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Prenatal air pollution exposure and growth and cardio-metabolic risk in preschoolers

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ABSTRACT

Objectives: We investigated the association between outdoor air pollutants exposure in the first trimester of pregnancy, and growth and cardio-metabolic risk at four years of age, and evaluated the mediating role of birth weight.
Methods: We included mother-child pairs (N = 1,724) from the Spanish INMA birth cohort established in 2003–2008. First trimester of pregnancy nitrogen dioxide (NO_2) and fine particles ($PM_{2.5}$) exposure levels were estimated. Height, weight, waist circumference, blood pressure, and lipids were measured at four years of age. Body mass index (BMI) trajectories from birth to four years were identified.
Results: Increased $PM_{2.5}$ exposure in the first trimester of pregnancy was associated with decreased *z*-scores of weight (zWeight) and BMI (zBMI) (zWeight change per interquartile range increase in $PM_{2.5}$ exposure = −0.12; 95% CI: −0.23, −0.01; zBMI change = −0.12; 95% CI: −0.23, −0.01). Higher NO_2 and $PM_{2.5}$ exposure was associated to a reduced risk of being in a trajectory with accelerated BMI gain, compared to children with the average trajectory. Birth weight partially mediated the association between $PM_{2.5}$ and zWeight and zBMI. $PM_{2.5}$ and NO_2 were not associated with the other cardio-metabolic risk factors.
Conclusions: This comprehensive study of many growth and cardio-metabolic risk related outcomes suggests that air pollution exposure during pregnancy may be associated with delays in physical growth in the early years after birth. These findings imply that pregnancy exposure to air pollutants has a lasting effect on growth after birth and require follow-up at later child ages.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; INMA, Infancia y Medio Ambiente; IQR, interquartile range; LUR, land-use regression; MET, metabolic equivalent of task; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μm; rMED, relative Mediterranean Diet Score; RRR, relative risk ratio; SBP, systolic blood pressure; SES, socio-economic status; SHS, second hand smoke; TG, triglycerides; WC, waist circumference

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1. Introduction

Air pollution represents the biggest environmental risk to health affecting all regions, settings, socioeconomic groups, and ages (World Health Organization, 2016). Several epidemiological studies indicate that prenatal exposure to outdoor air pollution is associated with health effects in children, such as lower birth weight, and adverse respiratory and neurodevelopmental effects (Vrijheid et al., 2016). However, very little is known about how prenatal air pollution exposure affects postnatal and early childhood physical growth (Clemente et al., 2017; Kim et al., 2016), a fundamental, intrinsic aspect of childhood health (Cooke et al., 2017).

Prenatal exposure to air pollution is robustly associated with fetal growth restriction and low birth weight (Vrijheid et al., 2016), a risk factor for altered growth trajectories and cardio-metabolic diseases later in life (Nobili et al., 2008; Ramadhani et al., 2006; Barker, 2004). For maternal smoking during pregnancy, the association found with lower birth weight (Abel, 1980; Naeye, 1981; Meredith, 1975) seems to be followed by increased body mass index (BMI) in childhood (Riedel et al., 2014; Behl et al., 2013), through a reduction in height growth (Howe et al., 2012). Although outdoor air pollution shares some mechanisms with smoking, e.g. inflammation and oxidative stress (Brook et al., 2010; Yanbaeva et al., 2007), its effects on postnatal growth have hardly been described. Air pollution interferes with the hypothalamic-pituitaryadrenal axis, which directly affects growth and cardio-metabolic outcomes (Thomson, 2013; Miller et al., 2016; Thomson et al., 2016). So far, two prospective studies have investigated the association between prenatal exposure to air pollutants and height and weight in infancy and early childhood (Clemente et al., 2017; Kim et al., 2016), and both reported decreased weight associated with increased exposure to air pollution. Another study exploring prenatal air pollution exposure and postnatal weight gain between birth and six months of age (n = 2,114) (Fleisch et al., 2015) found no association. Two further studies investigating prenatal exposure to air pollutants and BMI trajectories from birth to 10 years (n = 1,649) (Fleisch et al., 2018) and between 6 and 10 years (n = 2,318) (Kim et al., 2018) reported null results. Evidence for an association between air pollution exposure and childhood obesity is also limited and equivocal. Of the few studies evaluating prenatal exposure to different air pollutants in relation to childhood obesity (Huang et al., 2018; Chiu et al., 2017; Mao et al., 2017; Fleisch et al., 2017; Frondelius et al., 2018), two found mixed results (Huang et al., 2018; Mao et al., 2017), one a positive association (Chiu et al., 2017), and two found no association (Fleisch et al., 2017; Frondelius et al., 2018). In adults, there is good evidence that air pollution exposure is also related to other cardio-metabolic risk factors, such as hypertension, dyslipidemia and diabetes (Yang et al., 2018; Wallwork et al., 2017; Eze et al., 2015; Alderete et al., 2018; Cosselman et al., 2015). In young children there is little study thus far, with only a few previous reports of increased systolic blood pressure (SBP) (Zhang et al., 2018), and alteration of the glucose metabolism (Fleisch et al., 2017) with prenatal air pollution exposure.

