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Air Pollution Exposure during Pregnancy and Childhood Autistic Traits in Four European Population-Based Cohort Studies: The ESCAPE Project

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Running head: Prenatal air pollution and childhood autistic traits

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Abstract

Background: Prenatal exposure to air pollutants has been suggested as a possible etiologic factor for the occurrence of autism spectrum disorder.

Objectives: To assess whether prenatal air pollution exposure is associated with childhood autistic traits in the general population.

Methods: Collaborative study of four European population-based birth/child cohorts —CATSS (Sweden), GENERATION R (the Netherlands), GASPII (Italy), and INMA (Spain). Nitrogen oxides (NO_2, NO_x) and particulate matter (PM) with diameters of <2.5 μm ($PM_{2.5}$), <10 μm (PM_{10}), and between 2.5-10 μm (PM_{coarse}) and $PM_{2.5}$ absorbance— were estimated for birth addresses by land-use regression models based on monitoring campaigns performed between 2008 and 2011. Levels were extrapolated back in time to exact pregnancy periods. Autistic traits were assessed between four and ten years of age using quantitative assessments. Children were classified with autistic traits within the borderline/clinical range and within the clinical range using validated cut-offs. Adjusted cohort-specific effect estimates were combined using random-effects meta-analysis.

Results: A total of 8,079 children were included. Prenatal air pollution exposure was not associated with autistic traits within the borderline/clinical range (OR = 0.94; 95% CI: 0.81, 1.10 per each increase by 10 $\mu g/m^3$ in NO_2 pregnancy levels). Similar results were observed in the different cohorts, for the other pollutants, and assessing children with autistic traits within the clinical range or children with autistic traits as a quantitative score.

Conclusions: Prenatal exposure to NO_2 and PM was not associated with autistic traits in children from four to ten years of age in four European population-based birth/child cohort studies.

Introduction

Autism spectrum disorders (ASD) are lifelong developmental disabilities characterized by social interaction impairment, communication deficits, and repetitive behaviors (Van Engeland and Buitelaar 2008). The prevalence of ASD has increased in the past 20 years, reaching 1 in 86 children in Europe in 2007 (Posada et al.2007). Despite advances in genetic research, the causes of ASD remain unclear (Betancur 2011). A possible etiologic role for environmental factors has been suggested, particularly during pregnancy (Dietert et al. 2011).

Two recent case-control studies in California showed that ASD in children aged 2 to 6 years was associated with prenatal exposure to traffic-related air pollutants (Becerra et al. 2013; Volk et al. 2011; Volk et al. 2013), while the results of a twin study from Sweden did not confirm that finding (Gong et al. 2014). Another case-control study among children of Nurses' Health Study II participants reported an association between prenatal exposure to $PM_{2.5}$ (Raz et al. 2013) and other air pollutants such as diesel or metals at birth (Roberts et al. 2013) and ASD. Previously, two case-control studies were also carried out in the U.S., one showing a significant association of ASD with higher ambient air concentrations of metals at birth (Windham et al. 2006), and another one showing null associations between several pollutants at birth and ASD after adjusting for confounders (Kalkbrenner et al. 2010). Brain toxicity of urban air pollutants during development is well documented in animals and possible biological pathways have been suggested (Block et al. 2012).

Autistic traits are defined as subclinical deficits in socialization, communication, and repetitive behaviors that do not meet formal criteria for an ASD diagnosis (Constantino and Todd 2003). It has been shown that known genetic and environmental influences are consistent across

the range of impairment of the continuous autistic trait, indicating an etiologic overlap between very extreme scores, mild impairment, and subthreshold autism-like behavior (Robinson et al. 2011). To date, no study has examined the association of air pollution with the presence of autistic quantitative traits in the general population. This study aims to assess whether prenatal air pollution exposure including NO_2 and PM is associated with autistic traits in childhood in four European population-based birth/child cohort studies.

Methods

Population and study design

This study was part of the European Study of Cohorts for Air Pollution Effects (ESCAPE), in which the association between exposure to outdoor air pollution and health is being investigated within prospective cohort studies (www.escapeproject.eu). We included three European population-based birth cohorts: GENERATION R (the Netherlands) (Jaddoe et al. 2012), GASPII (Italy) (Porta et al. 2006), and INMA (Spain, including 3 sub-cohorts) (Guxens et al. 2013) and a European longitudinal child and adolescent twin study: CATSS (Sweden) (Anckarsäter et al. 2011) (Table 1). Mother-child pairs were recruited from 1992 to 2008. A total of 8,079 children with available data on exposures, outcome, and potential confounders were included (62.2% of the children recruited at baseline). Informed consent was obtained from all participants in each cohort and ethical approval was obtained from the local authorized Institutional Review Boards.

Air pollution exposure

Air pollution concentrations at the participants' birth home addresses were estimated for the whole pregnancy period of each woman by land-use regression models following a standardized procedure described elsewhere (Beelen et al. 2013; Eeftens et al. 2012a) (see Supplemental Material, Methods S1). Briefly, air pollution monitoring campaigns were performed in the study areas between October 2008 and January 2011. In all areas, three two-week measurements of NO_2 and nitrogen oxides (NO_x) were performed within one year (Cyrys et al. 2013). In all cohorts except in the Spanish cohorts of Valencia and Gipuzkoa, simultaneous measurements of PM_{10}, $PM_{2.5}$, PM with aerodynamic diameters between 2.5-10μm (PM_{coarse}), and $PM_{2.5}$ absorbance (determined as the reflectance of $PM_{2.5}$ filters) were performed (Eeftens et al. 2012b) (Table 1). Land-use regression models were developed for each pollutant metric using all measurement sites and used to estimate annual average air pollution concentration at the participants' birth home addresses. We used a back-extrapolation procedure to estimate pregnancy-average concentrations from annual average concentration using routine background monitoring network sites (Pedersen et al. 2013). Traffic intensity on the nearest road and total traffic load (intensity*length) on all major roads within a 100m buffer were available for some cohorts.

