Environmental Research 216 (2023) 114628

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Susceptible windows of exposure to fine particulate matter and fetal growth trajectories in the Spanish INMA (INfancia y Medio Ambiente) birth cohort

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ARTICLE INFO

Keywords:
Air pollution
$PM_{2.5}$
Fetal growth
Susceptible windows

ABSTRACT

While prior studies report associations between fine particulate matter ($PM_{2.5}$) exposure and fetal growth, few have explored temporally refined susceptible windows of exposure.

We included 2328 women from the Spanish INMA Project from 2003 to 2008. Longitudinal growth curves were constructed for each fetus using ultrasounds from 12, 20, and 34 gestational weeks. Z-scores representing growth trajectories of biparietal diameter, femur length, abdominal circumference (AC), and estimated fetal weight (EFW) during early (0–12 weeks), mid- (12–20 weeks), and late (20–34 weeks) pregnancy were calculated. A spatio-temporal random forest model with back-extrapolation provided weekly $PM_{2.5}$ exposure estimates for each woman during her pregnancy. Distributed lag non-linear models were implemented within the Bayesian hierarchical framework to identify susceptible windows of exposure for each outcome and cumulative effects [β_{cum}, 95% credible interval (CrI)] were aggregated across adjacent weeks. For comparison, general linear models evaluated associations between $PM_{2.5}$ averaged across multi-week periods (i.e., weeks 1–11, 12–19, and 20–33) and fetal growth, mutually adjusted for exposure during each period. Results are presented as %change in z-scores per 5 $\mu g/m^3$ in $PM_{2.5}$, adjusted for covariates.

Weeks 1–6 [$\beta_{cum} = -0.77\%$, 95%CrI (−1.07%, −0.47%)] were identified as a susceptible window of exposure for reduced late pregnancy EFW while weeks 29–33 were positively associated with this outcome [$\beta_{cum} = 0.42\%$,

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https://doi.org/10.1016/j.envres.2022.114628
Received 26 May 2022; Received in revised form 13 October 2022; Accepted 18 October 2022
Available online 21 October 2022

95%CrI (0.20%, 0.64%)]. A similar pattern was observed for AC in late pregnancy. In linear regression models, $PM_{2.5}$ exposure averaged across weeks 1–11 was associated with reduced late pregnancy EFW and AC; but, positive associations between $PM_{2.5}$ and EFW or AC trajectories in late pregnancy were not observed.

$PM_{2.5}$ exposures during specific weeks may affect fetal growth differentially across pregnancy and such associations may be missed by averaging exposure across multi-week periods, highlighting the importance of temporally refined exposure estimates when studying the associations of air pollution with fetal growth.

1. Introduction

Air pollution is among the most substantial global environmental threats (Cohen et al., 2017; Murray et al., 2020), impacting a range of human health outcomes. A growing body of literature implicates the adverse impacts of prenatal air pollution exposure on fetal growth (Fu et al., 2019), which in turn may increase the risk of neonatal morbidity and mortality (Kesavan and Devaskar, 2019), and possibly impact cognitive and behavioral impairments during childhood (Sacchi et al., 2020; Sucksdorff et al., 2015). Therefore, it is imperative to improve our understanding of the mechanism by which air pollution exposure may alter the fetal growth trajectory.

Particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) is an ambient air pollutant derived from natural and anthropogenic combustion-related sources (Adams et al., 2015). In addition to having a greater number of anthropogenic sources than larger particles, the relative pathogenicity of $PM_{2.5}$ is due to its relatively larger surface area to which potentially toxic compounds can bind; further, $PM_{2.5}$ particles can readily pass through the respiratory barrier of the lower airways (Feng et al., 2016). Exposure to $PM_{2.5}$ has been widely investigated as a risk factor for preterm birth and outcomes related to an infant's size at birth, such as low birth weight (LBW) or small-for-gestational-age (SGA) (Klepac et al., 2018; Simoncic et al., 2020; Tapia et al., 2020). However, these static outcomes do not adequately capture the dynamic nature of intrauterine growth (Smarr et al., 2013). While the use of attained weight at birth may represent late pregnancy growth, it likely does not reflect growth during early or mid-pregnancy (Hemachandra and Klebanoff, 2006), which may be relevant periods of susceptibility for environmental exposures. Further, the use of birth anthropometry does not allow the assessment of growth in specific body segments, which is important to consider as delays in specific fetal parameters may have unique health consequences (Yanney and Marlow, 2004). In a systematic review and meta-analysis encompassing studies published through 2017, Fu et al. (2019) recommended that more studies utilizing serial ultrasounds should be conducted to characterize fetal growth and accelerate our understanding of mechanisms through which air pollution impacts fetal health.