The first trimester of pregnancy may be a particularly critical period for cardio-metabolic health later in life, since it is characterized by highest human development rates (Livingstone, 2001), includes the embryonic phase and is fundamental for development of fetal cardiovascular and metabolic organs (Robinson, 1973). In our prior analysis of the INMA birth cohort, exposure to air pollution in the first trimester was associated with reduced height and weight in early life (Clemente et al., 2017), but whether this effect persists at older age is unclear.

The aim of this study was to investigate the association between exposure to traffic-related air pollutants, i.e. nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter lower than 2.5 μm ($PM_{2.5}$), in the first trimester of pregnancy, and growth and cardio-metabolic risk outcomes (height, weight, BMI, BMI trajectories, blood pressure (BP), waist circumference (WC), lipids, and a composite cardiometaboloc score) in preschoolers. We further aimed to assess the mediation role of birth weight in any association between air pollution and growth and cardio-metabolic risk factors.

2. Materials and methods

2.1. Participants

Data from the INMA (Infancia y Medio Ambiente) sub-cohorts in four Spanish regions (Asturias, Guipuzcoa, Sabadell, and Valencia) were used. 2765 pregnant women were recruited in the first trimester of pregnancy between 2003 and 2008 (Guxens et al., 2012). Inclusion criteria were age at least 16 years, intention to give birth in the reference hospital, no problems in communication, singleton pregnancy, and non-assisted conception. Follow-up visits were conducted during the third trimester of pregnancy, at birth and at child ages one and four years, and included interview-based questionnaires answered by the mother. Children underwent a follow-up visit at four years that included height, weight and WC measurement and blood samples collection by trained personnel. In Asturias, Sabadell and Valencia SBP and diastolic BP (DBP) were also measured. This study was approved by the regional ethical committees of each cohort (Guxens et al., 2012) and conducted according to principles of the Declaration of Helsinki. A signed informed consent was obtained from all women at recruitment and from parents at each follow-up visit.

2.2. Air pollution exposure assessment

NO_2 exposure was assessed as previously described (Iñiguez et al., 2009). Briefly, NO_2 levels were measured in four 7-days sampling periods using passive samplers distributed over each sub-cohort area according to geographic criteria, expected pollution gradients and population density. Temporally adjusted land-use regression (LUR) models were developed to estimate exposure to NO_2 in different time windows.

$PM_{2.5}$ exposure was assessed in all sub-cohorts but Asturias using land-use regression models temporally adjusted to measurements of local back ground monitoring stations and averaged over the trimesters of pregnancy, the whole pregnancy period and the first year. For Sabadell we used a site-specific LUR model developed in the context of the ESCAPE project (Eeftens et al., 2012). For Guipuzcoa and Valencia we applied the ESCAPE European-wide LUR model (Wang et al., 2014).

Our main focus was on exposure in the first trimester of pregnancy, a period that is characterized by the highest human development rates (Livingstone, 2001), includes the embryonic phase and is fundamental for development of fetal cardiovascular and metabolic organs (Robinson, 1973), and may therefore be a critical period for cardio-metabolic health later in life. We explored other exposure windows as sensitivity analysis, i.e. second and third trimesters of pregnancy, entire pregnancy period and first year of life. Exposures were assessed at participants' home addresses, taking into account changes in addresses between pregnancy and first year of life.

2.3. Outcome assessment

Anthropometric measurements. Height, weight and WC were measured using standard protocols. Age- and sex-standardized z-scores of height (zHeight), weight (zWeight) and BMI (zBMI) were calculated using the World Health Organization (WHO) reference curves (de Onis et al., 2009, World Health Organization, 2006). We calculated age-, sex-, and sub-cohort-specific z-scores of WC (zWC), as previously described (Manzano-Salgado et al., 2017).

BMI trajectories. Five zBMI trajectories from birth until four years were identified using latent class growth analysis (Fig. S1), (Slining et al., 2013) based on medical records of height and weight as previously described: (Montazeri et al., 2018) class 1, characterized by higher birth size followed by accelerated BMI gain; class 2, higher birth

size, slower BMI gain; class 3, lower birth size, accelerated BMI gain; class 4, average size at birth, average BMI gain (reference category in our analyses); and class 5, lower birth size, average BMI gain.

BP score. A single BP measurement was taken after 5 min resting in sited position using an automated oscillometric device and a special cuff adjusted to the upper right arm size of each child, in all sub-cohorts but Guipuzcoa. Age-, sex-, sub-cohort-, and height-specific SBP and DBP *z*-scores were calculated, as previously described (Manzano-Salgado et al., 2017). The mean of DBP and SBP z-scores was used for further analyses.

Lipids score. In a subsample of 870 children triglycerides (TG) and high-density lipoprotein (HDL) levels were measured in blood samples (fasting for Valencia, $n = 163$; not-fasting for the other sub-cohorts) using standard analytical techniques. We calculated age-, sex-, and sub-cohort-specific *z*-scores of TG (*z*TG) and HDL (*z*HDL), as previously described (Manzano-Salgado et al., 2017). A lipid score was used for further analyses, computed as the mean of *z*TG and *z*HDL, the latter multiplied by -1 due to the inverse association with the cardio-metabolic risk.

