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Prenatal and postnatal exposure to air pollution and emotional and aggressive symptoms in children from 8 European birth cohorts

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Abbreviations: ABCD, Amsterdam Born Children and their Development study; BC, black carbon; BMI, body mass index; CBCL/6–18, child behavior checklist for ages 6–18; EC, elemental carbon; EDEN, Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant; ESCAPE, European Study of Cohorts for Air Pollution Effects; GASPII, Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia; GINIplus, German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development; LISA, Influence of life-style factors on the development of the immune system and allergies in East and West Germany; LUR, Land Use Regression; INMA, Infancia y Medio Ambiente project; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OR, odd ratio; PM, particulate matter; PM_{10}, particulate matter with aerodynamic diameter of $\leq 10\,\mu m$; $PM_{2.5}$, particulate matter with aerodynamic diameter of $\leq 2.5\,\mu m$; PM_{coarse}, particulate matter with aerodynamic diameter between 10 and 2.5 μm; $PM2.5_{abs}$, the absorbance of particulate matter with aerodynamic diameter of $\leq 2.5\,\mu m$ filters; PAHs, polycyclic aromatic hydrocarbons; REPRO_PL, Polish Mother and Child Cohort Study; SDQ, strength and difficulties questionnaire

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ABSTRACT

Background: The association between air pollution exposure and emotional and behavioural problems in children is unclear. We aimed to assess prenatal and postnatal exposure to several air pollutants and child's depressive and anxiety symptoms, and aggressive symptoms in children of 7–11 years.

Methods: We analysed data of 13182 children from 8 European population-based birth cohorts. Concentrations of nitrogen dioxide (NO_2), nitrogen oxides (NO_x), particulate matter (PM) with diameters of $\leq 10\,\mu m$ (PM_{10}), $\leq 2.5\,\mu m$ ($PM_{2.5}$), and between 10 and 2.5 μm (PM_{coarse}), the absorbance of $PM_{2.5}$ filters ($PM_{2.5}$abs), and polycyclic aromatic hydrocarbons (PAHs) were estimated at residential addresses of each participant. Depressive and anxiety symptoms and aggressive symptoms were assessed at 7–11 years of age using parent reported tests. Children were classified in borderline/clinical range or clinical range using validated cut offs. Region specific models were adjusted for various socio-economic and lifestyle characteristics and then combined using random effect meta-analysis. Multiple imputation and inverse probability weighting methods were applied to correct for potential attrition bias.

Results: A total of 1896 (14.4%) children were classified as having depressive and anxiety symptoms in the borderline/clinical range, and 1778 (13.4%) as having aggressive symptoms in the borderline/clinical range. Overall, 1108 (8.4%) and 870 (6.6%) children were classified as having depressive and anxiety symptoms, and aggressive symptoms in the clinical range, respectively. Prenatal exposure to air pollution was not associated with depressive and anxiety symptoms in the borderline/clinical range (e.g. OR 1.02 [95%CI 0.95 to 1.10] per $10\,\mu g/m^3$ higher NO_2) nor with aggressive symptoms in the borderline/clinical range (e.g. OR 1.04 [95%CI 0.96 to 1.12] per $10\,\mu g/m^3$ higher NO_2). Similar results were observed for the symptoms in the clinical range, and for postnatal exposures to air pollution.

Conclusions: Overall, our results suggest that prenatal and postnatal exposure to air pollution is not associated with depressive and anxiety symptoms or aggressive symptoms in children of 7 to 11 years old.

1. Introduction

Exposure to air pollution is considered a potential hazard for healthy neurodevelopment (Grandjean and Landrigan, 2014). Neurodevelopment starts in fetal life with numerous processes continuing throughout childhood (Hines, 2018). During this developmental period, the detoxification mechanisms are still maturing, making early life a critical window of vulnerability to environmental exposures such as air pollution (Block et al., 2012; Backes et al., 2013; Grandjean and Landrigan, 2014).

The majority of epidemiological studies in this field has been conducted on prenatal or postnatal exposure to air pollution and children's cognition, psychomotor skills, and some specific behavioural problems, such as autism spectrum disorders and attention deficit and hyperactivity disorders (Becerra et al., 2013; Forns et al., 2016; Freire et al., 2012; Guxens and Sunyer, 2012; Guxens et al., 2014, 2016; Jedrychowski et al., 2015; Lubczyńska et al., 2017; Min and Min, 2017; Sentís et al., 2017; Suades-González et al., 2015; Volk et al., 2013). However, little is known whether prenatal or postnatal exposure to air pollution is associated with other common mental health problems in childhood, such as emotional and aggressive problems. Regarding prenatal exposure, the only existing studies have been conducted in New York City (Margolis et al., 2016) and in Krakow (Genkinger et al., 2015), showing that exposure to higher levels of airborne polycyclic aromatics hydrocarbons (PAHs) during pregnancy was associated with more depressive and anxiety symptoms in children of 4.8–11 years old, as well as with more aggressive symptoms in children of 6–11 years old. Conversely, three other studies of the relationship between postnatal air pollution exposure including elemental carbon (EC), black carbon (BC), particulate matter (PM) with aerodynamic diameter of $< 2.5\,\mu m$ ($PM_{2.5}$), and nitrogen dioxide (NO_2), with depressive and anxiety symptoms, and aggressive symptoms in children of 7–12 years old, conducted in Barcelona (Forns et al., 2016), in Ohio (Newman et al., 2013), and in London (Roberts et al., 2019), showed no associations. However, the study from London, found that higher postnatal exposures to NO_2 and $PM_{2.5}$ was associated with an increased odds of major depressive disorders at age 18 (Roberts et al., 2019).