Four additional studies have recently been published that were not included in the Fu et al. (2019) meta-analysis; these studies provide further evidence of negative associations between prenatal $PM_{2.5}$ exposure and ultrasound-measured fetal growth (Cao et al., 2019; Leung et al., 2022; Lin et al., 2020; Shao et al., 2020), though they varied in the specific exposure metrics used, all of the aforementioned studies averaged exposure across multi-week periods [i.e., trimesters (Shao et al., 2020), the first 16 weeks of pregnancy (Leung et al., 2022), or from conception to the time of the ultrasound examination (Cao et al., 2019; Leung et al., 2022; Lin et al., 2020)], and none of those studies evaluated growth trajectories of the fetus during different pregnancy periods. The timing of exposure is important in determining the specific nature of the relationship between prenatal air pollution exposure and fetal growth as fetal development is a period of increased vulnerability to environmental chemicals (Slama et al., 2008). Measuring air pollution exposure either during the entire pregnancy period or across broad windows defined *a priori* (e.g., trimesters) may limit the identification of critical windows of exposure during pregnancy, particularly if 'true' critical periods do not align with *a priori* defined clinical periods (Wilson et al., 2017). Thus, despite the increased use of ultrasound-measured fetal growth, assessment of precisely identified susceptible windows of prenatal $PM_{2.5}$ exposure on the fetal growth trajectories remains limited.

In the present study, our primary aim was to implement distributed lag non-linear models to identify weekly windows in which fetal growth trajectories may be related to prenatal $PM_{2.5}$ exposure. To demonstrate potential differences in the identification of windows of longer duration that might represent susceptible periods of exposure to $PM_{2.5}$ on fetal growth, we also provided analyses of associations between $PM_{2.5}$ and fetal growth trajectories using exposure estimates averaged across multi-week exposure periods that align with the timing of fetal growth measurement (gestational weeks 1–11, 12–19, and 20–33).

2. Materials and methods

2.1. Study design and population

This study was based on the *INfancia y Medio Ambiente* (INMA)—Environment and Childhood Study—a multi-site prospective population-based birth cohort study in Spain (Guxens et al., 2012). The present analysis includes mother and infant pairs from four INMA regions: Asturias (n = 426), Gipuzkoa (n = 561), Sabadell (n = 584), and Valencia (n = 757), who were recruited from the main public hospital or health center of each study area between November 2003 and February 2008. The detailed cohort profile, including the geographical location of each study site has been published previously (Guxens et al., 2012). Eligible women were aged 16 years or older and resided in one of the study areas, attended the first prenatal clinic visit between 10 and 13 gestational weeks, had a singleton pregnancy, did not follow any program of assisted reproduction, had no communication problems, and planned to deliver their child at the recruitment hospital. Consent was obtained from women to collect data on sociodemographic and lifestyle factors and multiple ultrasound measures of fetal growth during pregnancy. Ethical approval was obtained from the ethics committee of the reference hospitals. This study was approved by the Institutional Review Board of Baylor College of Medicine.

2.2. Prenatal $PM_{2.5}$ exposure assessment

Daily $PM_{2.5}$ levels were estimated for 2009 for the entire Spanish territory (except for the Canary Islands, Ceuta, and Melilla) at a 1 square kilometer resolution using a spatio-temporal land-use random forest model that combined ground-level air pollution and satellite-based measures of aerosol optical depth, land-use, meteorological, and traffic variables. These estimates were then adjusted to the exact locations of woman's reported residence(s) throughout their pregnancy using a second random forest model incorporating several spatial variables such as traffic, land use, and population. These models follow the methodology previously developed by Stafoggia and colleagues' and applied in Italy and Sweden (Stafoggia et al., 2019, 2020). The R^2 of our models for the year 2009 was estimated as 0.78 using out-of-bag sampling and 0.54 using 10-fold cross validation. Following the method of temporal adjustment from the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocol, daily $PM_{2.5}$ exposure estimates for 2003–2008 (i.e. the pregnancy period) were computed using the standardized methodology to temporally adjust the 2009 annual average concentrations of $PM_{2.5}$ at each women's residence with daily records from stationary ambient monitoring networks that operate continuously