Cardio-metabolic risk score. A continuous cardio-metabolic risk score was calculated as proposed in the IDEFICS study (Ahrens et al., 2014), and adapted to accommodate the lack of information on insulin resistance or glucose intolerance, as previously described (Manzano-Salgado et al., 2017). Briefly, a three-component cardio-metabolic risk score was built summing *z*WC, BP score, and lipid score. A higher score indicated a higher risk.

2.4. Covariates and mediators

Child sex, date of birth, and birth weight were obtained from clinical records. Information on key covariates was collected during pregnancy using questionnaires, and included maternal socio-demographic variables, pre-pregnancy BMI, physical activity, cigarette smoke exposure, and adherence to the Mediterranean diet assessed using the relative Mediterranean Diet Score (rMED), derived from a food frequency questionnaire, as previously described (Fernández-Barrés et al., 2016; Romaguera et al., 2010).

2.5. Statistical analysis

We tested the association between air pollution exposure during the first trimester of pregnancy and our outcomes using linear regression models for continuous outcomes, logistic regression for overweight/obesity status and multinomial logistic regression for *z*BMI trajectories. Linearity of relationships was checked and confirmed using penalized splines in generalized additive models (Figs. S2-S3). Covariates were selected using Directed Acyclic Graphs (Fig. S4). The final model included sub-cohort, season of birth, maternal age at delivery (continuous), maternal country of birth (Spain/not Spain), parity (nulliparous/primiparous/multiparous), maternal cigarette smoke exposure at 12 weeks, categorized as previously described (Robinson et al., 2016) and detailed in the Supplemental methods (non smoker/second hand smoke/partial smoker/current smoker), maternal education (low, $\leq$11 years of education/medium, 12–15 years/high, $>$ 15 years), maternal occupational class, based on the maternal current or last occupation before pregnancy or on the husband's occupation, in the case of unemployed women (manual, class IV-V of the Spanish adaptation of the British Registrar General's Social Class classification (Domingo-Salvany et al., 2000)/non-manual, class I-III) (details in the Supplemental methods), maternal pre-pregnancy BMI (continuous), maternal physical activity at 32 weeks, expressed as overall metabolic equivalent of task levels (Ridley et al., 2008) (continuous), and rMED at 12 weeks (continuous). Following pairwise deletion, complete data on all included variables were available in more than 95% children with BMI and NO_2 or $PM_{2.5}$ data (Fig. 1).

Mediation analyses. To determine whether birth weight is a potential mediator between air pollution exposure and outcomes we performed a mediation analysis using the approach based on the counterfactual framework (Robins and Greenland, 1992; Pearl, 2001), provided the associations between exposure and outcome, exposure and mediator, and mediator and outcome were all statistically significant. For the mediation analysis to have a causal interpretation, the adjustment for the following four types of confounding needs to be addressed: (1) confounding of the exposure-outcome relationship; (2) confounding of the mediator-outcome relationship; (3) confounding of the exposure-

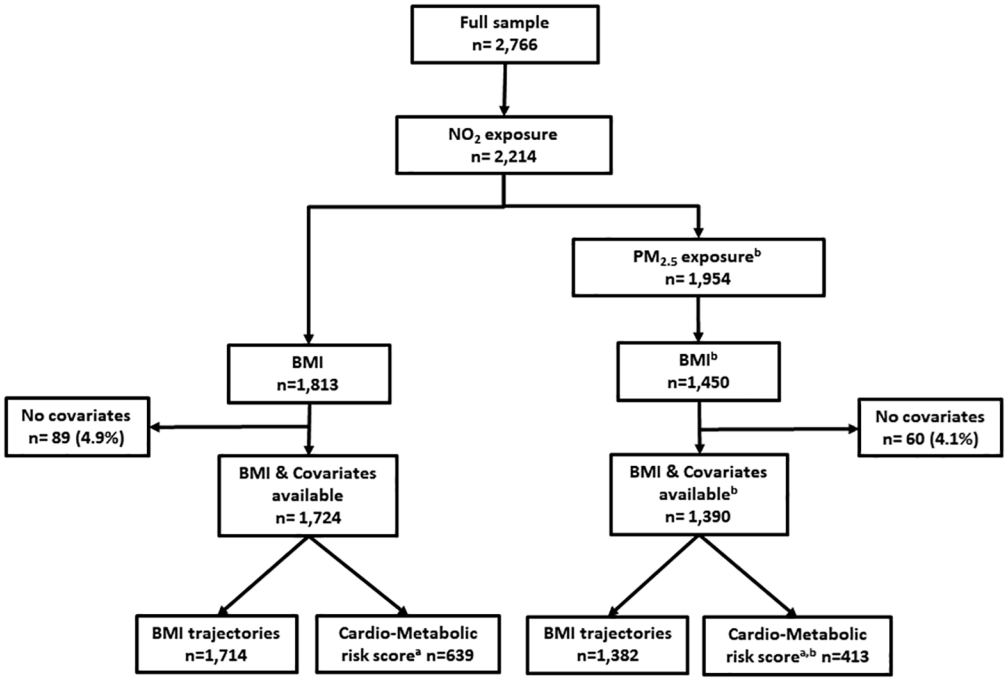

Fig. 1. Flow chart of study population. Abbreviations: BMI, body mass index; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm. [a] Cardio-metabolic risk score data not available for Guipuzcoa; [b] $PM_{2.5}$ data not available for Asturias.

