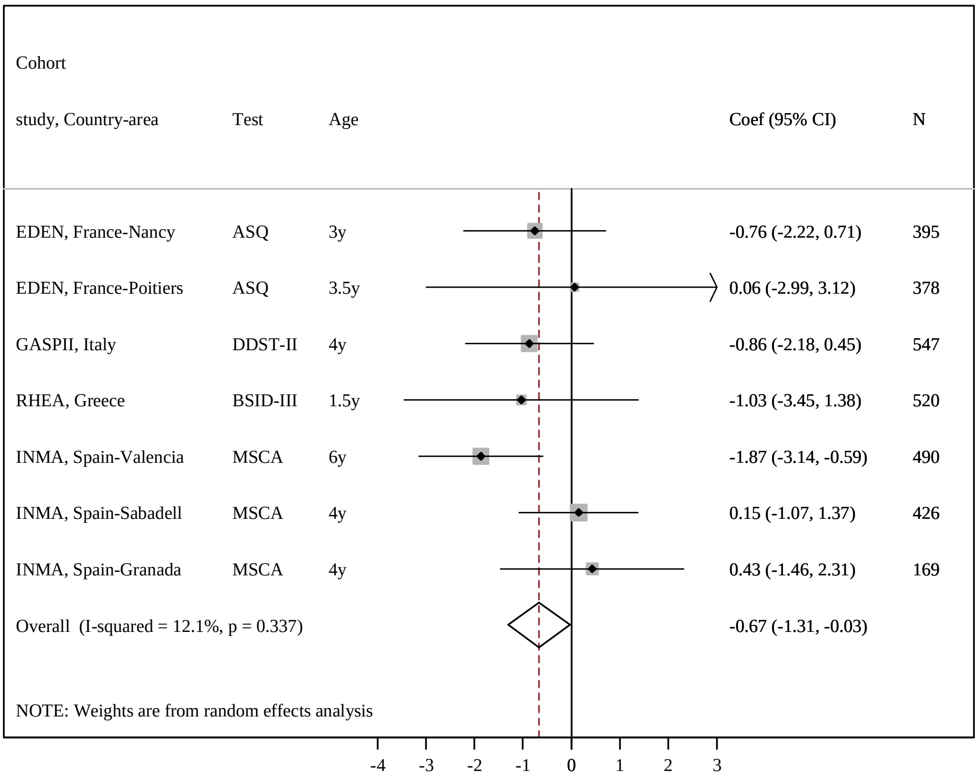
95% CI, 95% Confidence Interval; Coef, Coefficient; NO_2, nitrogen dioxide; NOx, nitrogen oxides; PM_{10}, particle matter less than 10µm; $PM_{2.5}$, particle matter less than 2.5µm; PM_{coarse}, particle matter between 2.5 and 10µm; $PM_{2.5}$absorbance, reflectance of $PM_{2.5}$ filters

[a] Region-specific and summary risk estimates (Coefficient and 95% CI) for global psychomotor development expressed for an increase of 10µg/m^3 in NO_2 levels (A), 20µg/m^3 in NO_x levels (B), 10µg/m^3 in PM_{10} levels (C), 5µg/m^3 in $PM_{2.5}$ levels (D), 5µg/m^3 in PM_{coarse} levels (E), 10^{-5}m^{-1} in $PM_{2.5}$ absorbance levels (F) during pregnancy, adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the global psychomotor development assessment, and evaluator and quality of the global psychomotor development test. Grey squares around region-specific coefficient represent the relative weight that the estimate contributes to the summary coefficient.

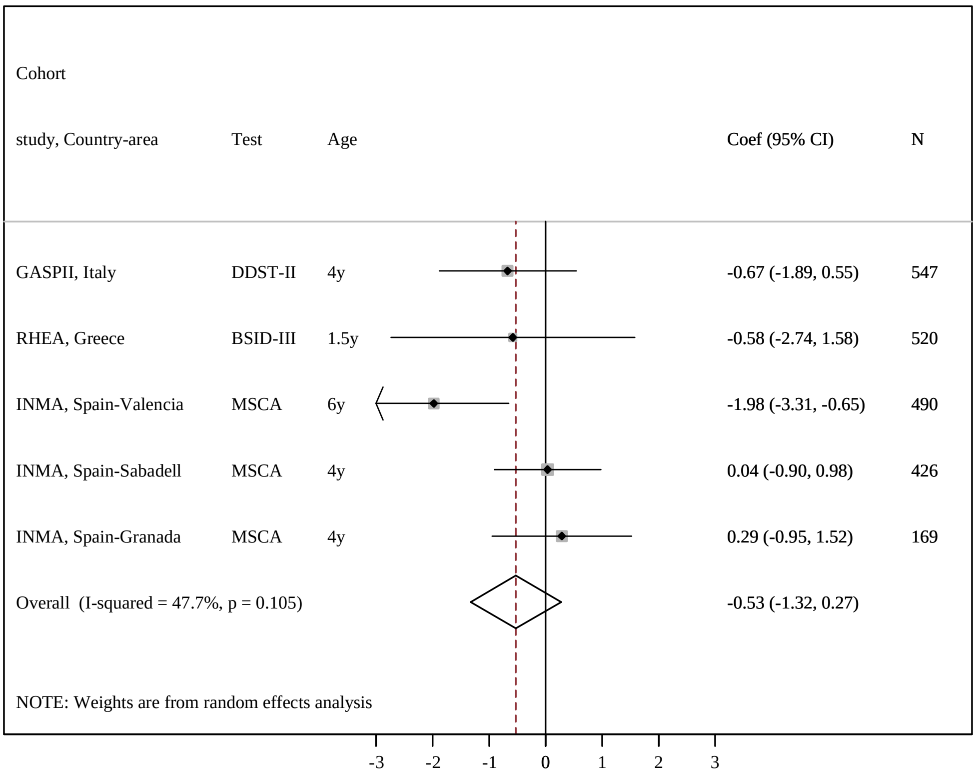
[b] Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohort

Figure 5. Fully-adjusted associations[a] between air pollution exposure during pregnancy[b] and fine psychomotor development

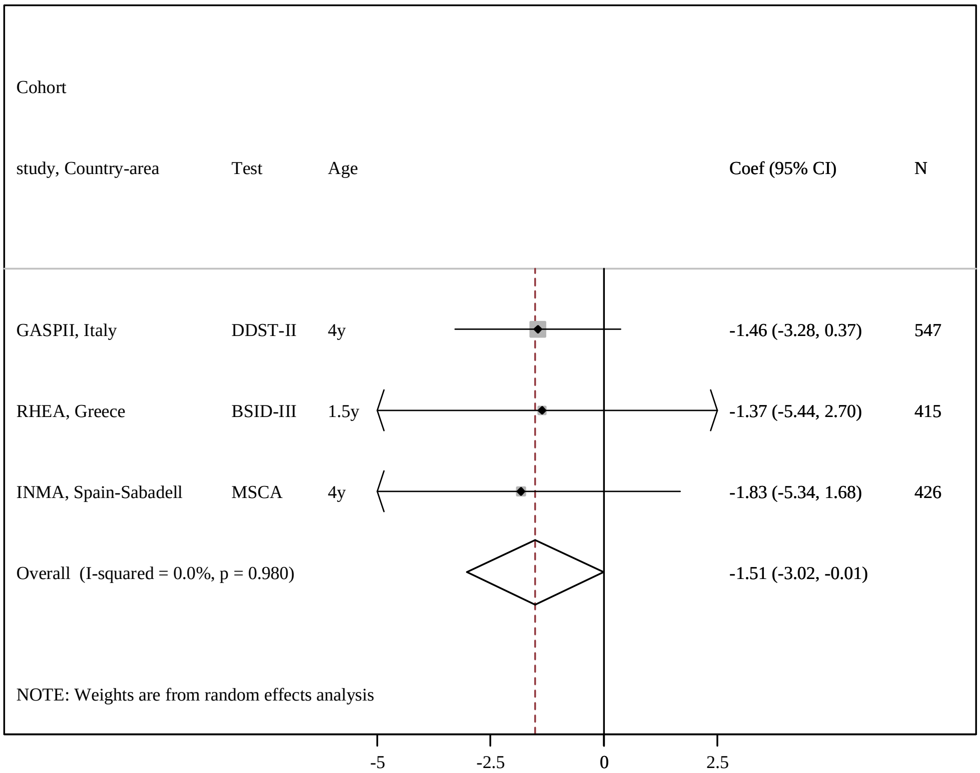
NO_2 (per $\Delta 10\ \mu g/m^3$)



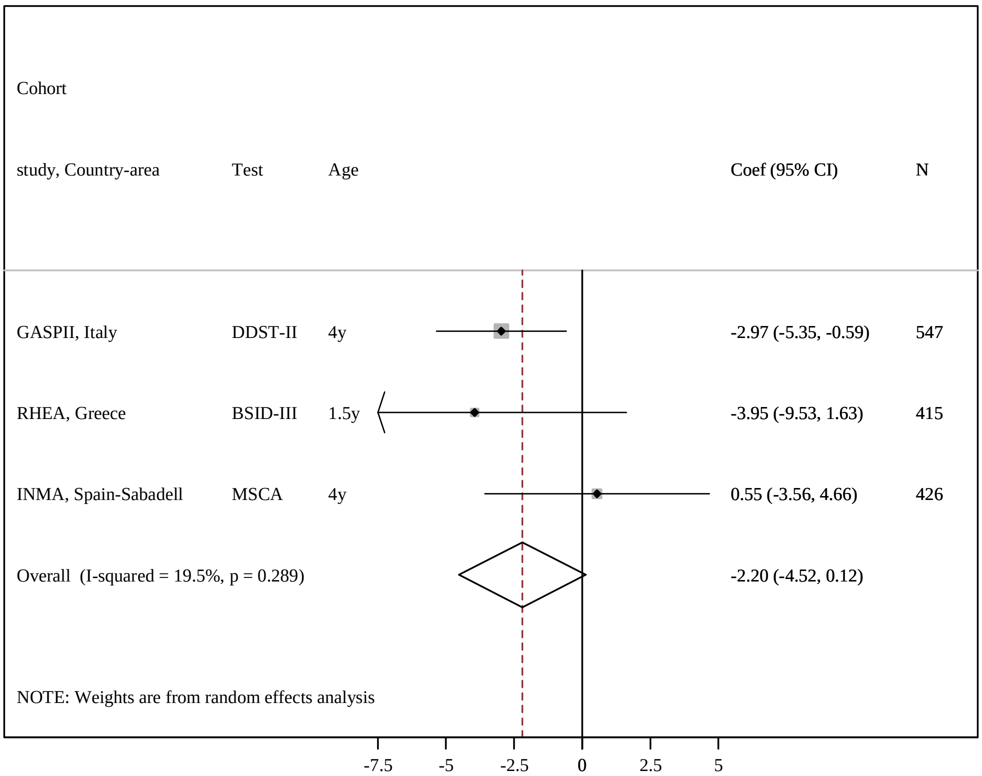
NO_X (per $\Delta 20\ \mu g/m^3$)