Autistic traits

Autistic traits were assessed in children using the Autism Spectrum Disorder module of the Autism-tics, Attention Deficit and Hyperactivity Disorders, and Other Comorbidities (A-TAC) inventory (Anckarsäter et al. 2011) in the Swedish cohort at age 9 or 12 years; the Pervasive Developmental Problems (PDP) subscale of the Child Behavior Checklist for Toddlers (CBCL1½-5) (Achenbach and Rescorla 2000) in the Dutch cohort at age 6 years and in the

Italian cohort at age 4 years; an adapted 18-item version of the Social Responsiveness Scale (SRS) (Constantino and Gruber 2005; Román et al. 2013) in the Dutch cohort at age 6 years; and the Childhood Autism Spectrum Test (CAST) (Baron-Cohen et al. 2009) in the Spanish cohorts at age 4-5 years (Table 1, see Supplemental Material, Methods S2 and Table S1). The A-TAC, the CBCL1½-5, and the adapted 18-item SRS were parental-reported questionnaires while the CAST was a questionnaire administered to the parents by a psychologist. For all tests, higher scores indicated more autistic traits. We considered all scores as quantitative traits. We also used validated cut-offs to yield proxies for autistic traits within the borderline/clinical (borderline or clinical) range and within the clinical range only, specific for each test (Larson et al. 2010; Tick et al. 2007; Williams et al. 2005), except for the adapted 18-item SRS for which these cut-offs are not defined. Validation studies reported high sensitivity (0.85-0.99) for borderline/clinical cut-offs and high specificity (0.95-0.97) for clinical cut-offs (see Supplementary Material, Methods S2).

Potential confounding variables

Potential confounding variables were defined a priori as similarly as possible across cohorts given available information. Maternal characteristics were collected by questionnaires during pregnancy or at birth: age at delivery, educational level (≤9, 10-12, ≥12 years in the Swedish cohort; ≤11, 12-15, ≥16 years in the Spanish cohort; primary, secondary, or ≥university in the Dutch and Italian cohorts), country of birth, prenatal smoking, and parity . Maternal height and pre-pregnancy weight were measured or self-reported in the 1st trimester of pregnancy or at birth. Pre-pregnancy body mass index (kg/m^2) was calculated. Child's sex and date of birth were obtained from hospital or national registries. Child's age at autistic trait assessment and evaluator

(parents, psychologist) of the autistic traits were also collected. Urbanicity at child's birth address (urban, rural) was defined (urban classification: municipalities with >40 inhabitants per hectare in the Swedish cohort; municipalities with >2,000 inhabitants in the Dutch, Italian, and Spanish cohorts). Mothers reported on changes in residence (since birth until autistic trait assessment) through questionnaires.

Statistical analyses

All analyses were performed following a consensus protocol. We used logistic regression models to assess the association between air pollution exposure and autistic traits within the borderline/clinical and within the clinical range. For both analyses we considered children with scores below the borderline cut-off as controls. Since few children were classified as having autistic traits within the clinical range in the Spanish cohorts of Gipuzkoa and Sabadell, we did not include them in that analysis. We used negative binomial regression models to assess the association between air pollution exposure and autistic traits as a quantitative score. Models for the Swedish cohort include a random intercept to take into account that children were clustered in twin pairs.

First, models were adjusted for child's age and sex (minimally-adjusted models). When child's age did not have a linear relationship with the autistic traits scales, we used the best transformation of the age found using fractional polynomials. Secondly, models were additionally adjusted for all covariates described above (fully-adjusted models). Generalized additive models were used to assess the linearity of the relationship between each air pollutant and autistic trait scales by graphical examination and deviance comparison. Linear function provided a good fit in all cases. Spatial clustering of observations was explored by adding

random cohort-level intercepts (Swedish cohort: small administrative units; Dutch cohort: neighborhood; Italian and Spanish cohorts: census area) to fully-adjusted models without the air pollution data. The inclusion of the spatial clustering component had a negligible impact on the Akaike Information Criterion. We used a two-stage approach to estimate the associations of air pollution exposure on autistic traits in children. First, associations were analyzed separately for each cohort. Secondly, cohort-specific effect estimates from the logistic regression models were combined using random-effects meta-analysis. We assessed heterogeneity in the estimates using the Q test and the I^2 statistic. Since quantitative scales of the autistic trait tests used in different cohorts did not share a common metric, meta-analyses of cohort-specific effect estimates on the autistic traits as continuous variables was not possible.

We perform several sensitivity analyses: i) meta-analyses leaving out one cohort at a time to determine the influence of a particular cohort; ii) meta-analyses including the cohorts with information on both NO_2 and PM (89% of the children); iii) meta-analyses using the 90^{th} percentile as a cut-off irrespective of the scale since borderline/clinical and clinical cut-offs were specific to the scale used in each cohort; iv) meta-analyses stratified by type of evaluator of the autistic traits (psychologist, parents); v) meta-analyses assessing the non-back-extrapolated air pollution variables; vi) meta-analyses including children who had a stable residence from birth until the autistic traits assessment; vii) meta-analyses restricted to children of highly educated mothers and meta-analysis restricted to children of mothers who did not smoke during pregnancy in order to assesspotential modifications of the air pollution effects by these factors; and viii) meta-analyses stratified by child's sex since some studies found different association in boys and girls. Power sample calculation can be found at Supplemental Material, Table S2. Statistical tests

of hypotheses were two-tailed with significance set at $P<0.05$. Statistical analyses were conducted using STATA (version 12.1; StataCorporation, College Station, TX, USA).

Results

Between 3.2% and 12.3% of children were classified as having autistic traits within the borderline/clinical range, while between 0.7% and 3.6% were classified as having autistic traits within the clinical range (Table 1). Children defined as having autistic traits within the borderline/clinical range or within the clinical range showed consistent associations with the assessed child and maternal characteristics across all cohorts (Table 2). Children with autistic traits within the borderline/clinical range and within the clinical range were mostly boys and had a higher proportion of mothers with low educational level and mothers who smoked during pregnancy compared to children without autistic traits (Table 2).

Median air pollution levels ranged from 17.9μg/m^3 (the Swedish cohort) to 42.2μg/m^3 (the Italian cohort) for NO_2 and from 8.4μg/m^3 (the Swedish cohort) to 22.4μg/m^3 (the Italian cohort) for $PM_{2.5}$ (Figure 1). Different correlation patterns between air pollution variables were found in the different cohorts (see Supplemental Material, Table S3). Overall, the correlation among air pollutants was strong (between 0.72 and 0.98) while the correlation between air pollutants and traffic variables was moderate or low (between 0.17 and 0.53).