mediator association; (4) mediator-outcome confounders also affected by exposure (VanderWeele, 2016). To adequately address assumption 1, 2 and 3, we used DAGs for confounders selection to include all the covariates that may confound these relationships (Fig. S4). To address assumption 4, we ran a sensitivity analysis excluding maternal BMI (which is possibly affected by prenatal air pollution exposure *via* a backdoor pathway through pre-conceptional air pollution exposure) from the list of mediator-outcome confounders. When assumptions of the mediation analysis hold, the direct effect represents the effect of exposure on the outcome after controlling for birth weight, and the indirect effect is the estimated effect of exposure via birth weight (Valeri and Vanderweele, 2013). The natural direct effect, the natural indirect effect, and total effect were estimated fitting a causal mediation framework with parametric regression models (STATA *paramed* command), not including an interaction term between exposure and mediator. The proportion of mediation was calculated as the ratio of indirect effect to total effect.

Sensitivity analyses. We ran a number of sensitivity analyses. (1) We explored exposure to air pollution during the second and third trimesters of pregnancy, during the entire pregnancy period, and during the first year of life. (2) Since *z*-scores were age- and sex-standardized, these variables were not included in the final model. We ran a sensitivity analyses including them. (3) As developmental tracks for growth and obesity vary by sex (Wang and Beydoun, 2007), we included an interaction term between pollutant and sex, and stratified by sex when p-values for interaction were lower than 0.1. (4) We computed sub-cohort-specific estimates and evaluated between-sub-cohort heterogeneity of associations using the I^2 statistic as guidance (Higgins and Thompson, 2002).

We interpreted our results as estimates (95% confidence interval, CI) for an interquartile range (IQR) increase in the exposure. P-value lower than 0.05 was considered statistically significant. Analysis were conducted in STATA 14.0 and R x64 3.3.1.

3. Results

The main study population included 1,724 mother–child pairs with NO_2 exposure data available (Table 1). Mothers were predominantly of Spanish origin (94.1%), with a mean age at delivery of 32.3 years. Most mothers received secondary education or higher (78.4%), and approximately half belonged to the non-manual/skilled occupational class (51.1%). The majority of mothers were nulliparous (57.8%) and 32.7% were non-smokers during the first trimester of pregnancy. The prevalence of overweight/obesity was 31.5%, with 9.6% of the children being obese (Table 1). The subpopulation with $PM_{2.5}$ exposure data had similar characteristics (Table S1). Median (IQR) levels of exposure to NO_2 and $PM_{2.5}$ were 28.4 (20.2) $\mu g/m^3$ and 15.6 (5.3) $\mu g/m^3$ respectively (Table 2; exposure levels by cohort in Table S2). NO_2 and $PM_{2.5}$ levels were moderately correlated (Pearson's r = 0.27) (Table 2).

Exposure to NO_2 and $PM_{2.5}$ during the first trimester of pregnancy tended to be inversely associated with growth parameters, height, weight, and BMI, although most associations did not reach statistical significance. Higher exposure to $PM_{2.5}$ in the first trimester of pregnancy was associated with a statistically significant decrease in *z*Weight (beta for an IQR increase in exposure = −0.13; 95% CI: −0.23, −0.02) and *z*BMI (beta = −0.12; 95% CI −0.23, −0.01) (Table 3, unadjusted estimates in Table S3). Exposure to $PM_{2.5}$ and NO_2 was also associated with reduced risk of being in a BMI trajectory characterized by accelerated BMI gain, compared to the reference category, i.e. children with average size at birth and average BMI gain (e.g. RRR for an IQR increase in $PM_{2.5}$ for class 1, higher birth size and accelerated BMI gain = 0.62; 95% CI: 0.42, 0.91; and RRR for class 3, lower birth size and accelerated BMI gain = 0.65; 95% CI: 0.45, 0.96) (Table 4, unadjusted estimates in Table S4). Early life exposure to NO_2 and $PM_{2.5}$ was not associated with risk of overweight/obesity, BP score, lipid score, WC, or the composite cardio-metabolic risk score (Tables 3 and 4,

Table 1
Characteristic of the study population.