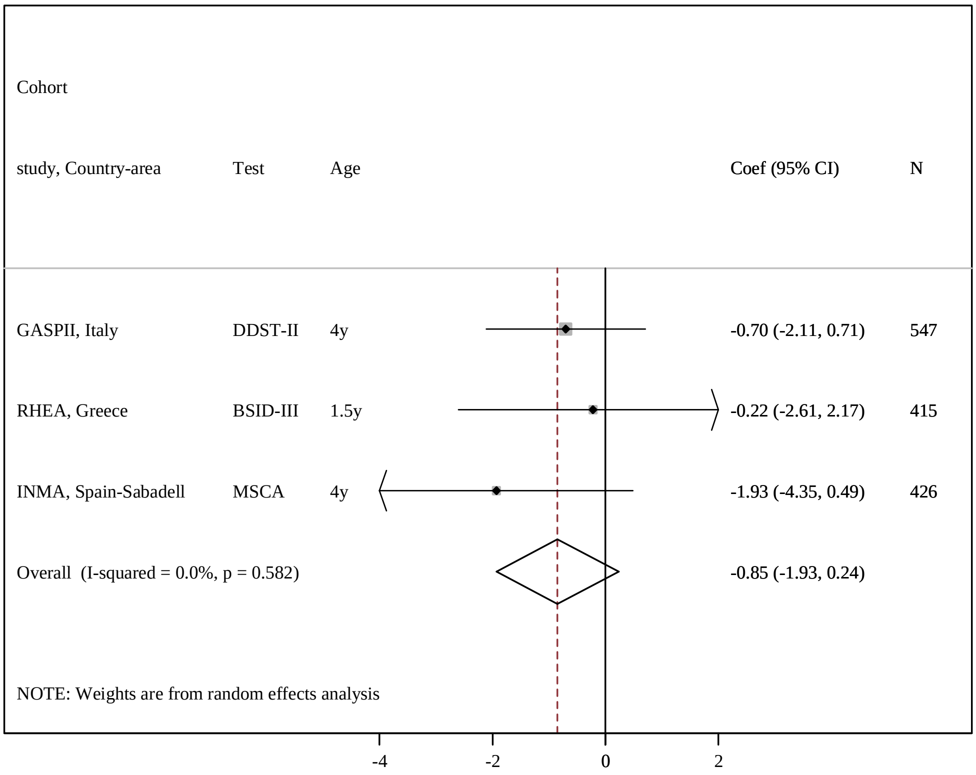
PM_{10} (per $\Delta 10\ \mu g/m^3$)



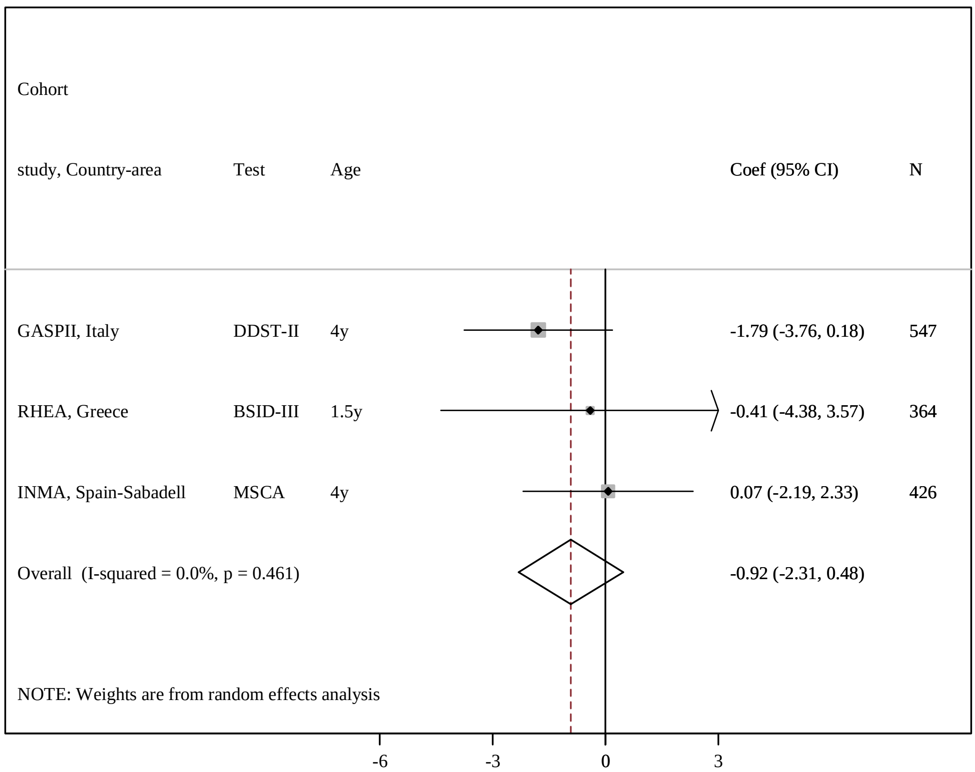
$PM_{2.5}$ (per $\Delta 5\ \mu g/m^3$)