Awareness of, and concern about, mental health disorders in childhood, which are often chronic in nature, is increasing (Pitchforth et al., 2018). Worldwide prevalence of any anxiety disorder, depressive disorder or aggressive problems is currently around 6.5%, 2.6%, and 2.1% respectively (Polanczyk et al., 2015). Such disorders can often have serious negative consequences for children's development and wellbeing, academic achievement, and social development later in life (Polanczyk et al., 2015). Thus, the identification of potential risk factors for these mental health problems is crucial for their prevention. Therefore, the aim of the current study in different Europe countries was to assess whether prenatal and postnatal exposure to air pollutants highly ubiquitous in urban settings was associated with depressive and anxiety symptoms, and aggressive symptoms in childhood across Europe.

2. Methods

2.1. Population and study design

We included 8 European population-based birth cohorts: Amsterdam Born Children and their Development study (ABCD) from the Netherlands (van Eijsden et al., 2011), the Generation R Study from the Netherlands (Kooijman et al., 2016), the German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus), and the Influence of lifestyle factors on the development of the immune system and allergies in East and West Germany Study (LISA) from two regions in Germany (Berg et al., 2010; Heinrich et al., 2002), Polish Mother and Child Cohort Study (REPRO_PL) from Poland (Polańska et al., 2016), Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant (EDEN) from two regions in France (Drouillet et al., 2009), Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia (GASPII) from Italy (Porta et al., 2007), and the INfancia y Medio Ambiente (INMA) project from five regions in Spain (Guxens et al., 2012) (Table 1). Mother-child pairs were recruited between 1995 and 2008, depending on the cohort (Table 1). A total of 13,182 children (from singleton births) with available data on exposures and outcomes were included in the current study. Informed consent was obtained from all participants, and local authorized Institutional Review Boards granted

the ethical approval for the studies.

2.2. Air pollution exposure

Air pollution exposure data used in this study originated from the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (http://www.escapeproject.eu), except for the REPRO_PL cohort and Gipuzkoa region of the INMA cohort where different air pollution exposure assessments were used, as described subsequently.

Within ESCAPE, land use regression (LUR) models were developed following a standardized procedure described elsewhere (Beelen et al., 2013; Eeftens et al., 2012a). Briefly, air pollution monitoring campaigns were performed in the study areas between October 2008 and January 2011, except in EDEN where they were done in 2002 (Nancy) and 2005 (Poitiers) (Sellier et al., 2014). In all regions, NO_2 and nitrogen oxides (NO_x) were measured in three 2 week periods within 1 year, with the exceptions of EDEN for which no NO_x measurements were done (Cyrys et al., 2012) (Table 1). PM with aerodynamic diameter of < 10 µm (PM_{10}) and $PM_{2.5}$ were measured 3 times during a 2 week period at 40 sites in the Netherlands/Belgium (applied for ABCD and the Generation R Study) and Sabadell region of INMA, and at 20 sites in Munich and the Ruhr area (GINIplus/LISA) and in Rome (GASPII) (Eeftens et al., 2012b). PM measurements were not available in EDEN and Asturias, Valencia and Granada regions of INMA. Coarse particle concentration (PM_{coarse}) was calculated as the difference between PM_{10} and $PM_{2.5}$. The absorbance of the $PM_{2.5}$ filters ($PM_{2.5}$abs) was measured to serve as a proxy for elemental carbon. Additionally, $PM_{2.5}$ filters were also analysed for PAHs in the Netherlands and the Sabadell region of INMA (Jedynska et al., 2014). Next, LUR models were developed for each pollutant, based on the measurements, and on a variety of potential land use predictors derived from geographic information systems (Beelen et al., 2013; Eeftens et al., 2012a; Jedynska et al., 2014; Sellier et al., 2014). These models were then used to assign annual average air pollution concentration to all the collected home addresses of each participant. If more than one address was collected during the prenatal period, we calculated the weighted average concentration level of all the addresses according to the time spent at each address, resulting in one concentration level per pollutant for each participant. The same procedure was followed for the postnatal period. In this study, the postnatal period is defined as the period stretching from birth until the emotional and behavioural problems assessment. No analyses relying on postnatal exposures could be performed in ABCD for NO_2, NO_x and PM, EDEN for NO_2 and Asturias, Gipuzkoa, Valencia, and Granada regions of INMA cohort for NO_x.

In the REPRO_PL cohort, universal kriging methodology was used. Average concentrations of air pollutants from the entire country were used, covering the period between 2006 and 2016 for NO_2 and PM_{10}, and the period between 2010 and 2016 for $PM_{2.5}$ (http://www.gios.gov.pl/en/) and assigned to the residential addresses of the participants.

In the Gipuzkoa region of the INMA cohort, while NO_2 average concentrations were based on ESCAPE methodology, the average concentrations of $PM_{2.5}$ and PM_{10} were obtained through 24-h sampling campaigns, monthly rotating between Urola Medio Valley, Urola Alto Valley, and Oria Valley, covering the period between May 2006 and December 2007, and assigned to residential addresses for each participant (Lertxundi et al., 2010).

2.3. Emotional and behavioural problems assessment

Emotional and behavioural problems were measured in each participating cohort/region using the Child Behaviour Checklist for ages 6–18 (CBCL/6-18) or the Strength and Difficulties Questionnaire (SDQ) (Table 1). All symptoms scores were reported by the parents.

CBCL/6-18 was administered when the children were between 7 and 10 years old, depending on the cohort/region. The CBCL/6-18 consists of 9 syndrome scales, from which we selected four scales. The anxious/depressed syndrome scale (13 items) and withdrawn/depressed syndrome scale (8 items) were selected as indicators of child's depressive and anxiety symptoms. The rule-breaking syndrome scale (17 items) and aggression scale (18 items) were selected as measures of children's aggressive symptoms. Higher scores indicate more symptoms. We used the 93rd and 98th percentile of the region specific total population as cut offs, which have been validated and standardized, to classify children symptoms in the borderline and clinical range (from now on named borderline/clinical range) and in the clinical range,

Table 1
Description of the participating cohort studies.