	Study population with NO_2 (n = 1,724)
Child characteristics	
Age at 4 years follow-up visit (years) [mean (SD)]	4.41 (0.18)
Sex (%)	
Female	48.6
Male	51.4
Birth weight (g) [mean (SD)]	3,266.56 (460.3)
Sub-cohort (%)	
Asturias	21.4
Guipuzcoa	22.4
Sabadell	24.3
Valencia	32.2
Season of birth (%)	
Winter	26.3
Spring	23.3
Summer	24.7
Fall	25.7
Growth and obesity outcomes at age 4 years	
*z*Height [mean (SD)]	−0.02 (0.94)
*z*Weight [mean (SD)]	0.40 (1.02)
*z*BMI [mean (SD)]	0.62 (1.07)
Child overweight/obese status (%)	
Normal or underweight	68.5
Underweight	0.5
Overweight or obese	31.5
Obese	9.6
BMI trajectory[a] (%)	
Class 1 - Higher birth size, accelerated BMI gain	12.0
Class 2 - Higher birth size, slower BMI gain	25.7
Class 3 – Lower birth size, accelerated BMI gain	13.4
Class 4 - Average birth size, average BMI gain	36.4
Class 5 - Lower birth size, average BMI gain	12.4
Cardio-metabolic risk outcomes[b] at age 4 years	
Lipids score [mean (SD)]	−0.01 (0.78)
*z*WC [mean (SD)]	−0.02 (0.96)
BP score [mean (SD)]	−0.05 (0.88)
Cardio-metabolic risk score [mean (SD)]	−0.08 (1.52)
Maternal characteristics	
Age at delivery (years) [mean (SD)]	32.3 (4.06)
Country of origin (%)	
Spain	94.1
Not Spain	5.9
Occupation (%)	
Non-manual/skilled	51.1
Manual	48.9
Education (%)	
Low	21.6
Medium	41.6
High	36.8
Parity (%)	
Nulliparous	57.8
One child	35.8
Two or more children	6.4
Cigarette smoke exposure (%)	
No smoker	32.7
Second hand smoke	37.2
Partial smoker	13.2
Current smoker	16.9
Physical activity during pregnancy (METs/hour/day) [mean (SD)]	36.91 (3.54)
Pre-pregnancy BMI (kg/m^2) [mean (SD)]	23.61 (4.29)
Relative Mediterranean Diet Score [mean (SD)]	8.04 (2.57)

Abbreviations: BMI, body mass index; BP, blood pressure; MET, Metabolic Equivalent of Task; SD, standard deviation; WC, waist circumference.

[a] n = 1,714.

[b] Only available for Asturias, Sabadell and Valencia (n = 639).

Table 2
Exposure levels to NO_2 (n = 1,724) and $PM_{2.5}$ (n = 1,390)[a] during the first trimester of pregnancy and Pearson's correlation coefficient (r).

Pollutant	Median (IQR)	5th perc – 95th perc	Pearson's r NO_2
NO_2 (μg/m^3)	28.44 (20.19)	10.56–61.44	1
$PM_{2.5}$ (μg/m^3)	15.55 (5.31)	9.30–20.94	0.27***

Abbreviations: IQR, interquartile range; NO_2, nitrogen dioxide; perc, percentile; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm; WC, waist circumference.
***p value < 0.001.
[a] Available for Guipuzcoa, Sabadell and Valencia.

unadjusted estimates in Tables S3 and S4).

We tested whether birth weight was a mediator of the association between $PM_{2.5}$ exposure during the first trimester of pregnancy and zBMI and zWeight at four years. We did not tested birth weight as a mediator for BMI trajectories because the trajectories that we used included the weight of the child measured in the first days of life, which is highly correlated with birth weight. An IQR increase in $PM_{2.5}$ exposure was associated with a 51.9 g (95% CI −11.32, −0.86) decrease in birth weight. A 100 g increase in birth weight was associated with a 0.07 (95% CI 0.06, 0.08) increase in zWeight and a 0.04 (95% C.I. 0.03, 0.06) increase in zBMI at four years of age. In our mediation analysis birth weight mediated 31% and 19% of the effects of $PM_{2.5}$ on weight and zBMI, respectively, although mediation estimates were only marginally significant (e.g. proportion of mediation for zWeight = 30.7% (95% CI: −11.5; 133.4) (Fig. 2). The natural direct and indirect effects were negative, although at most marginally significant (e.g. beta direct effect of $PM_{2.5}$ on zWeight = -0.10; CI −0.20, 0.002; and beta indirect effect of $PM_{2.5}$ on zWeight = -0.03; CI −0.07, 0.006) (Fig. 2).

In sensitivity analyses, we did not observe significant associations between exposure to NO_2 and $PM_{2.5}$ during the second and third trimesters of pregnancy, the entire pregnancy period, and first year of life and the investigated outcomes, except for an association between exposure to $PM_{2.5}$ during the first year of life and zBMI (change in zBMI for an IQR increase in $PM_{2.5}$ = -0.07; CI: −0.15, −0.01) (Tables S5–S6). Adjusting the model of $PM_{2.5}$ in the first trimester of pregnancy for $PM_{2.5}$ in the first year of life did not change the direction and the magnitude of the association (change in zBMI for an IQR increase in $PM_{2.5}$ exposure in the first trimester of pregnancy = -0.09; CI: −0.21, −0.03). Further adjustment of our models for sex and exact age at four years visit returned results similar to our main analyses (Tables S7–S8).