PM_{coarse} (per Δ5 μg/m^3)



$PM_{2.5}$absorbance (per Δ$10^{-5}m^{-1}$)



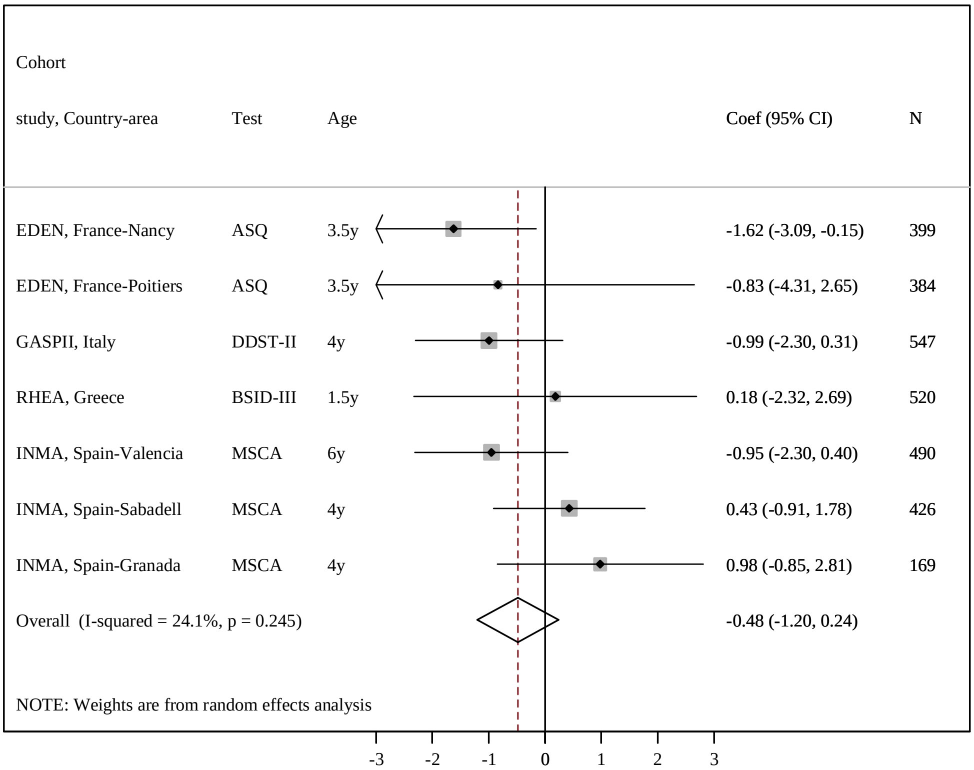
95% CI, 95% Confidence Interval; Coef, Coefficient; NO_2, nitrogen dioxide; NOx, nitrogen oxides; PM_{10}, particle matter less than 10µm; $PM_{2.5}$, particle matter less than 2.5µm; PM_{coarse}, particle matter between 2.5 and 10µm; $PM_{2.5}$absorbance, reflectance of $PM_{2.5}$ filters

[a] Region-specific and summary risk estimates (Coefficient and 95% CI) for fine psychomotor development expressed for an increase of 10µg/m^3 in NO_2 levels (A), 20µg/m^3 in NO_x levels (B), 10µg/m^3 in PM_{10} levels (C), 5µg/m^3 in $PM_{2.5}$ levels (D), 5µg/m^3 in PM_{coarse} levels (E), $10^{-5}m^{-1}$ in $PM_{2.5}$ absorbance levels (F) during pregnancy, adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the fine psychomotor development assessment, and evaluator and quality of the fine psychomotor development test. Grey squares around region-specific coefficient represent the relative weight that the estimate contributes to the summary coefficient.