							Depressive and anxiety symptoms		Aggressive symptoms	
			%				%		%	
	Pregnancy		urban				borderline/	%	borderline/	%
	period	Pollutants	area*	Test	Age	n[a]	clinical range	clinical range	clinical range	clinical range
ABCD, The Netherlands[1]	2003-2004	NO_2,NO_x, PM	100	SDQ	11y	2701	18.2	11.0	6.4	2.6
GENERATION R, The Netherlands[1]	2001-2005	NO_2, NO_x, PM, PAHs	100	CBCL	10y	3120	6.9	2.3	6.9	2.3
GINIplus/LISA, Germany-Wesel[1]	1995-1998	NO_2, NO_x, PM	0	SDQ	10y	1696	17.6	10.0	16.2	10.7
GINIplus/LISA, Germany- Munich[1]	1995-1998	NO_2, NO_x, PM	57	SDQ	10y	2514	17.5	11.7	26.4	13.0
REPRO_PL, Poland[b,2]	2007	NO_2,PM	85	SDQ	7y	327	22.9	13.7	28.7	9.8
EDEN, France-Nancy[3]	2003-2006	NO_2	66	SDQ	8y	323	29.4	20.8	26.6	14.2
EDEN France-Poitiers[3]	2003-2006	NO_2	52	SDQ	8y	247	27.1	17.4	23.0	13.0
GASPII, Italy[1]	2003-2004	NO_2, NO_x, PM	100	CBCL	7y	461	7.3	3.2	6.1	1.7
INMA, Spain-Asturias[1]	2004-2006	NO_2,NO_x	95	SDQ	7y	357	22.9	15.0	25.8	11.2
INMA, Spain-Gipuzkoa[4]	2006-2008	NO_2, NO_x, PM	89	CBCL	8y	397	7.1	2.4	4.5	2.6
INMA, Spain-Sabadell[1]	2004-2006	NO_2, NO_x, PM, PAHs	100	CBCL	9y	484	8.3	2.8	7.4	5.4
INMA, Spain-Valencia[1]	2003-2005	NO_2, NO_x	94	CBCL	9y	427	5.7	7.2	8.0	6.0
INMA, Spain-Granada[1]	2000-2002	NO_2, NO_x	85	CBCL	9y	153	5.2	0.0	5.9	0.0

CBCL/6-18, child behavior checklist school age 6-18; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter (PM); PAHs, polycyclic aromatic hydrocarbons; SDQ, Strengths and Difficulties Questionnaire.

Air pollution assessment were performed during the following years: '2008-2011; [2]2006-2016; [3] 2002-2005; [4]2006-2007.

* Urbanicity at child's birth address.

[a] Number of children with air pollution, depressive and anxiety symptoms, and aggressive symptoms data available (n = 13182).

[b] Monitoring campaigns used to estimate annual pollution concentrations were different than the rest of the cohorts that used land use regression models from the ESCAPE project.

Table 2
Distribution of the child, maternal and paternal characteristics.

	N	Sex of the child % female	Maternal educational level % % % low	medium	high	Paternal educational level % % % low	medium	high	Maternal country of birth % foreign	Paternal country of birth % foreign
ABCD, The Netherlands	2701	50.8	9.9	34.2	55.8	7.7	17.8	74.5	20.6	21.9
GENERATION R, The Netherlands	3120	50.7	5.7	39.8	54.5	4.9	38.6	46.5	39.2	30.0
GINIplus/LISA, Germany-Wesel	1696	49.2	17.7	49.8	32.5	38.5	26.0	35.5	0.0	0.0
GINIplus/LISA, Germany-Munich	2514	47.3	6.5	26.7	66.8	11.6	14.5	73.9	NA	NA
REPRO_PL,Poland	327	52.0	2.8	33.6	63.6	2.6	54.4	43.0	NA	NA
EDEN, France-Nancy	323	49.8	14.7	12.2	73.1	27.7	14.4	57.9	3.7	7.5
EDEN, France-Poitiers	247	41.3	23.1	20.7	56.2	30.7	22.3	47.0	3.3	7.7
GASPII, Italy	461	48.8	11.6	50.1	38.3	1.4	64.9	33.7	3.3	2.7
INMA, Spain-Asturias	357	47.3	13.7	44.8	41.5	29.4	46.2	24.44	1.1	1.1
INMA. Spain-Gipuzkoa	397	50.4	10.1	36.0	53.9	20.9	48.9	30.3	2.5	1.5
INMA, Spain-Sabadell	484	47.9	23.7	41.8	34.5	32.2	42.9	24.9	7.7	8.9
INMA, Spain-Valencia	427	49.4	27.2	43.8	29.0	43.1	39.5	17.4	5.6	9.8
INMA, Spain-Granada	153	0.0	51.5	30.6	17.9	53.0	23.9	23.1	0.0	0.0