We found evidence of sex interaction only for exposure to $PM_{2.5}$ and zWeight (p-value interaction = 0.09); following stratification, the association was negative in both sexes, but statistically significant only in males (change in zWeight for an IQR increase in $PM_{2.5}$ exposure = -0.19; 95% CI: −0.34, −0.03 in males; and −0.08; 95% CI: −0.23,0.08 in females). We observed little evidence for heterogeneity between the INMA sub-cohorts in the association between $PM_{2.5}$ exposure and zBMI (I^2 = 40.6) (Figs. S5–S6). To address the assumption of the mediation analysis of no mediator-outcome confounder also affected by exposure, we ran a sensitivity analysis excluding maternal BMI (possibly affected by prenatal air pollution exposure) from the list of mediator-outcome confounders in our mediation analyses, and the results did not differ meaningfully.

4. Discussion

In this prospective study we found that higher exposure of mothers to $PM_{2.5}$, a common traffic-related air pollutant, during the first trimester of pregnancy was associated with reduced weight and BMI of the children at 4 years of age. Results for NO_2 exposure were similar to those of $PM_{2.5}$, but did not reach statistical significance. Higher exposure to $PM_{2.5}$ and NO_2 was also associated with a reduced risk of the child being in a BMI trajectory characterized by accelerated BMI gain between birth and four years. The association between $PM_{2.5}$ and weight and BMI was partially mediated by a reduction in birth weight. Prenatal exposure to NO_2 and $PM_{2.5}$ was not associated with other cardio-metabolic outcomes in the children.

Our results are in keep with the only two studies available so far investigating prenatal exposure to outdoor air pollutants and weight in infants and children (Clemente et al., 2017; Kim et al., 2016). In a South Korean multiregional prospective birth cohort study (n = 1,129), higher prenatal (and postnatal) exposure to particles with an aerodynamic diameter lower than 10 μm (PM_{10}) was associated with reduced weight from one year up to five years (Kim et al., 2016). In a subset of our cohort (n = 336), prenatal NO_2 exposure was associated with an overall decrease in weight at 12 months (Clemente et al., 2017). Our findings of an association between air pollution and lower BMI or lower risk of being in an accelerated BMI trajectory (departing from either low or high birth size) are in agreement with a large prospective study conducted in Hong Kong (n = 7,301) that found higher prenatal exposure to PM_{10} to be associated with reduced BMI attained at age 9 up to 15 years (Huang et al., 2018). On the contrary, in a small lower-income birth cohort (mainly Hispanic and African-American) (n = 239), exposure to $PM_{2.5}$ in early pregnancy was significantly

Table 3
Estimated change (95% CI) in growth, obesity and cardio-metabolic risk outcomes for an IQR increase in NO_2 (20.19 μg/m^3) and $PM_{2.5}$ (5.31 μg/m^3) exposure in the first trimester of pregnancy.

	NO_2		$PM_{2.5}$[a]	
Outcome	N	Beta (95% CI)[b]	N	Beta (95% CI)[b]
Growth and obesity outcomes				
zHeight	1,724	−0.05 (−0.13, 0.03)	1,390	−0.07 (−0.17, 0.03)
zWeight	1,724	−0.07 (−0.15, 0.02)	1,390	−0.13 (−0.23, −0.02)
zBMI	1,724	−0.05 (−0.14, 0.03)	1,390	−0.12 (−0.23, −0.01)
Cardio-metabolic risk outcomes[c]				
BP score	639	0.07 (−0.04, 0.19)	413	0.11 (−0.07, 0.29)
zWC	639	0.02 (−0.11, 0.15)	413	−0.06 (−0.23, 0.11)
Lipids score	639	−0.03 (−0.14, 0.07)	413	−0.11 (−0.25, 0.03)
CMR score	639	0.06 (−0.15, 0.26)	413	−0.07 (−0.36, 0.23)

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CMR, cardio-metabolic risk; IQR, interquartile; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm; WC, waist circumference.
[a] Available for Asturias, Sabadell and Valencia.
[b] Adjusted for sub-cohort, season of birth, and maternal age at delivery, country of origin, education, occupation, parity, cigarette smoke exposure during pregnancy, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet.
[c] Available for Guipuzcoa, Sabadell and Valencia.

Table 4
Odds ratio (95% CI) in overweight/obese status and relative risk ratio (95% CI) in child zBMI trajectory classes for an IQR increase in NO_2 (20.19 μg/m$^{3)}$ and $PM_{2.5}$[b] (5.31 μg/m^3) exposure in the first trimester of pregnancy.

	NO_2		$PM_{2.5}$[a]	
Outcome	N	OR or RRR[b] (95% CI)	N	OR or RRR[b] (95% CI)
Child overweight/obese status				
Normal or underweight	1,180	1.00 (reference)	964	1.00 (reference)
Overweight/obese	544	0.93 (0.77, 1.13)	426	0.89 (0.70, 1.14)
zBMI trajectory class				
Class 1: Higher birth size + accelerated BMI gain	206	0.85 (0.64, 1.14)	158	0.62 (0.42, 0.91)
Class 2: Higher birth size + slower BMI gain	441	1.15 (0.93, 1.43)	366	1.03 (0.78, 1.37)
Class 3: Lower birth size + accelerated BMI gain	230	0.72 (0.54, 0.96)	156	0.65 (0.45, 0.96)
Class 4: Average birth size + average BMI gain	624	1.00 (reference)	519	1.00 (reference)
Class 5: Lower birth size + average BMI gain	213	1.02 (0.78, 1.34)	183	1.08 (0.76, 1.55)