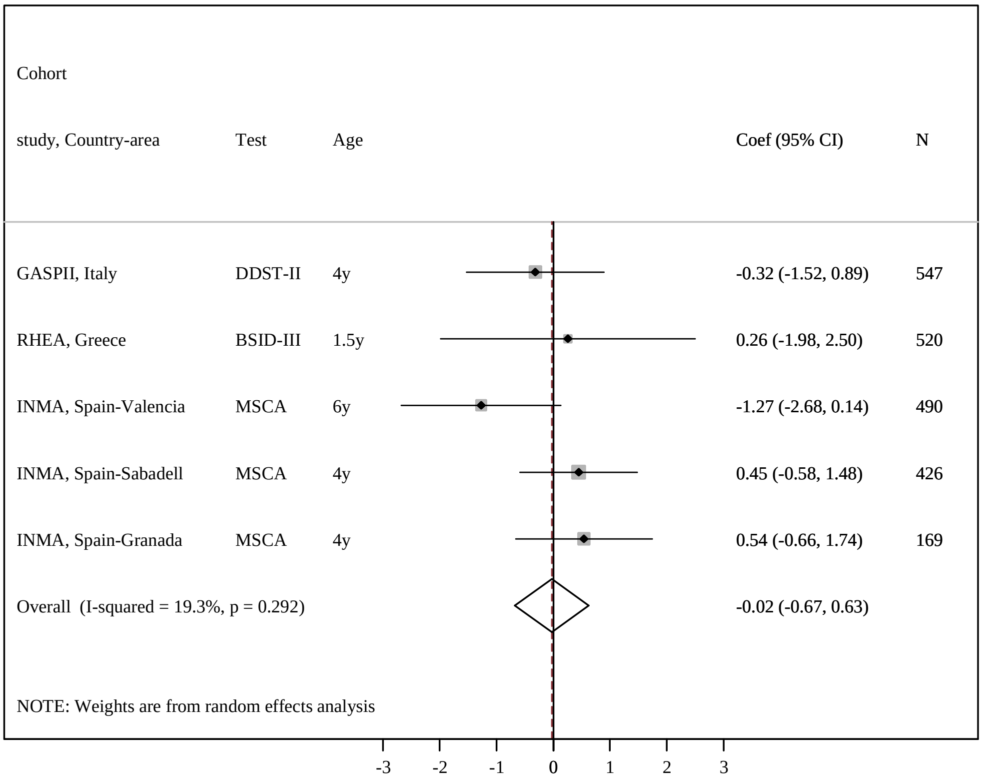
[b] Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohort

Figure 6. Fully-adjusted associations[a] between air pollution exposure during pregnancy[b] and gross psychomotor development

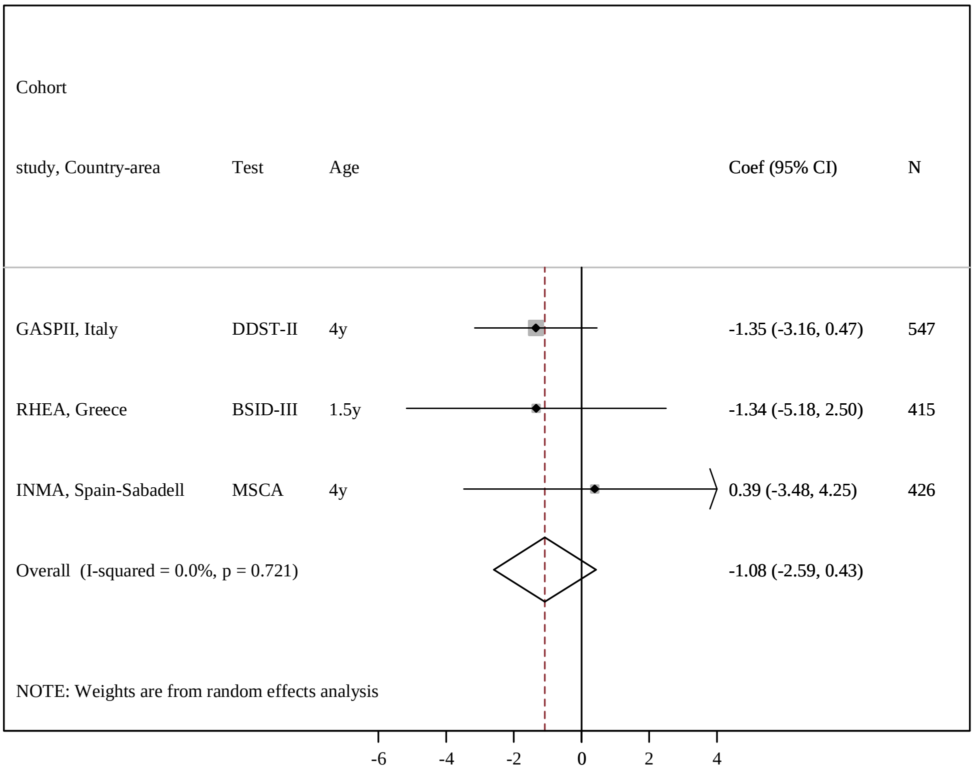
NO_2 (per Δ10 μg/m^3)