NA, not available

	Maternal age at delivery (years) mean (SD)	Paternal age at delivery (years) mean (SD)	Household status during pregnancy % single parents	Maternal prepregnancy body mass index (kg/m^2) mean(SD)	Maternal height (cm) mean (SD)	Maternal alcohol use during pregnancy % yes	Maternal smoking during pregnancy % yes	Parity % nulliparous
ABCD, The Netherlands	33.1 (4.3)	40.5 (5.5)	8.3	22.7 (3.5)	169.8 (7.0)	0.0	6.9	57.9
GENERATION R, The Netherlands	31.2 (4.7)	33.7 (4.2)	9.9	24.5 (4.2)	168.3 (7.3)	44.2	12.1	60.6
GINIplus/LISA, Germany-Wesel	30.7 (3.7)	32.8 (4.5)	8.5	23.4(3.6)	169.4 (6.1)	45.6	13.3	45.7
GINIplus/LISA, Germany-Munich	32.9 (3.8)	35.4 (5.1)	12.4	22.3(3.6)	168.5 (5.9)	63.2	12.7	52.9
REPRO_PL,Poland	29.1 (4.0)	31.3 (5.2)	23.2	22.1(3.7)	166.0 (5.7)	9.7	9.2	52.6
EDEN, France-Nancy	30.2 (4.4)	32.3 (5.2)	2.8	22.7(4.1)	164.8 (6.2)	58.2	15.0	50.2
EDEN, France-Poitiers	30.7 (4.6)	32.6 (5.3)	2.5	23.2(4.4)	163.0 (6.3)	66.8	19.8	50.0
GASPII, Italy	33.6 (4.2)	36.2 (4.9)	0.7	22.1(3.4)	164.7 (6.1)	36.4	11.1	59.0
INMA, Spain-Asturias	33.3 (4.1)	35.3 (5.2)	2.0	23.7(4.1)	162.4 (5.8)	7.2	27.1	61.3
INMA. Spain-Gipuzkoa	32.6 (3.2)	35.1 (4.5)	0.0	22.9(3.4)	163.8 (6.0)	6.3	21.8	56.9
INMA, Spain-Sabadell	31.9 (4.1)	33.7 (4.8)	1.4	23.8(4.6)	162.3 (6.1)	11.1	27.3	56.6
INMA, Spain-Valencia	31.5 (4.1)	33.5 (4.7)	1.2	23.6(4.3)	162.2 (6.2)	9.4	36.8	56.4
INMA, Spain-Granada	30.6 (4.6)	33.2 (4.9)	1.5	23.3 (3.5)	162.2 (6.2)	3.7	21.6	28.8

SD, standard deviation

respectively (Achenbach and Rescorla, 2000). Validation studies reported high sensitivity (> 0.80) for borderline/clinical cut off's and medium specificity (> 0.60) for clinical cut offs (eMethods 1 and eTable 1).

The SDQ was administered when the children were between 7 and 11 years old, depending on the cohort/region. The SDQ comprises 5 scales from which we selected 2 scales. The emotional problem scale was selected as indicators of child's depressive and anxiety symptoms. The selected scale is composed of 5 items that can be scored with 0, 1 or 2, with higher scores indicating more symptoms. Validated and standardized cut offs were used to classify children (Goodman, 1997). A cut off of 4 points was considered as cut off to classify children in the borderline/clinical range, and a cut off of 5 points was used to classify children in the clinical range. The conduct problems scale was selected as the scale measure of children's aggressive symptoms. The selected scale is composed of 5 items, with higher scores indicating higher number of symptoms. A cut off of 3 points was considered as the threshold to classify children in the borderline/clinical range, and a cut off of 4 points was used to classify children in the clinical range (Goodman, 1997). The cut offs used have a sensitivity of 0.64 for emotional symptoms and 0.60 sensitivity for aggressive symptoms, and a high specificity (0.95) for clinical cut offs (eMethods 1 and eTable 1).

2.4. Potential confounding variables

Potential confounding variables were defined a priori based on previous literature and selected as similarly as possible across the participating cohorts. The potential confounding variables related to family characteristics were: maternal and paternal age at child's birth (in years); maternal and paternal countries of birth (country of cohort/foreign country); household status during pregnancy (parents living together/single parent household), and maternal and paternal education levels child's during pregnancy (low/medium/high based on cohort specific classifications). We selected the following potential confounding maternal characteristics: tobacco use during pregnancy (no/yes); alcohol use during pregnancy (no/yes); and parity (nulliparous/one child/two or more children). All these variables were collected during pregnancy or at the birth of the child. Maternal height and pre-pregnancy weight were measured or self-reported in the 1st trimester of the pregnancy or at birth to calculate pre-pregnancy body mass index (BMI) was then calculated (kg/m^2). Child's sex was obtained either from the hospital, national registries, or from questionnaires. Child's age at the emotional and behavioural symptoms assessment was also collected.

2.5. Statistical analyses

Among children with exposure and outcome data, we performed multiple imputation of missing confounding variables using chained equations, where 25 completed data sets were generated and analysed using standard combination rules for multiple imputation (Spratt et al., 2010; Sterne et al., 2009). The percentage of missing covariates in all the cohorts was lower than 15% with exception of paternal country and education in Generation R, which had 19.6% and 26.8% of missing values respectively. Distributions in the imputed datasets were very similar to those observed (data not shown).

Children included in this analysis (n = 13,182) were more likely to have mothers who did not smoke during pregnancy, parents living together, and parents with higher educational levels than children not included (n = 8494) (data not shown). We used inverse probability weighting to correct for the potential selection bias that can arise when only children with available exposure and outcome data are included (Weisskopf et al., 2015; Weuve et al., 2012). Briefly, we used information available for all participants at recruitment to predict the probability of participation in the study and used the inverse of those probabilities as weights in the analyses so that results would be representative for the initial populations of the cohorts.

Generalized additive models were used to assess the linearity of the relationships of each air pollutant with depressive, anxiety, and aggressive symptom scales, by visual examination and deviance comparison. In all cases linear function provided a good fit. We then applied logistic regression models to estimate the associations between each air pollutant and depressive and anxiety symptoms, and between each air pollutant and aggressive symptoms, with the borderline/clinical range and the clinical range being analysed as separate outcomes. For all analyses, children with a score below the borderline cut off were the reference group. Models were first minimally adjusted, only including child age and sex as potential confounding variables. We then performed fully adjusted regression analyses with the potential confounding variables. We applied a two-step approach: first, the associations were analysed separately for each cohort/region, and subsequently the cohorts/regions estimates were pooled using random-effects meta-analysis. We assessed the heterogeneity in the estimates using Cochran Q test and I^2 statistic.