Abbreviations: BMI, body mass index; CI, confidence interval; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm; RRR, relative risk ratio.
[a] Available for Guipuzcoa, Sabadell and Valencia.
[b] Adjusted for sub-cohort, season of birth, and maternal age at delivery, country of origin, education, occupation, parity, cigarette smoke exposure during pregnancy, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet.

associated with higher BMI in boys but not in girls at preschool age (Chiu et al., 2017). Three studies reported null associations between prenatal exposure to $PM_{2.5}$ and obesity and growth outcomes in children around pre-school age (Fleisch et al., 2018; Mao et al., 2017; Fleisch et al., 2017). In a low-income birth cohort, no association was found between prenatal exposure to $PM_{2.5}$ and risk of overweight/obesity status in children between 2 and 6 years of age (Mao et al., 2017). In another cohort, no association was observed between prenatal $PM_{2.5}$ exposure and either BMI at 3.3 and 7.7 years (n = 1,418) (Fleisch et al., 2017), or BMI trajectories from birth up to 10 years (n = 1,649) (Fleisch et al., 2018). We should note though that the exposure levels reported in these three studies were lower than in our study, which may explain the null associations. The sizes of our estimates were comparable to those from previous studies, e.g. (Huang et al., 2018).

This is the first study investigating the mediation role of birth weight in the association between $PM_{2.5}$ and weight and BMI. Our results showed that roughly one third and one fifth of the association between prenatal exposure to $PM_{2.5}$ and weight and BMI respectively

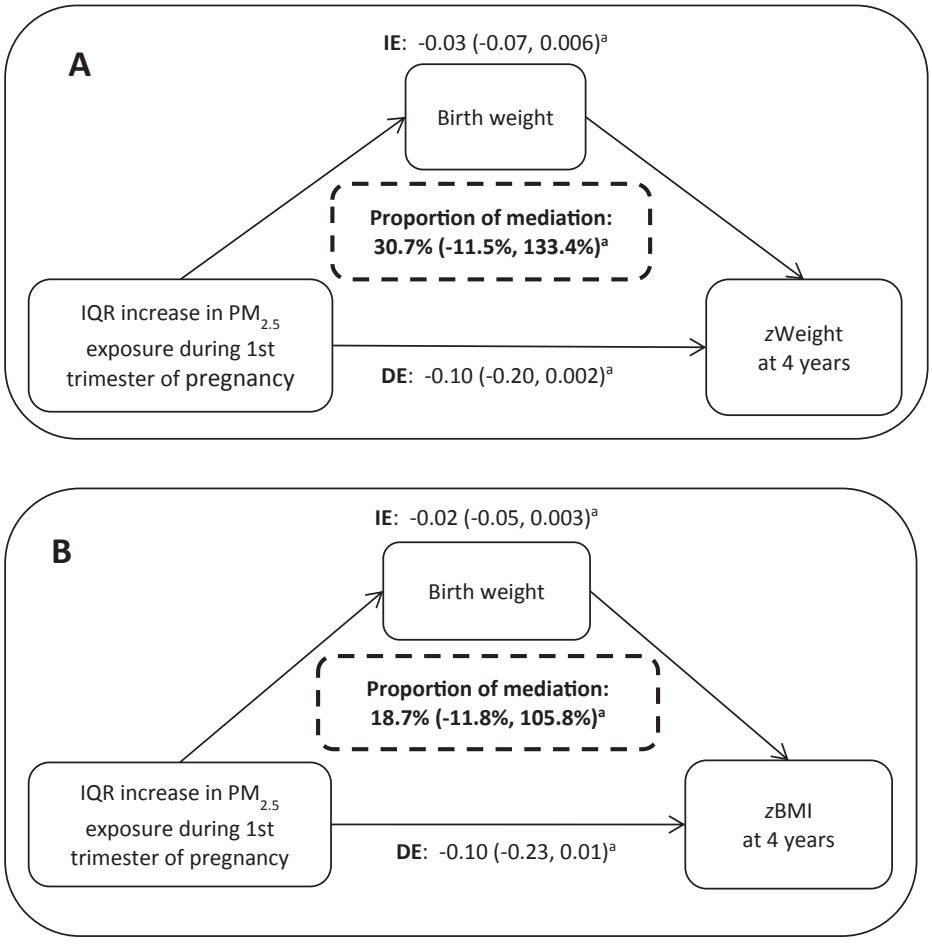

Fig. 2. Mediation through birth weight of the effect of $PM_{2.5}$ exposure during the first trimester of pregnancy on zWeight (A) and zBMI (B) at four years (n = 1,390). The figures show the estimated effect (95% CI) of an IQR increase in $PM_{2.5}$ exposure during the first trimester of pregnancy on the outcomes at four years, through birth weight. The estimates of indirect effect and of the direct effect, and the proportion of mediation are provided. Abbreviations: CI, confidence interval; DE, direct effect; IE, indirect effect; IQR, interquartile range; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm. [a]Models adjusted for sub-cohort, season of birth, and maternal age at delivery, country of origin, parity, cigarette smoke exposure during pregnancy, education, occupation, physical activity during pregnancy, pre-pregnancy BMI, and adherence to the Mediterranean diet.

was potentially mediated through birth weight. This proportion should be taken with caution because it was only marginally significant and both direct and indirect effects were small and did not reach statistical significance, probably due to limited variability and sample size. However, our results for BMI trajectories support this potential partial mediation through birth weight, and also suggest other mechanisms independent of birth weight could operate, as we found a reduction in the risk of being in the trajectories of accelerated BMI gain departing from either lower or higher birth sizes.