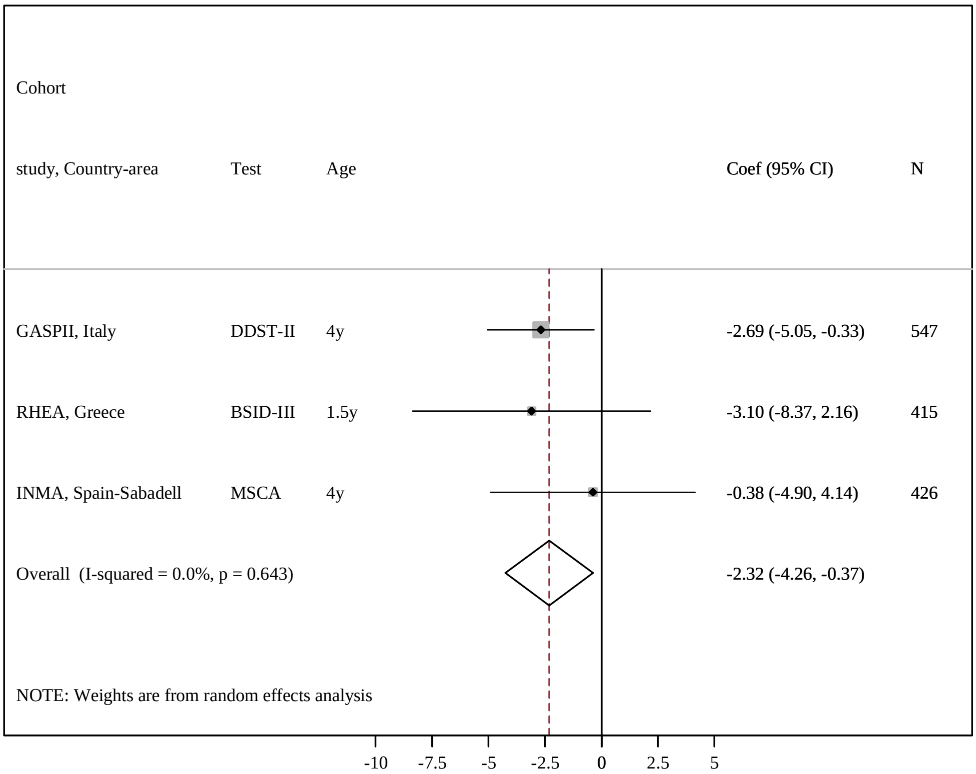
NO_X (per Δ20 μg/m^3)



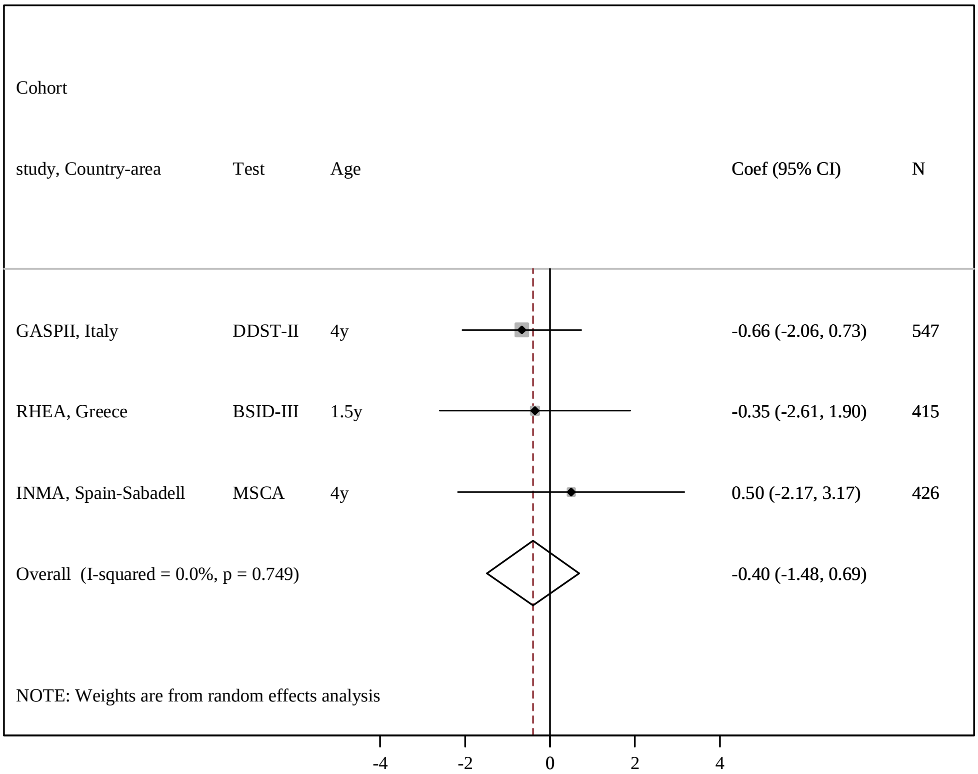
PM_{10} (per $\Delta 10\ \mu g/m^3$)