None of the air pollutants were associated with autistic traits within the borderline/clinical range in the minimally-adjusted models (OR = 1.02; 95% CI: 0.87, 1.19 per 10μg/m^3 increase average NO_2 levels) (see Supplemental Material, Table S4). OR only changed slightly in the fully-adjusted models (changes of OR ranged from 0% (PM_{10}) to 10% ($PM_{2.5}$)) (Table 3). Fully-

adjusted associations of NO_2 and children with autistic traits within the borderline/clinical range including all the potential confounding variables are shown in Supplemental Material, Table S5. As shown in Figure 2, in most cohorts the associations with the different pollutants were consistently close to one. However, for the Spanish cohorts of Valencia and Gipuzkoa, NO_2 and NO_x exposure tended to have a slightly higher odds of autistic traits within the borderline/clinical range (Figure 2). Analysis with autistic traits within the clinical range (Table 4) and with autistic traits as quantitative scores (see Supplemental Material, Table S6) did not reveal any association with air pollution exposure.

We observed a similar lack of association in all sensitivity analyses: i) when cohorts were excluded one by one (see Supplemental Material, Table S7); ii) when meta-analyses were restricted to cohorts with information on both NO_2 and PM (see Supplemental Material, Table S8); iii) when we used the 90^{th} percentile of each autistic traits scale (see Supplemental Material, Table S9); iv) when we stratified the meta-analyses by the type of evaluator (psychologist, parents) (see Supplemental Material, Table S10); v) when we assessed the non-back-extrapolated air pollution variables (see Supplemental Material, Table S11); vi) when meta-analyses were restricted to children with postnatal stable residence (see Supplemental Material, Table S12); vii) when meta-analyses were restricted to children of highly educated mothers (see Supplemental Material, Table S12) and children of mothers who did not smoke during pregnancy (see Supplemental Material, Table S12); and viii) when meta-analyses were stratified by child's sex (see Supplemental Material, Table S13).

Discussion

The present study assessed the relationship between prenatal air pollution exposure including NO_2 and PM and autistic traits in more than 8,000 children of four European population-based birth/child cohorts. We found no evidence for an association between prenatal air pollution exposure and autistic traits in children aged 4 to 10 years. These results were consistent for all air pollutants assessed, across countries, using different cut-offs of autistic traits, examining autistic traits as continuous variables, and after adjusting for several socioeconomic status variables and urbanicity.

The strengths of our study were the large sample size in combination with the prospective and longitudinal study design, the use of a standardized and validated air pollution assessment in all countries, the assessment of exposure to a large number of air pollutants including NO_2 and PM at individual level, the assessment of autistic traits in childhood using standardized and validated neuropsychological tests, and the statistical analysis following a consensus protocol. Additionally, we adjusted for many socioeconomic and lifestyle variables known to be associated with air pollution exposure and/or autistic traits in children. .

The main limitation of our study was that four different tests were used in the different cohorts to assess autistic traits. All four tests are valid tools for assessment of children's behavior in epidemiological studies (Larson et al. 2010, Sikora et al. 2008, Constantino and Gruber 2005, Williams et al. 2005), though only two were developed to specifically address autistic traits (SRS and CAST). The other two (CBCL and A-TAC) have been most commonly used as screening test for a broader range of behavioral profile and disorders including autistic traits. Although all tests include items corresponding to the three core features of the ASD –social interaction deficits, communication deficits, and repetitive behaviors–, each test includes a different number

of items and gives a slightly different weight to each feature. These differences might imply that each instrument classifies children at risk for ASD in a slightly different way. However, children defined as having autistic traits within the borderline/clinical range or within the clinical range only showed consistent associations with the assessed child and maternal characteristics across all cohorts (Table 2). Moreover, we found consistent null association between prenatal air pollution exposure and autistic traits among cohorts regardless of the type of instrument, the age of assessment, the type of evaluator of the test, and the treatment of the scales using different cut-offs or using it as a quantitative trait. Another limitation of our study is related to the exposure assessment. Air pollution levels were back-extrapolated to the pregnancy period and this could lead to a non-differential misclassification of the exposure. Air pollution campaigns were performed when children were between 3 to 10 years, depending on the cohort. We used long-term routine monitoring data for the back-extrapolation to the exact pregnancy period for which we assumed that the spatial distribution of the sources and predictors of air pollution levels were stable with time. Previous research support this by showing a stability of measured and modeled spatial contrast in air pollutants over a period of 10 and 12 years (Cesaroni et al. 2012; Eeftens et al. 2011). However, since monitoring data were not available for all pollutants in all cohorts, particularly for PM, we used background monitoring network sites of other pollutants in the cases of missing information. Nevertheless, we found that back-extrapolated and non-back-extrapolated results were essentially similar. Since correlation between whole pregnancy and trimester-specific air pollution concentrations was high in a previous ESCAPE study (Pedersen et al. 2013), we did not attempt to calculate trimester-specific associations as these would not be expected to be different. Finally, paternal exposure to air pollution during the

preconception phase may also play a role in the development of ASD but this information was not available in our study.

Previous studies carried out in the U.S. found a consistently positive association between exposure to several air pollutants during pregnancy or during the 1st year of life and diagnosis of ASD (Becerra et al. 2013; Raz et al. 2013; Roberts et al. 2013; Volk et al. 2011; Volk et al. 2013; Windham et al. 2006). Moreover, a study carried out in Taiwan found that postnatal exposure to NO_2, ozone, carbon monoxide, and sulfur dioxide was associated with ASD in children from 3 to 9 years of age (Jung et al. 2013). Results from previous studies seem contradictory to our findings. However, previous case-control studies selected children with a diagnosis of ASD whereas in our study we studied children with autistic traits from population-based birth/child cohorts. A possible explanation for inconsistent findings could be that our study population does not represent the phenotypic extreme present in the case-control studies as only a small number of children surpassed the threshold for ASD. We hypothesize that prenatal exposure to air pollution could be related to ASD but not with broad autistic traits in children. In our study we defined children with autistic traits within the clinical range using the clinical cut-off, which is shown to be specific for detecting children at risk for ASD, but resulting in small sample sizes. We found no indication of an association between prenatal air pollution exposure and autistic traits within the clinical range.