To test the sensitivity of the results, we repeated the meta-analysis i) leaving out one cohort at the time to test the individual influence of that cohort; ii) using the 90th percentile of the depressive and anxiety symptoms scale, and of the aggressive scale, as cut off; iii) stratifying the results by test; iv) analyzing each symptom scales separately as quantitative scores using negative binomial regression models and performing meta-analyses grouping the cohorts by the test used; and v) analyzing the association between prenatal exposure to air pollution and depressive and anxiety symptoms, and aggressive symptoms only in the subset of cohort, for which the exposure measurements were carried out during pregnancy period or at most the first 2 years of life. After accepting a type I error of 5% in a two-sided test, we had an 80% power to detect ORs between 1.06 and 1.21 depending on the pollutant and the outcome variable. The statistical analyses were carried out using STATA (version 14.0; Stata Corporation, College Station, TX).

3. Results

In our study population, 14.4% (n = 1896) of children were classified in the borderline/clinical range of depressive and anxiety symptoms, of whom 8.4% (n = 1108) in the clinical range. Regarding aggressive symptoms, 13.4% (n = 1778) children were classified in the borderline/clinical range, of whom 6.6% (n = 870) in the clinical range (Table 1). Distribution of child, maternal and paternal characteristics varied across the cohorts (Table 2).

We observed a higher percentage of children in the borderline/clinical range of symptoms among mothers with lower education, as compared to mothers with higher education (with exception of the Nancy region of EDEN). Also, higher percentage of children was observed in the borderline/clinical range of symptoms among mothers who smoked during pregnancy than non-smoking mothers (with exception of the Nancy region of EDEN, and the Granada and Valencia regions of INMA) (data not shown).

Regarding region-specific mean NO_2 levels, the prenatal levels ranged from 15.9 μg/m^3 (the Poitiers region of EDEN) to 43.5 μg/m^3 (GASPII), whereas postnatal levels ranged from 14.0 μg/m^3 (the Gipuzkoa region of INMA) to 43.5 μg/m^3 (GASPII) (eTable 2). The region specific prenatal mean $PM_{2.5}$ levels ranged from 13.9 μg/m^3 (ABCD) to 23.0 μg/m^3 (GASPII) while the postnatal levels ranged from 11.8 μg/m^3 (the Gipuzkoa region of INMA) to 28.4 μg/m^3 (REPRO_PL) (eTable2).

In our study population, higher educated mothers were more likely to live in areas with higher levels of NO_2 during pregnancy, except for Nancy region of EDEN, REPRO_PL and Gipuzkoa and Valencia regions of INMA (data not shown). The results with the postnatal exposures to NO_2 showed more variability across the cohorts. The population characteristics did not vary substantially by $PM_{2.5}$ levels (data not shown).

Overall, we found that the correlations between prenatal levels of

different pollutants in each cohort were stronger in the Generation R Study and in the Sabadell region of INMA as compared to other cohorts/regions. This was also observed with postnatal exposures (eTable 3 and eTable 4). We observed weaker correlations between prenatal and postnatal levels of pollutants in Generation R Study (0.47 between NO_2 prenatal and NO_2 postnatal) and in Gipuzkoa region of INMA (0.41 between NO_2 prenatal and NO_2 postnatal) in comparison to other cohorts/regions, such as in GASPII cohort (0.88 between NO_2 prenatal and NO_2 postnatal) or in Sabadell region of INMA (0.70 between NO_2 prenatal and NO_2 postnatal) (eTable 5).

Logistic regression analyses showed that prenatal exposures were not associated with depressive and anxiety symptoms in the borderline/clinical range (Table 3, Fig. 1A-B), except for the Generation R Study, where we did observe per 10μg/m^3 higher NO_2 a higher odds ratio for depressive and anxiety symptoms (OR 1.15 [95%CI 1.01 to 1.30] per 10 μg/m^3 higher NO_2). The analysis of the relationship between prenatal exposures and aggressive symptoms in the borderline/clinical range also did not show any significant associations (Table 4, Fig. 1C–D), but we did observe a higher odds ratio for aggressive symptoms in the Poitiers region of EDEN (OR 3.04 [95%CI 1.56 to 16.25] per 10 μg/m^3 higher NO_2). Similarly negative results were observed when the analyses were restricted to clinical ranges of symptoms only (eTable 6 and eTable 7). Postnatal exposures of NO_2, NO_x, PM and PAH were not associated with depressive and anxiety symptoms or aggressive symptoms in the borderline/clinical or in the clinical range. Overall, there was little to no heterogeneity in the analyses performed. When we tested the influence of confounding variables through minimally-adjusted models, the influence of each cohort on the overall estimates, and the influence of the validated and standardized cut off points in the symptom scales by changing it to the 90th percentile of the symptom scales, the results did not change meaningfully (eTable 8 – eTable 15). However, when we tested the influence of the stratification of the results by test, the analyses with postnatal exposure to air various pollutants showed lower odds of depressive and anxiety symptoms in borderline/clinical range when the symptoms were assessed with CBCL test (OR 0.67 [95% 0.49;0.91] per 10 μg/m^3 higher $PM_{10,}$ and OR 0.56 [95% 0.38;0.82] per 5 μg/m^3 higher $PM_{2.5}$) (eTable 16) as compared to SDQ test (OR 0.96 [95% 0.81;1.15] per 10 μg/m^3 higher $PM_{10,}$ and OR 0.81 [95% 0.65;1.03] per 5 μg/m^3 higher $PM_{2.5}$) (eTable 17). Moreover, a lower prenatal exposure to air pollution was associated with a higher odds of aggressive symptoms (OR 1.16 [95% 1.05;1.26] per 10 μg/m^3 higher $NO_{2,}$ and OR 1.14 [95% 1.03;1.21] per 20 μg/m^3 higherNO_x) when only the cohorts using SDQ were included (eTable 18 and eTable 19). When we assessed the relationship of exposure to air pollution with depressive, anxiety, and aggressive symptoms using quantitative scores of the symptoms scales, the analysis did not show notable changes compared to the results using dichotomized outcomes (data not shown). When we tested the association of prenatal air pollution exposure and depressive and anxiety symptoms, and aggressive symptoms in those cohorts for which exposure measurements were carried out during pregnancy and within the first 2 years of life, the results did not change substantially (data not shown).