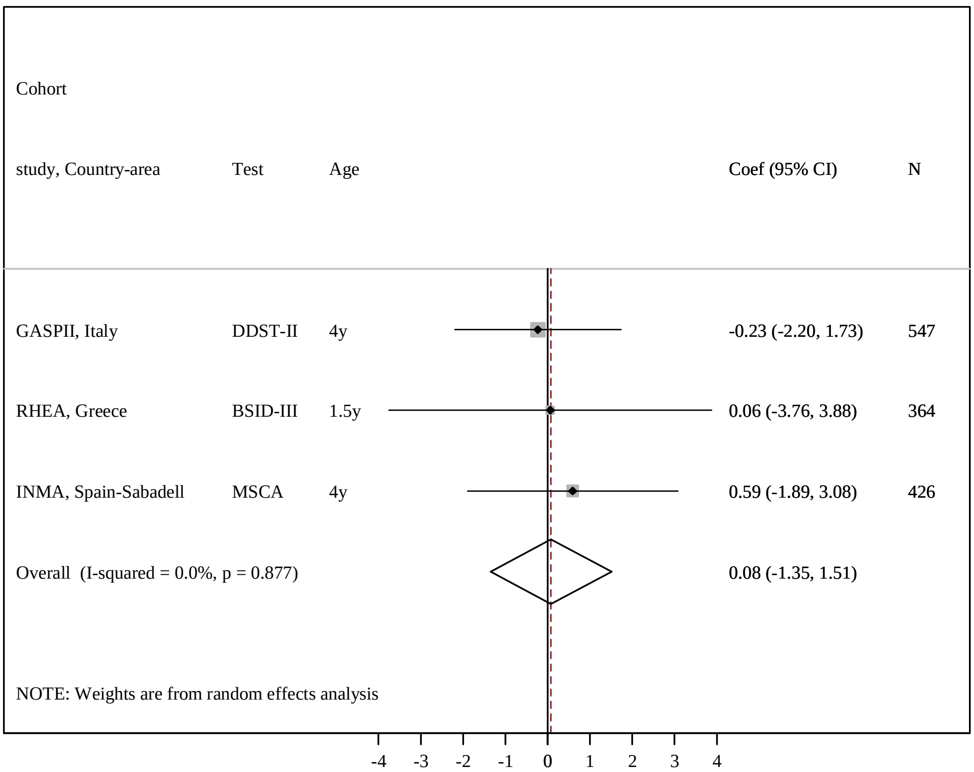
$PM_{2.5}$ (per $\Delta 5\ \mu g/m^3$)



PM$_{coarse}$ (per Δ5 μg/m^3)



PM$_{2.5}$absorbance (per Δ10^{-5}m^{-1})



95% CI, 95% Confidence Interval; Coef, Coefficient; NO_2, nitrogen dioxide; NOx, nitrogen oxides; PM$_{10}$, particle matter less than 10µm; PM$_{2.5}$, particle matter less than 2.5µm; PM$_{coarse}$, particle matter between 2.5 and 10µm; PM$_{2.5}$absorbance, reflectance of PM$_{2.5}$ filters

[a] Region-specific and summary risk estimates (Coefficient and 95% CI) for gross psychomotor development expressed for an increase of 10µg/m^3 in NO_2 levels (A), 20µg/m^3 in NO_x levels (B), 10µg/m^3 in PM$_{10}$ levels (C), 5µg/m^3 in PM$_{2.5}$ levels (D), 5µg/m^3 in PM$_{coarse}$ levels (E), 10^{-5}m^{-1} in PM$_{2.5}$ absorbance levels (F) during pregnancy, adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the gross psychomotor development assessment, and evaluator and quality of the gross psychomotor development test. Grey squares around region-specific coefficient represent the relative weight that the estimate contributes to the summary coefficient.

[b]Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohort

Table 4. Fully-adjusted combined associations[a] between traffic indicator variables and general cognitive, language, global psychomotor, fine psychomotor, and gross psychomotor development

	Traffic density on nearest street (per Δ5000 mv/day)					Traffic load on major road in 100m buffer (per Δ4,000,000 mv/day*m)				
	N[b]	Coef.	95% CI	p-heter	I^2	N[b]	Coef.	95% CI	p-heter	I^2
General cognitive	na					na				
Language	4	-0.03	-0.41; 0.35	0.128	47.2%	4	-0.04	-0.62; 0.54	0.584	0.0%
Global psychomotor	5	-0.08	-0.34; 0.18	0.778	0.0%	5	-0.23	-0.78; 0.32	0.851	0.0%
Fine psychomotor	3	-0.02	-0.43; 0.40	0.387	0.0%	3	-0.33	-1.79; 1.13	0.824	0.0%
Gross psychomotor	3	-0.06	-0.60; 0.47	0.248	28.2%	3	-0.51	-2.07; 1.06	0.346	5.8%

95% CI, 95% Confidence Interval; Coef, Coefficient; I^2 =Percentage of the total variability due to between-areas heterogeneity; na, not applicable since there are insufficient number of regions with these data (N<3); p-heter, P value of heterogeneity using the Cochran's *Q* test

[a]Coefficient and 95% confidence interval estimated by random-effects meta-analysis by region. Models were adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the cognitive or psychomotor development assessment, evaluator and quality of the cognitive or psychomotor development test, and background levels of NO_2

[b]Number of regions included in the meta-analysis

Table 5. Fully-adjusted combined associations[a] between non-back-extrapolated air pollution exposure at child's birth address and general cognition, language, and global psychomotor development