Residual confounding could be another possible explanation of the discrepant findings between previous studies and our study. Most of the previous studies accounted, similar to our study, for several potential confounding variables including maternal education, maternal age, prenatal maternal smoking, and urbanicity. Becerra et al. found an association between ASD and

air pollution exposure only after adjusting for maternal educational level (Becerra et al. 2013), while associations were similar between unadjusted and adjusted models in the other studies (Volk et al. 2011; Volk et al 2013). In our study, results were also materially unchanged after adjusting for confounders. Moreover, we observed similar results when we restricted our analyses to children of mothers with high educational levels or mothers who did not smoke during pregnancy. It is worth noting that children with diagnosis of ASD in some of the previous studies were more likely to come from high maternal socioeconomic backgrounds (Becerra et al. 2013, Kalkbrenner et al. 2010; Windham et al. 2006) while children with autistic traits in all our cohort studies were more likely to have mothers with a low maternal socioeconomic status. This finding may reflect a systematic difference between the study of broad autistic traits and children with ASD diagnosis, or that the previous studies share a common bias, possibly a diagnostic bias related to socioeconomic status related differences in access to care, that was not operating in the European cohorts (Rai et al. 2012).

An alternative explanation of the contradictory findings could be differences in air pollution levels and sources. Air pollution levels at the extremes of the distributions in several of the previous studies are higher than those observed in our study, though exposure ranges do overlap (mean NO_2 levels about 32μg/m^3-58μg/m^3 in California or Los Angeles county (Becerra et al. 2013; Volk et al. 2013) *vs.* 19μg/m^3-43μg/m^3 in our European cohorts; mean PM_{10} levels around 26μg/m^3-36μg/m^3 in California or Los Angeles county (Becerra et al. 2013; Volk et al. 2013) *vs.* 17μg/m^3-44μg/m^3 in our European cohorts; mean $PM_{2.5}$ levels around 14μg/m^3-20μg/m^3 in California or Los Angeles (Becerra et al. 2013; Volk et al. 2013) county *vs.* 8μg/m^3-23μg/m^3 in our European cohorts). In our study, NO_2 and PM are markers of traffic air pollution

but also sources such as space heating since small-scale traffic and population/household density variables were the most frequently used predictors in the land use regression models (Beelen et al. 2013; Eeftens et al. 2012a). In some previous studies associations with ASD were also observed with traffic indicators such as living near a freeway or modeled traffic-related air pollution exposure (Volk et al. 2011; Volk et al. 2013). However, null association was observed in another study (Gong et al. 2014) when air pollutant levels were estimated using dispersion models. Although NO_2 or PM levels are similar, different exposure mixtures among study areas may result in different health effects. Based on experimental models, it has been hypothesized that PM soluble components are one of the major suspected culprits of the neurological effects of air pollution, primarily metals, since they may translocate from the respiratory tract into the systemic circulation and reach the fetus and promote oxidative stress and inflammation (Block et al. 2012). Further research including trace metal content of the PM such as lead or manganese is warranted to better understand the discrepant findings.

In conclusion, this study showed a null association between prenatal exposure to several air pollutants, including NO_2 and PM, and autistic traits in children aged 4 to 10 years in four European population-based birth/child cohorts. Additional research including European studies of children with a diagnosis of ASD, a comparison of ASD manifestation and detection between the US and Europe, and the study of the air pollutants mechanisms underlying the association with ASD is needed to further understand the different findings between previous studies and the present study.

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Table 1. Description of the participating birth cohort studies.

	Setting		Air pollution		Autistic traits					
Cohort study	**Location**	**Pregnancy period**	**Pollutants**	**% of birth addresses in urban areas**	**Test**	**Age**	**Evaluator**	**n[a]**	**n (%) within borderline or clinical range**	**n (%) within clinical range only**
CATSS	Stockolm (Sweden)	1992-2000	NO_2, NO_x, PM, Traffic intensity, Traffic load	45.7	ASD module (A-TAC)	10y	Parents	2,437	78 (3.2)	27 (1.1)
GENERATION R	Rotterdam (the Netherlands)	2001-2005	NO_2, NO_x, PM, Traffic intensity, Traffic load	100.0	PDP subscale (CBCL½-5)	6y	Parents	3,955	336 (8.5)	143 (3.6)
					Adapted 18-item version of SRS	6y	Parents	3,231	na[b]	na[b]
GASPII	Rome (Italy)	2003-2004	NO_2, NO_x, PM, Traffic intensity, Traffic load	100.0	PDP subscale (CBCL½-5)	4y	Parents	514	63 (12.3)	15 (2.9)
INMA	Gipuzkoa (Spain)	2006-2008	NO_2, NO_x	89.1	CAST	4y	Psychologist	357	17 (4.8)	3 (0.8)
	Sabadell (Spain)	2004-2006	NO_2, NO_x, PM, Traffic load	100.0	CAST	4y	Psychologist	295	10 (3.4)	2 (0.7)
	Valencia (Spain)	2004-2005	NO_2, NO_x, Traffic load	92.7	CAST	5y	Psychologist	521	37 (7.1)	10 (1.9)

ASD, autism spectrum disorder; A-TAC, autism-tics, attention deficit and hyperactivity disorders, and other comorbidities inventory; CBCL, child behavior checklist; CAST, childhood autism spectrum test; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PDP, pervasive developmental problems; PM, particle matter that refers to PM less than 10µm (PM_{10}), PM less than 2.5µm ($PM_{2.5}$), PM between 2.5 and 10µm (PM_{coarse}), $PM_{2.5}$absorbance (reflectance of $PM_{2.5}$ filters); SRS, Social Responsiveness Scale; Traffic intensity, traffic intensity on the nearest road; Traffic load, total traffic load (intensity*length) on all major roads within 100m buffer.

[a]number of children with air pollution, autistic traits, and potential confounders variables available. [b]na=not applicable since the cut-off points for autistic traits within the borderline/clinical range and within the clinical range have not been defined for the 18-item version of the SRS; score only evaluated as a continuous quantitative outcome.

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Table 2. Distribution of the child and maternal characteristics.