4. Discussion

In this study of 13182 children from population-based birth cohorts from across Europe, we did not observe an association between prenatal and postnatal exposure to several ubiquitous air pollutants with depressive and anxiety symptoms, and aggressive symptoms, in children between 7 and 11 years old.

This study has several strengths. One of the main strengths is the use of data from several prospective population-based birth cohorts with a wide European geographical extent, granting a large sample size within Europe. Also, we used exposure data from pollutants during prenatal and postnatal exposure periods, taking into account residential moving. Seven key air pollutants were included, all highly ubiquitous in urban settings, where around 75% of the European population lives nowadays (Eurostat, 2016). Also, we used multiple imputation and inverse probability weighting to reduce a possible attrition bias in the cohort studies, thereby adding to the representativeness of the study population with respect to the full cohorts. Additionally, the models were adjusted for a large number of socioeconomic and lifestyle variables that are known to be associated with neuropsychological development in children. Regarding the assessment of the emotional and aggressive symptoms in childhood, two standardized and validated behavioural assessments were used, both equally suitable to distinguish between children with and without clinical symptoms (Goodman, 1997; Klasen et al., 2000). Although the use of clinical diagnostic data might be of greater importance for policy making and health interventions than the use of data with quantitatively assessed disorders, clinical data is often not available. Moreover, quantitatively assessed data allows examination of the symptoms on the whole spectrum, which, while often not qualifying for clinical diagnosis, might still have a great impact on individual's mental health and well-being (Kagee et al., 2013).

A limitation of our study is the slight inconsistency in exposure assessment as two cohorts (REPRO_PL and the Gipuzkoa region of INMA) used a different method to estimate air pollution levels at participant's residential addresses, as compared to the remaining cohorts.

Table 3
Fully-adjusted combined associations[a] between exposure to each air pollutant and depressive and anxiety symptoms in the borderline/clinical range.

	Prenatal exposure					Postnatal exposure				
	N[b]	OR	(95% CI)	p-heter	I^2	N[b]	OR	(95% CI)	p-heter	I^2
NO2	13	1.02	0.95; 1.10	0.421	2.51	9	0.92	0.82;1.03	0.891	0.00
NOx	10	1.02	0.96;1.09	0.916	0.00	5	0.94	0.82;1.07	0.960	0.00
PMjc	7	0.93	0.76; 1.15	0.378	6.42	6	0.77	0.57;1.03	0.438	0.00
PM2.5	7	0.83	0.64;1.09	0.896	0.00	6	0.69	0.47; 1.01	0.904	0.00
PMcoarse	6	0.88	0.74;1.04	0.440	0.00	6	0.79	0.62; 1.01	0.726	0.00
PM_{25}abs	6	0.92	0.76; 1.10	0.569	0.00	5	0.79	0.58;1.06	0.711	0.00
PAH	2	0.93	0.66; 1.31	0.664	0.00	2	0.93	0.67;1.22	0.452	0.00

CI, Confidence Interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; p-heter, P value of heterogeneity using the Cochran's Q test; PM_{coarse}, particulate matter between 2.5 and 10pm; PMi_0, particulate matter < 10pm; $PM_{2.5}$, particulate matter < 2.5pm; $PM_{2.5}$abs, reflectance of $PM_{2.5}$ filters; I^2 = Percentage of the total variability due to between-areas heterogeneity; PAH, polycyclic aromatic hydrocarbon; OR, Odds Ratio. [a]Odds Ratio and 95% confidence interval estimated by random-effects meta-analysis by cohort/region, calculated per increments of: 10pg/m^3 for NO_2; 20pg/m^3 for NO_x; 10pg/m^3 for PM_{10}; 5 pg/m^3 for $PM_{2.5}$; 5 pg/m^3 for PM_{coarse}; $10^{-5}m^1$ for $PM_{2.5}$abs; 1 ng/m^3 for PAH. Models were adjusted for maternal characteristics (education level, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, prenatal alcohol use, parity), paternal characteristics (education level, country of birth, age at delivery), household status during pregnancy, and child's sex and age at assessment.

[b] Number of cohorts/regions included in the meta-analysis. Cohorts/regions with < 10 children with depressive and anxiety symptoms in the border/clinical were excluded.