	General cognition					Language development					Global psychomotor development				
	N[b]	Coef.	95% CI	p-heter	I^2	N[b]	Coef.	95% CI	p-heter	I^2	N[b]	Coef.	95% CI	p-heter	I^2
NO_2 (per Δ10 µg/m^3)	7	-0.20	-0.98; 0.59	0.146	37.0%	8	0.24	-0.26; 0.73	0.314	14.8%	11	-0.42	-0.98; 0.14	0.177	28.1%
NOx (per Δ20 µg/m^3)	7	-0.21	-0.88; 0.46	0.184	31.9%	6	0.19	-0.27; 0.54	0.597	0.0%	9	-0.33	-0.86; 0.19	0.156	32.7%
PM_{10} (per Δ10 µg/m^3)	3	0.86	-1.97; 3.69	0.305	15.7%	4	0.22	-0.92; 1.37	0.484	0.0%	5	-0.03	-1.47; 1.41	0.981	0.0%
$PM_{2.5}$ (per Δ5 µg/m^3)	3	-0.49	-5.56; 4.58	0.136	49.9%	4	-0.25	-1.75; 1.25	0.904	0.0%	5	-0.63	-2.42; 1.16	0.911	0.0%
PM_{coarse} (per Δ5 µg/m^3)	3	0.69	-0.67; 2.05	0.631	0.0%	4	0.05	-0.72; 0.82	0.427	0.0%	5	0.61	-1.21; 2.43	0.022	65.0%
$PM_{2.5}$absorbance (per Δ$10^{-5}m^{-1}$)	3	-0.26	-3.25; 2.73	0.248	28.3%	4	0.16	-0.86; 1.18	0.667	0.0%	5	-0.20	-1.36; 0.96	0.897	0.0%

95% CI, 95% Confidence Interval; Coef, Coefficient; I^2 =Percentage of the total variability due to between-regions heterogeneity; NO_2, nitrogen dioxide; NOx, nitrogen oxides; p-heter, P value of heterogeneity using the Cochran's *Q* test; PM_{10}, particle matter less than 10µm; $PM_{2.5}$, particle matter less than 2.5µm; PM_{coarse}, particle matter between 2.5 and 10µm; $PM_{2.5}$absorbance, reflectance of $PM_{2.5}$ filters

[a]Coefficient and 95% confidence interval estimated by random-effects meta-analysis by region. Models were adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the cognitive or psychomotor development assessment, and evaluator and quality of the cognitive or psychomotor development test

[b]Number of regions included in the meta-analysis

Table 6. Fully-adjusted combined associations[a] between air pollution exposure during pregnancy[b] and global psychomotor development selecting those children with stable residence and good quality tests, and including the scores at young ages

	Children with stable residence from birth until the global psychomotor development assessment[c]					Children with good quality global psychomotor development test[d]					Inclusion of scores measured at younger ages when the assessment was done at different ages				
	N[e]	Coef.	95% CI	p-heter	I^2	N[e]	Coef.	95% CI	p-heter	I^2	N[e]	Coef.	95% CI	p-heter	I^2
NO_2 (per Δ10 µg/m^3)	8	-0.51	-1.00; -0.02	0.562	0.0%	6	-0.85	-1.81; 0.11	0.112	44.0%	11	-0.39	-0.78; 0.01	0.640	0.0%
NOx (per Δ20 µg/m^3)	8	-0.32	-0.66; 0.03	0.595	0.0%	6	-0.69	-1.57; 0.19	0.046	55.7%	9	-0.24	-0.54; 0.06	0.723	0.0%
PM_{10} (per Δ10 µg/m^3)	4	-1.00	-2.15; 0.16	0.441	0.0%	3	-1.29	-4.06; 1.49	0.893	0.0%	5	-0.92	-1.91; 0.08	0.762	0.0%
$PM_{2.5}$ (per Δ5 µg/m^3)	4	-1.84	-4.02; 0.34	0.114	49.5%	3	-2.04	-5.93; 1.85	0.300	17.0%	5	-1.46	-2.79; -0.12	0.305	17.2%
PM_{coarse} (per Δ5 µg/m^3)	4	-0.64	-1.59; 0.31	0.691	0.0%	3	-0.56	-2.37; 1.25	0.961	0.0%	5	-0.49	-1.30; 0.33	0.814	0.0%
$PM_{2.5}$absorbance (per Δ10^{-5}m^{-1})	4	-0.86	-1.90; 0.18	0.713	0.0%	3	-0.15	-2.17; 1.87	0.589	0.0%	5	-0.90	-1.81; 0.01	0.976	0.0%

95% CI, 95% Confidence Interval; Coef, Coefficient; I^2 =Percentage of the total variability due to between-regions heterogeneity; NO_2, nitrogen dioxide; NOx, nitrogen oxides; p-heter, P value of heterogeneity using the Cochran's *Q* test; PM_{10}, particle matter less than 10µm; $PM_{2.5}$, particle matter less than 2.5µm; PM_{coarse}, particle matter between 2.5 and 10µm; $PM_{2.5}$absorbance, reflectance of $PM_{2.5}$ filters

[a]Coefficient and 95% confidence interval estimated by random-effects meta-analysis by region. Models were adjusted for maternal education, maternal country of birth, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal smoking during pregnancy, parity, child's sex, season at child's birth date, urbanicity at child's birth address, child's age at the global psychomotor development assessment, and evaluator and quality of the global psychomotor development test

[b]Air pollution levels were temporally adjusted to the exact pregnancy period, except for NO_2 and NO_X in the Greek cohorts

[c]Information on residential changes from birth until the test assessment was not available for the German and the French cohorts

[d]Information on good quality test was not available for the Dutch, the French, the Italian, and the Spanish cohort from Granada

[e]Number of regions included in the meta-analysis

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