		Child's sex	Maternal educational level			Maternal country of birth	Maternal age at delivery (years)	Maternal pre-pregnancy body mass index (kg/m^2)	Maternal height (cm)	Prenatal maternal smoking	Parity
	N	% female	% low	% medium	%high	% foreign	mean (SD)	mean (SD)	mean (SD)	% smokers	% nulliparous
All population											
CATTS, Sweden	2437	49.1	10.5	48.6	40.9	13.0	31.6 (4.6)	23.5 (3.6)	167.5 (6.2)	14.3	23.6
GENERATION R, the Netherlands	3955	50.4	6.1	38.1	55.8	37.2	31.6 (4.6)	24.3 (4.1)	168.7 (7.3)	12.7	59.4
GASPII, Italy	514	49.0	10.3	51.2	38.5	3.9	33.8 (4.2)	22.2 (3.4)	164.6 (5.9)	10.7	57.0
INMA, Spain-Gipuzkoa	357	50.1	11.2	36.4	52.4	2.5	32.8 (3.4)	22.9 (3.5)	163.6 (6.0)	23.2	55.5
INMA, Spain-Sabadell	295	49.8	26.8	35.6	37.6	8.1	31.7 (4.1)	23.5 (4.5)	162.4 (5.8)	27.1	60.3
INMA, Spain-Valencia	521	48.0	27.8	43.8	28.4	8.1	31.8 (4.2)	23.8 (4.4)	162.2 (6.3)	37.6	54.1
CATTS, Sweden											
Children without autistic traits	2359	50.0	10.2	48.2	41.6	13.1	31.7 (4.6)	23.5 (3.6)	167.5 (6.2)	14.0	23.3
Children within the borderline or clinical range	78	23.1	21.8	59.0	19.2	7.7	30.4 (4.6)	24.6 (5.1)	167.0 (6.7)	23.1	33.3
Children within the clinical range only	27	18.5	18.5	66.7	14.8	11.1	30.3 (4.2)	27.2 (6.8)	165.3 (7.1)	25.9	29.6
GENERATION R, the Netherlands											
Children without autistic traits	3619	51.8	5.6	37.7	56.6	36.3	31.7 (4.5)	24.3 (4.1)	168.8 (7.2)	12.1	58.8
Children within the borderline or clinical range	336	36.0	11.0	42.0	47.0	47.9	30.5 (5.0)	24.3 (4.6)	167.6 (7.6)	18.5	66.7
Children within the clinical range only	143	26.6	12.6	42.0	45.5	51.7	30.1 (5.2)	24.5 (5.1)	166.5 (7.8)	19.6	69.2
GASPII, Italy											
Children without autistic traits	451	50.1	9.1	51.2	39.7	4.4	33.8 (4.2)	22.1 (3.4)	164.6 (5.9)	11.1	55.2
Children within the borderline or clinical range	63	41.3	19.0	50.8	30.2	0.0	33.7 (4.2)	23.0 (3.6)	164.5 (5.9)	7.9	69.8
Children within the clinical range only	15	60.0	20.0	60.0	20.0	0.0	34.6 (3.4)	22.9 (3.2)	165.1 (6.2)	20.0	60.0
INMA, Spain-Gipuzkoa[a]											
Children without autistic traits	340	50.3	10.0	36.5	53.5	2.4	32.8 (3.3)	22.9 (3.4)	163.7 (6.1)	22.9	55.3
Children within the borderline or clinical range	17	47.1	35.3	35.3	29.4	5.9	33.0 (3.7)	23.2 (4.6)	162.2 (5.4)	29.4	58.8

	N	Child's sex	Maternal educational level			Maternal country of birth	Maternal age at delivery (years)	Maternal pre-pregnancy body mass index (kg/m^2)	Maternal height (cm)	Prenatal maternal smoking	Parity
		% female	% low	% medium	%high	% foreign	mean (SD)	mean (SD)	mean (SD)	% smokers	% nulliparous
INMA, Spain-Sabadell[a]											
Children without autistic traits	285	50.5	26.3	35.4	38.2	8.4	31.7 (4.1)	23.6 (4.5)	162.4 (5.8)	27.0	60.7
Children within the borderline or clinical range	10	30.0	40.0	40.0	20.0	0.0	31.2 (5.0)	22.7 (4.6)	163.7 (6.7)	30.0	50.0
INMA, Spain-Valencia											
Children without autistic traits	484	49.8	26.7	43.2	30.2	7.9	31.9 (4.1)	23.7 (4.4)	162.2 (6.3)	36.0	54.5
Children within the borderline or clinical range	37	24.3	43.2	51.4	5.4	10.8	30.6 (4.7)	24.8 (4.4)	162.0 (6.3)	59.5	48.6
Children within the clinical range only	10	30.0	60.0	30.0	10.0	0.0	28.0 (2.4)	24.9 (4.5)	161.9 (6.6)	60.0	50.0

SD, Standard Deviation

[a]Since few children were classified as having autistic traits within the clinical range only in the Spanish cohorts of Gipuzkoa and Sabadell, we did not include that classification in the analysis.

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Table 3. Fully adjusted combined associations[a] between air pollution during pregnancy[b] and autistic traits within the borderline/clinical range.

	Autistic traits within the borderline/clinical range				Autistic traits within the clinical range			
	N[c]	OR (95% CI)	p-heter	I^2	N[c]	OR (95% CI)	p-heter	I^2
NO_2 (per Δ10 µg/m^3)	6	0.95 (0.81, 1.10)	0.431	0.00%	4	0.87 (0.67, 1.14)	0.955	0.00%
NO_X (per Δ20 µg/m^3)	6	0.98 (0.88, 1.09)	0.438	0.00%	4	0.93 (0.78, 1.11)	0.640	0.00%
PM_{10} (per Δ10 µg/m^3)	4	0.90 (0.68, 1.19)	0.419	0.00%	3	0.92 (0.55, 1.54)	0.368	0.00%
$PM_{2.5}$ (per Δ5 µg/m^3)	4	0.71 (0.37, 1.37)	0.052	61.24%	3	1.01 (0.63, 1.63)	0.472	0.00%
PM_{coarse} (per Δ5 µg/m^3)	4	0.96 (0.72, 1.28)	0.300	18.16%	3	0.87 (0.55, 1.38)	0.320	12.33%
$PM_{2.5}$absorbance (per $\Delta 10^{-5} m^{-1}$)	4	0.82 (0.57, 1.18)	0.244	27.95%	3	0.70 (0.44, 1.12)	0.899	0.00%
Traffic intensity on the nearest road (per Δ5000 mv/day)	3	1.00 (0.92, 1.09)	0.721	0.00%	3	0.98 (0.85, 1.14)	0.508	0.00%
Total traffic load on all major roads within 100m buffer (per Δ4000000 mv/day*m)	5	1.02 (0.89, 1.16)	0.752	0.00%	3	0.90 (0.70, 1.16)	0.691	0.00%