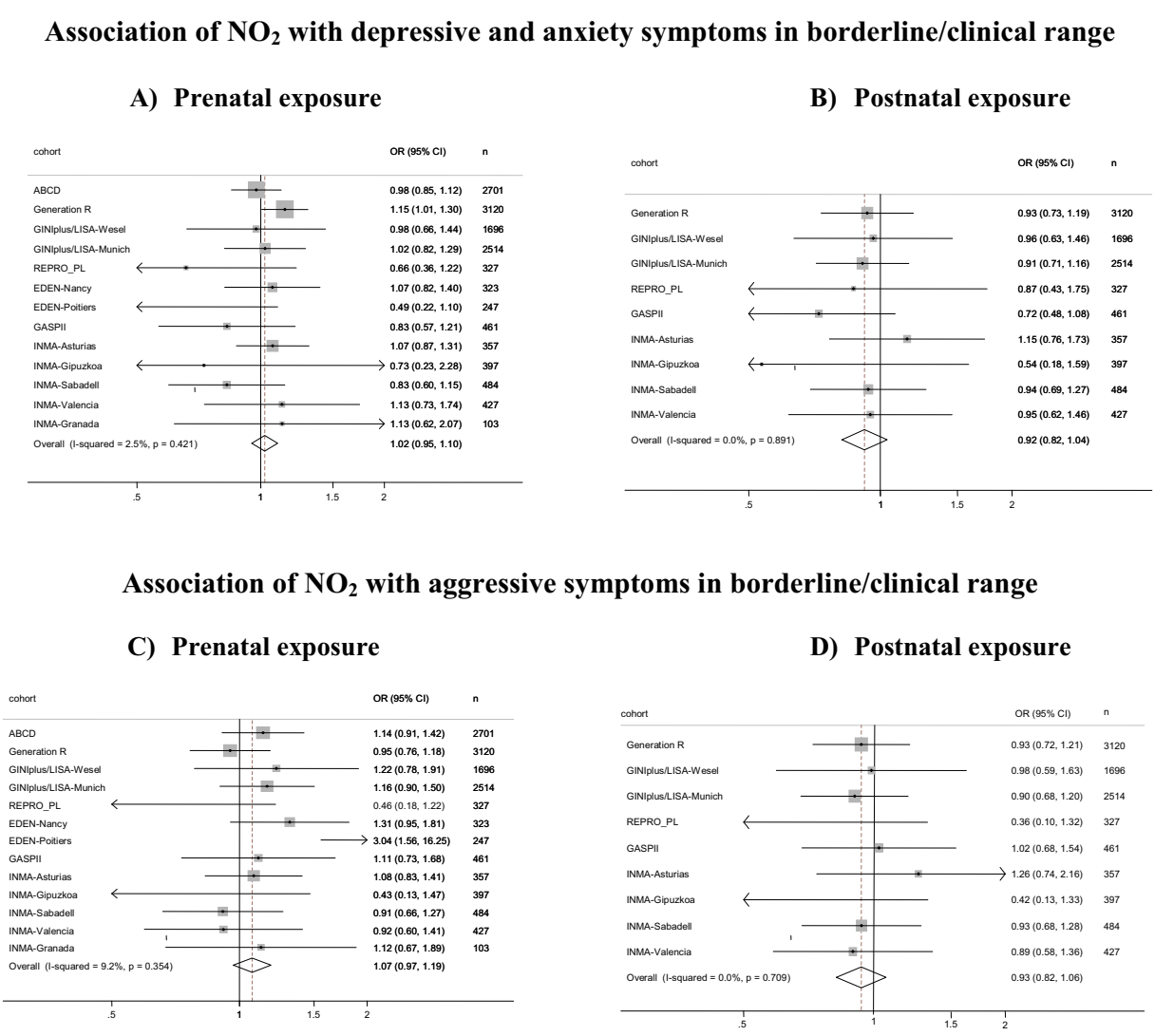

Fig. 1. Fully-adjusted associations of prenatal and postnatal exposure to NO_2 and depressive and anxiety symptoms or aggressive behaviour symptoms in borderline/clinical range at average age of 11y in ABCD cohort, 10y in Generation R, GINIplus and LISA cohort, 9y in INMA Sabadell, Valencia and Granada cohorts, 8y in EDEN cohort and INMA Gipuzkoa cohort and 7y in REPRO_PL cohort and GASPII cohort. Cohort/region-specific and summary odd ratio estimates (coefficient and 95% confidence interval) expressed in 10 μg/m^3, adjusted for maternal characteristics (education level, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, prenatal alcohol using, parity), paternal characteristics (education level, country of birth, age at delivery) child's sex and child's age at assessment. Grey squares around region-specific coefficients represent the relative weight that the estimate contributes to the summary coefficient. Weights are from random-effects analyses. Coef, coefficient; CI, confidence intervals; NO2, nitrogen dioxide.

Both methodologies are commonly used to estimate air pollution exposure (Mercer et al., 2011; Xie et al., 2017) and our assessment of individual influences of each cohort did not show substantial differences. Another limitation is that only NO_2 was available for all cohorts, whereas the other pollutants were available for only a selection of the included cohorts. A further limitation related to the exposure assessment is that the air pollution measurements were performed between 0 and 10 years after the pregnancies of the participating mothers, meaning that we had to assume that the spatial distribution of air pollutants remained stable over that period. This assumption is supported by previous research suggesting that the spatial distribution of air pollution concentrations and its predictors can indeed be considered stable over time for periods up to 10 or 20 years (Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2013). Moreover, the results did not change when we tested the associations between prenatal air pollution exposure and depressive and anxiety symptoms, and aggressive symptoms, using only a subset of cohorts which had the exposure measurements carried out either during pregnancy or the first 2 years of life. Another limitation related to the exposure assessment is that the postnatal period is defined as the period between birth and the emotional and behavioural assessment, which translates to a time window of 7 up to 11 years. Taking an average over such a long period of time, might prevent the identification of critical windows in postnatal exposure that would be identifiable if exposure data would be assessed on a finer time scale. However, such data were not available, and therefore we used one value for the entire postnatal period which might lead to more conservative results. The use of two different tests (CBCL and SDQ) to assess emotional and behavioural symptoms is another limitation of our study. Each of these tests includes a different number of items, gives a slightly different weight to various symptoms, and validated cut-offs lead to different proportion of children within the borderline and clinical range. Overall, the results did not change substantially when we stratified the cohorts by test, except for the associations between postnatal exposure to various pollutants and lower odds of depressive and anxiety symptoms assessed with the CBCL test. Another limitation was that socioeconomic area-level variables were not available to test the potential spatial autocorrelation.

In the current study, we did not observe associations of prenatal

Table 4
Fully-adjusted combined associations[a] between exposure to each air pollutant and aggressive symptoms in the borderline/clinical range.