Overall, our results suggest that, if the observed associations are indeed causal, fetal growth restriction caused by exposure to air pollution (Vrijheid et al., 2016) could lead to impaired growth trajectories beyond infancy and up to four years. Results from some studies suggest that effects of prenatal exposure on growth may vary according to child age (Mao et al., 2017; Nikolić et al., 2014); thus, follow up studies until later ages in childhood and adolescence will be important.

The biological mechanisms underlying the adverse effects of air pollution on children's growth are still unclear. The hypothesized mechanisms proposed so far include oxidative stress and inflammation (Clemente et al., 2017; Kim et al., 2016), interference with thyroid hormones (Kim et al., 2016), increased risk of respiratory related diseases and other health problems that could delay growth (Kim et al., 2016; Nikolić et al., 2014), and induction of cell apoptosis due to DNA damage (Nikolić et al., 2014). Oxidative stress is also one of the mechanisms proposed for the effects of air pollution on birth weight (Li et al., 2019), and this fits with the results of our mediation analysis.

The fact that our study observes associations mainly with child anthropometry, but not with other cardio-metabolic outcomes, may be due to the young age of children, since at this young age the prevalence of cardio-metabolic risk factors is still low (Margolis et al., 2014). The low prevalence of pediatric cardio-metabolic syndrome in young children (Ahrens et al., 2014), and the lack of clinical measures of glucose metabolism and insulin resistance in our study may also explain the null results for cardio-metabolic risk score. Further, we note that our analyses of cardio-metabolic outcomes had a smaller sample size, and this could have prevented us to find significant associations. Therefore, larger studies with follow up at an older age are required to fully understand whether there are any potential adverse cardio-metabolic effects of air pollution exposure in children.

The main strengths of this study are its prospective design and the follow up of our study population from birth to four years of age that allows examining the effects of prenatal exposure to pollutants across the whole early childhood period. Further, this study includes a uniquely comprehensive range of multiple outcomes related to growth and cardio-metabolic risk. The use of strict protocols for collection of anthropometric variables, BP and blood samples for lipids measurement, and the use of structured questionnaires ensured high-quality outcome, exposure and covariate data. Another strength is the use of causal mediation analysis that allowed us to study the potential role of birth weight in the associations of interest (Valeri and Vanderweele, 2013), although the method only provide estimates of direct, indirect and total effects. The validity of our mediation analysis is based on the assumption that we have adequately controlled the following three types of confounding: (1) confounding of the exposure–mediator relationship; (2) confounding of the exposure–outcome relationship; and (3) confounding of the mediator–outcome relationship. We used DAGs for confounders selection and, as far as possible, we included all the covariates that may confound these relationships, however we cannot exclude residual confounding from unknown factors related to our exposure, outcome or mediator. Our study has some limitations. Exposure was only assessed at residential address; air pollution at residency is, however, a commonly used tool in epidemiological research (Jerrett et al., 2005). Also, $PM_{2.5}$ exposure was estimated using different methods in different cohorts, which may have given rise to different levels of measurement error, but is unlikely to explain our overall associations.

5. Conclusions

This study suggests that air pollution exposure during pregnancy may be associated with a reduction of growth outcomes, particularly weight and BMI at preschool age, and in the risk of being in a trajectory with accelerated BMI gain between birth and four years. These findings imply that pregnancy exposure to air pollutants has a lasting effect on growth after birth and require follow-up at later child ages.

CRediT authorship contribution statement

Serena Fossati: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Damaskini Valvi:** Investigation, Writing - review & editing. **David Martinez:** Investigation, Formal analysis, Writing - review & editing. **Marta Cirach:** Investigation, Formal analysis, Writing - review & editing. **Marisa Estarlich:** Investigation, Writing - review & editing. **Ana Fernández-Somoano:** Investigation, Writing - review & editing. **Mònica Guxens:** Investigation, Writing - review & editing. **Carmen Iñiguez:** Investigation, Writing - review & editing. **Amaia Irizar:** Investigation, Writing - review & editing. **Aitana Lertxundi:** Investigation, Writing - review & editing. **Mark Nieuwenhuijsen:** Investigation, Writing - review & editing. **Ibon Tamayo:** Investigation, Writing - review & editing. **Jesus Vioque:** Investigation, Writing - review & editing. **Adonina Tardón:** Investigation, Writing - review & editing. **Jordi Sunyer:** Supervision, Writing - review & editing. **Martine Vrijheid:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article to disclose.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105619.

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