95% CI, 95% Confidence Interval; OR, Odds Ratio; I^2 =Percentage of the total variability due to between-areas heterogeneity; NO_2, nitrogen dioxide; NO_x, 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

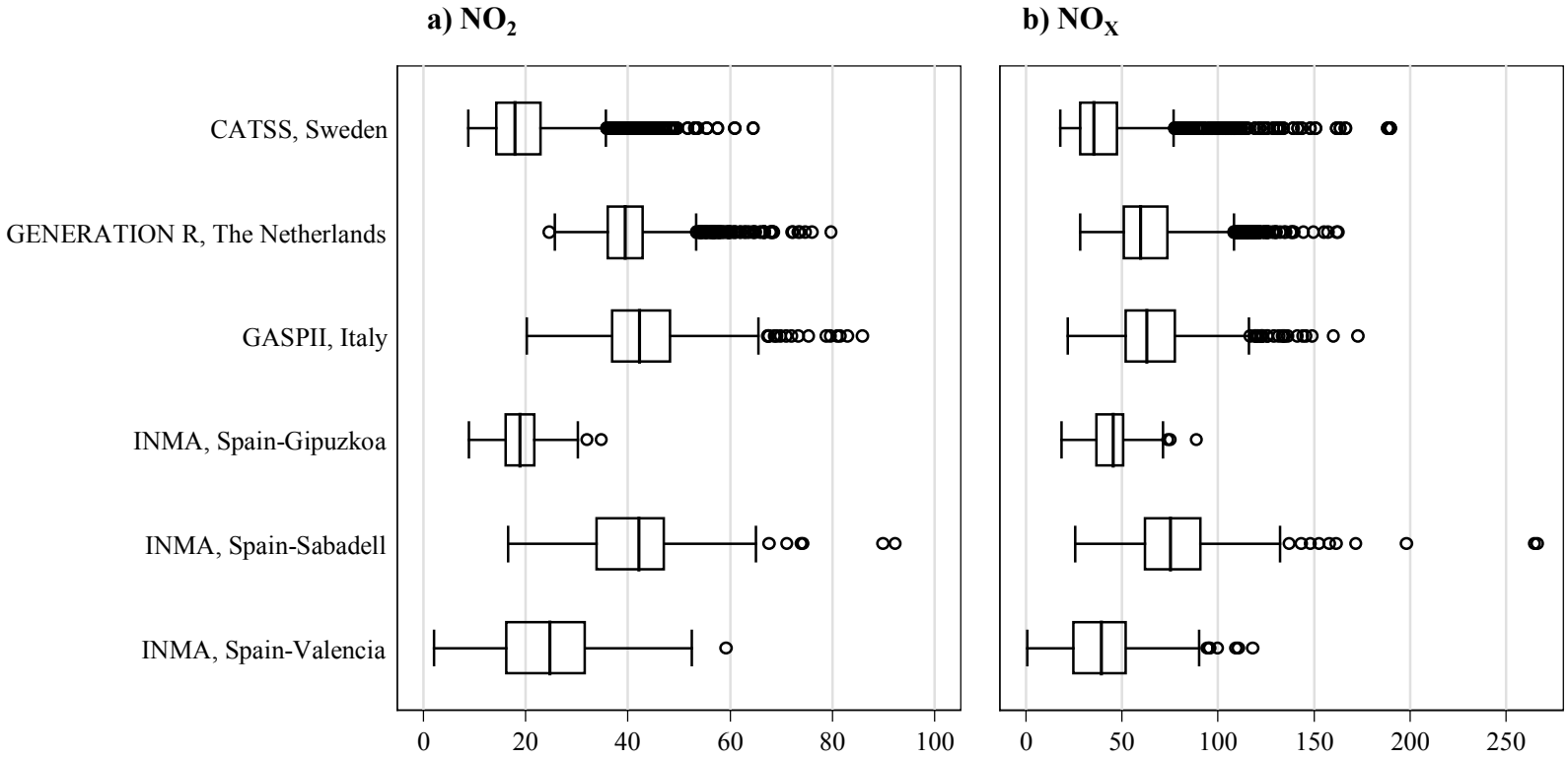
[a]Odds Ratio and 95% confidence interval estimated by random-effects meta-analysis by area. Models were adjusted for maternal characteristics (education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity), child's sex, season at child's birth, urbanicity at child's birth address, and child's age at autistic traits assessment, and evaluator of the autistic traits. Models of traffic variables were additionally adjusted for non-back-extrapolated background levels of NO_2. [b]Air pollution levels were temporally adjusted to the exact pregnancy period except for traffic variables. [c]Number of cohorts included in the meta-analysis.