	Prenatal exposure					Postnatal exposure				
	N[b]	OR	(95% CI)	p-heter	I^2	N[b]	OR	(95% CI)	p-heter	I^2
NO2	13	1.07	0.97; 1.19	0.354	9.2	9	0.93	0.82;1.06	0.709	0.00
NOx	10	1.03	0.95;1.12	0.664	0.0	5	0.91	0.78;1.06	0.685	0.00
PM!0	7	0.98	0.72;1.34	0.231	25.9	6	0.81	0.59;1.12	0.473	0.00
PM2.5	7	0.94	0.67; 1.31	0.896	0.0	6	0.72	0.46; 1.14	0.333	12.8
PM $^{A\ Iv}$-^{L}coarse	6	1.07	0.87;1.33	0.653	0.0	6	0.82	0.59; 1.16	0.192	32.5
PM_{25}abs	6	0.98	0.78;1.25	0.659	0.0	5	0.92	0.67;1.25	0.466	0.0
PAH	2	0.78	0.54; 1.13	0.625	0.0	2	0.83	0.53; 1.32	0.160	46.5

CI, Confidence Interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; p-heter, P value of heterogeneity using the Cochran's Q test; PM_{coarse}, particulate matter between 2.5 and 10gm; PM_{10}, particulate matter < 10gm; $PM_{2\cdot5}$, particulate matter < 2.5gm; $PM_{2\cdot5}$abs, reflectance of $PM_{2\cdot5}$ filters; I^2 = Percentage of the total variability due to between-areas heterogeneity; PAH, polycyclic aromatic hydrocarbon; OR, Odds Ratio. [a] Odds Ratio and 95% confidence interval estimated by random-effects meta-analysis by cohort/region, calculated per increments of: 10gg/m^3 for NO_2; 20gg/m^3 for NO_x; 10gg/m^3 for PM_{10}; 5 gg/m^3 for $PM_{2\cdot5}$; 5 gg/m^3 for PM_{coarse}; $10^{-5}m^1$ for $PM_{2\cdot5}$abs; 1 ng/m^3 for PAH. Models were adjusted for maternal characteristics (education level, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, prenatal alcohol use, parity), paternal characteristics (education level, country of birth, age at delivery), household status during pregnancy, and child's sex and age at assessment.

[b] Number of cohorts/regions included in the meta-analysis. Cohorts/regions with less than 10 children with aggressive symptoms in the border/clinical were excluded.

exposure to air pollution with depressive and anxiety symptoms or aggressive symptoms. The lack of associations is in line with the results of two previous meta-analyses on the relationships of prenatal exposure to air pollution and with autistic traits and ADHD symptoms, including several European birth cohorts, in which also no associations were found (Guxens et al., 2016; Forns et al., 2018). However, the results of our current study are not consistent with others studies assessing air pollution and depression, anxiety, and aggressive symptoms, as they found an association between prenatal exposure to PAH and depression and anxiety symptoms, and aggressive symptoms in children between 4.8 and 11 years of age (Margolis et al., 2016; Genkinger et al., 2015). A possible explanation for the discrepancy between these previous findings and ours might be the difference in exposure assessment. In our study we assessed air pollution levels at home addresses of the participants. In the previous studies PAHs exposure was measured using personal air monitors that pregnant mothers carried with them 48-h in the third trimester of pregnancy (Margolis et al., 2016). These previously used methods are certainly more accurate to assess individual exposure, but are likely less representative as indicator of long-term exposure in comparison to the estimations at residential level assessed using land use regression or kriging methods (Park and Kwan, 2017).

Regarding the associations between postnatal exposure to air pollution and emotional and aggressive symptoms in children, three studies assessed the relationship between exposure to EC, BC, and NO_2 and depressive and anxiety symptoms and aggressive symptoms at ages 7–12 years (Newman et al., 2013; Forns et al., 2016; Roberts et al., 2019). In the study in Barcelona, NO_2 and EC levels were measured at the schools of the participating children by air pollution monitors, and BC levels were estimated at residential addresses using LUR models (Forns et al., 2016). The results showed that there was no association between EC, BC and NO_2 exposure and odds of depressive and anxiety symptoms, and aggressive symptoms. In the study in Ohio, residential levels of EC were estimated using LUR models and no association was found between EC and odds of aggressive symptoms. In the study in London, residential levels of NO_2 and $PM_{2.5}$ were estimated using King's College London urban model (Roberts et al., 2019). The results showed that there was no association between NO_2 and $PM_{2.5}$, and odds of depressive and anxiety symptoms, and aggressive symptoms. In line with these previous findings, we did not find an association between postnatal exposure to NO_2, or any other pollutant, and depressive anxiety, or aggressive symptoms.

To date, studies on the association between exposure to air pollution and emotional symptoms have been mainly carried out in adults. Overall, the results of these studies suggest that higher levels of NO_2 and $PM_{2.5}$ are positively associated with onset of depression, depressive symptoms, anxiety symptoms, and with antidepressant use (Kioumourtzoglou et al., 2017; Pun et al., 2017; Vert et al., 2017; Power et al., 2015). While the exact biological mechanisms underlying these associations are not yet fully understood, there is increasing evidence from animal studies suggesting that exposure to NO_2 or $PM_{2.5}$ is associated with increased inflammation in the brain, oxidative stress, cerebrovascular impairment and neurodegeneration (Block and Calderón-Garcidueñas, 2009; Mohankumar et al., 2008). These mechanisms have been shown to be associated with many neurological and neuropsychological disorders in humans, including depression and anxiety (Fonken et al., 2011). Therefore, in light of the results from the studies performed in adults, the lack of associations in our study might suggest that our study population is too young to have developed emotional and behavioural problems related to air pollution exposure, and that such problems are likely to develop later in life. This hypothesis is supported by findings from a recent study from London, where exposure to NO_2 and $PM_{2.5}$ was not associated with mental health problems in school-age children, while it did predict higher odds of mental disorders in 18-year-old adolescents (Roberts et al., 2019). Therefore, we suggest future studies focus on follow-up studies on adolescents and young adults, which will give insight into the period between childhood and adulthood, and will potentially help to understand the discrepancies between the results of the studies carried out in these two life stages.

5. Conclusions

In conclusion, we did not find evidence for an association between prenatal and postnatal exposure to several air pollutants and emotional and aggressive symptoms in a large sample of children between 7 and 11 years from various regions across Europe.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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