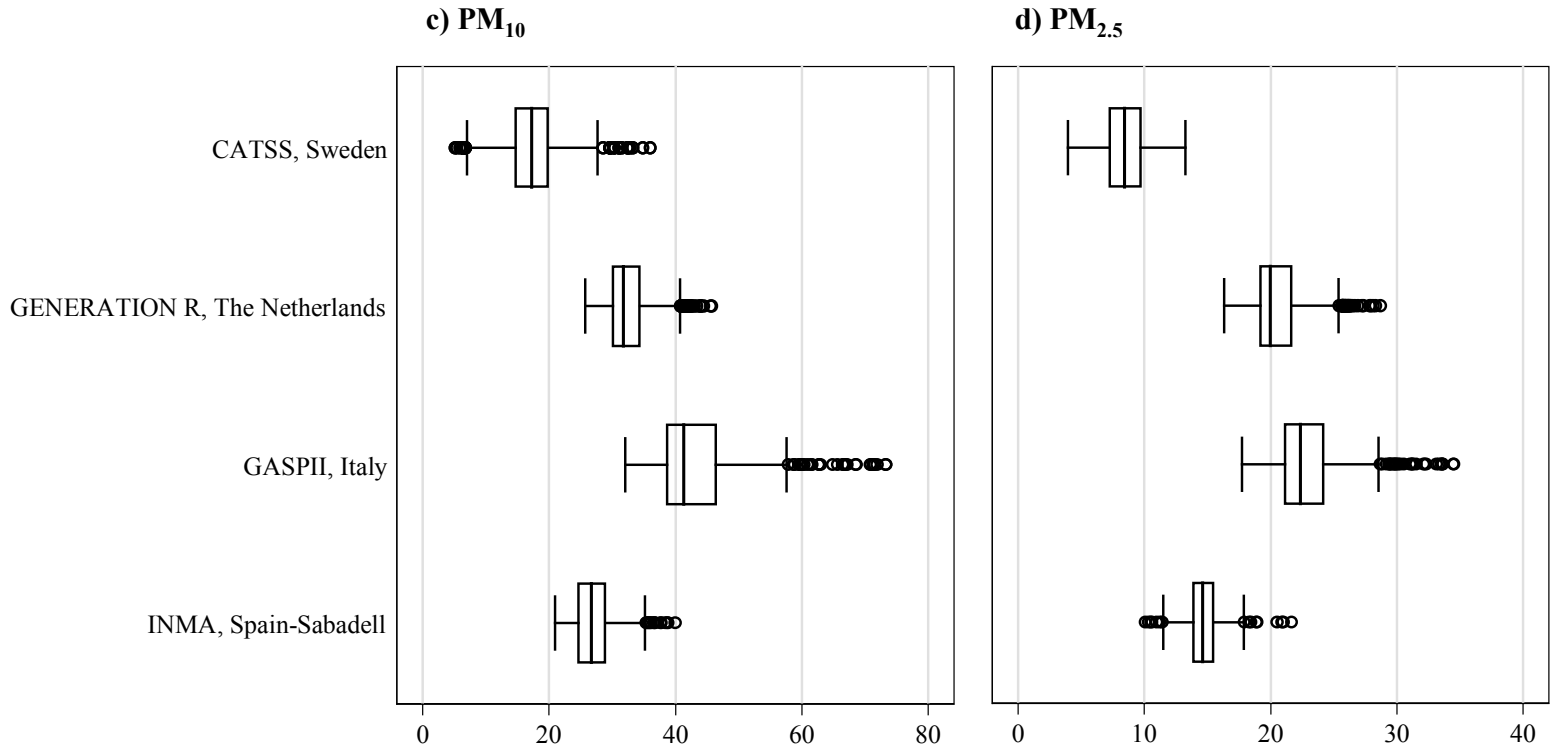
Figure Legends

Figure 1. Distribution of air pollutant levels during pregnancy. 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. Air pollution levels were temporally adjusted to the exact pregnancy period. Boxes extended from the 25^{th} to the 75^{th} percentile, horizontal bars represent the median, whiskers extend 1.5 times the length of the interquartile range (IQR) above and below the 75^{th} and 25^{th} percentiles, respectively, and outliers are represented as points. PM_{10}, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$absorbance were not available in the Spanish cohorts of Gipuzkoa and Valencia.

Figure 2. Fully adjusted associations between air pollution exposure during pregnancy and autistic traits within the borderline/clinical range. 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. Coefficient and 95% confidence interval by cohort and overall estimate obtained by random-effects meta-analysis. Models were adjusted for maternal characteristics (education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, parity), child's sex, season at child's birth, urbanicity at child's birth address, child's age at the autistic traits assessment, and evaluator of the autistic traits. PM_{10}, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$absorbance were not available in the Spanish cohorts of Gipuzkoa and Valencia.

Figure 1.


a) NO_2
b) NO_X
CATSS, Sweden
GENERATION R, The Netherlands
GASPII, Italy
INMA, Spain-Gipuzkoa
INMA, Spain-Sabadell
INMA, Spain-Valencia
0
20
40
60
80
100
0
50
100
150
200
250


c) PM10
d) PM2.5
CATSS, Sweden
GENERATION R, The Netherlands
GASPII, Italy
INMA, Spain-Sabadell
0
20
40
60
80
0
10
20
30
40

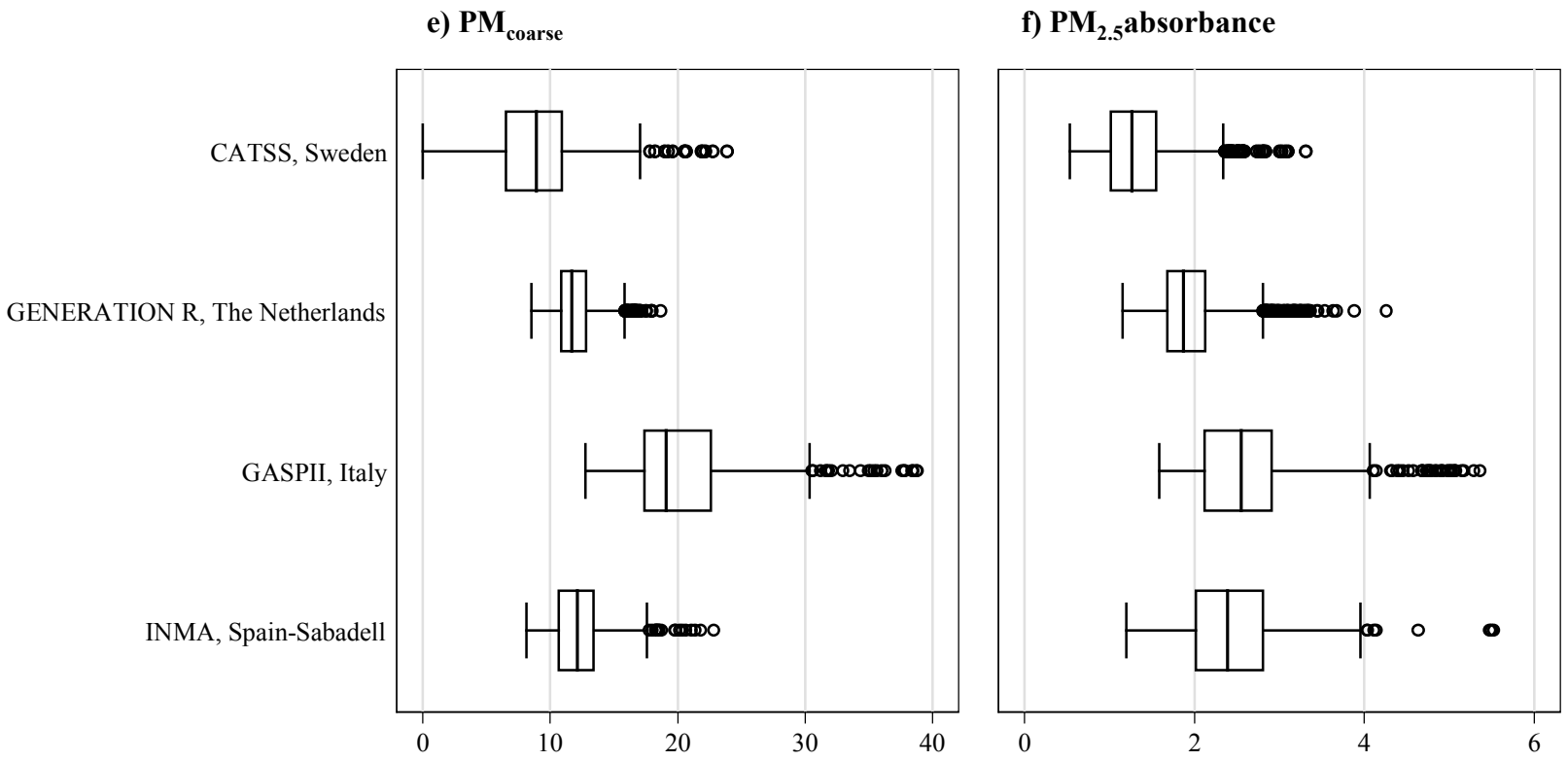

e) PMcoarse
f) PM2.5absorbance
CATSS, Sweden
GENERATION R, The Netherlands
GASPII, Italy
INMA, Spain-Sabadell
0
10
20
30
40
0
2
4
6

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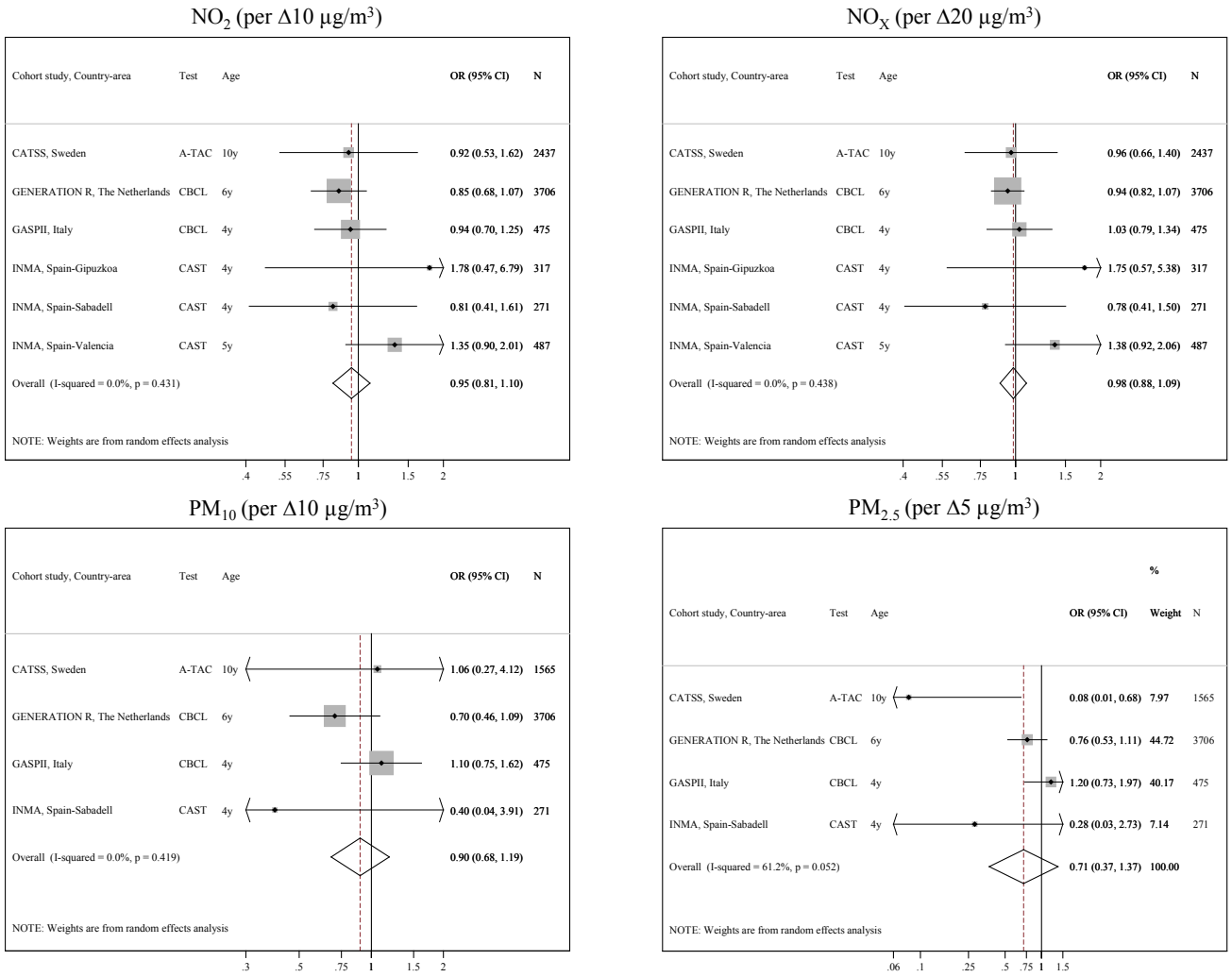
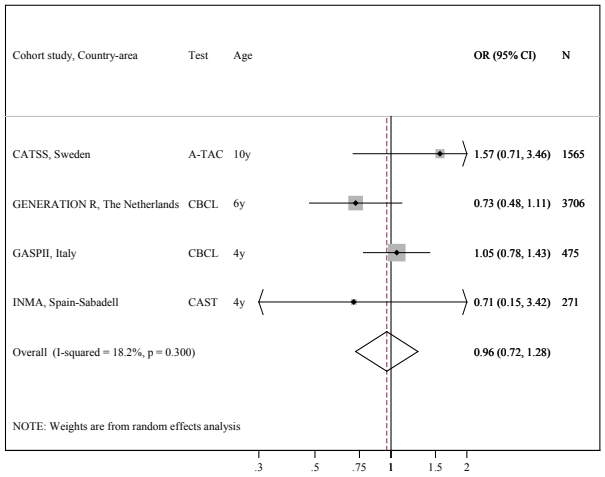
Figure 2.



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



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