in each study area (Procedure for Back-Extrapolation: Manual by the ESCAPE project, 2012). In Gipuzkoa where $PM_{2.5}$ monitoring data was available, the temporal adjustment was conducted by multiplying the annual 2009 $PM_{2.5}$ estimates at each woman's residence from the random forest model by the ratio of the daily $PM_{2.5}$ estimates from the stationary monitoring site to the 2009 annual average $PM_{2.5}$ estimate from the same monitoring site. In the case of Asturias, Sabadell, and Valencia where $PM_{2.5}$ levels from stationary monitoring networks for the years 2003–2008 were not available, the annual 2009 $PM_{2.5}$ estimates for each woman's residence computed from the random forest model were first multiplied by the ratio of daily PM_{10} estimates from the stationary monitoring site to the 2009 annual average PM_{10} estimate from the same monitoring site and then further multiplied by the median ratio of 2009 average PM_{10} to 2009 average $PM_{2.5}$ levels from ambient monitoring stations in which both pollutants were measured. This method assumes a similar temporal variation in PM_{10} and $PM_{2.5}$ concentrations and is recommended when there are insufficient ground-level $PM_{2.5}$ data for temporal adjustment (Procedure for Back-Extrapolation: Manual by the ESCAPE project, 2012). Predicted $PM_{2.5}$ concentrations at each woman's residence (weighting for residential mobility) were averaged for each week of each woman's specific gestational period. Lastly, we calculated three additional exposure metrics to assess $PM_{2.5}$ exposure across longer pregnancy periods, representing average $PM_{2.5}$ exposure during gestational weeks 1–11, 12–19, and 20–33.

2.3. Fetal growth assessment

Women had two to eight ultrasound exams, with an average of 3.1 ultrasounds per woman, which included ultrasound scans that were conducted at approximately 12, 20, and 34 weeks of gestation at routinely scheduled antenatal care visits by obstetricians. The following fetal parameters were recorded from each ultrasound: femur length (FL), abdominal circumference (AC), and biparietal diameter (BPD) (in millimeters) and used to calculate an estimated fetal weight (EFW, in grams) using the Hadlock algorithm (Hadlock et al., 1985). Gestational age was estimated based on the last menstrual period. An early crown-rump length was used for gestational age dating when the participant's self-reported last menstrual period differed from the estimate based on the first ultrasound by $\geq$ 7 days (Westerway et al., 2000).

To estimate longitudinal growth curves for fetal parameters, our group previously applied linear mixed models to establish the relationship between gestational age and each fetal growth parameter, for each region separately (Iñiguez et al., 2016). These models were adjusted for the following constitutional factors known to affect fetal growth: maternal age, height, pre-pregnancy weight, country of birth, parity, paternal height, and fetal sex (Mamelle et al., 2001). These fetal growth curves were used to calculate unconditional z-scores at 12, 20, and 34 weeks of gestation, which are predictions of fetal size at the given time points. This method allows the growth trajectory of the fetus during a given time interval to be calculated by conditioning a z-score at a given time point on the z-score from the previous time point (Hadlock et al., 1985; Royston, 1995). For example, the growth trajectory of EFW for 12–20 gestational weeks is represented by the conditional z-score for EFW at 20 weeks, which is calculated by conditioning EFW at week 20 on EFW at week 12. Previously, growth trajectories for each fetal parameter (i.e., EFW, FL, AC, and BPD) were calculated for the periods of 12–20 weeks (representing mid-pregnancy) and 20–34 weeks (representing late pregnancy) (Iñiguez et al., 2016). For each fetal parameter, the outcomes of interest in our analysis were focused on the unconditional z-score at 12 weeks of gestation (which necessarily represents fetal growth from 0 to 12 weeks) as well as the conditional z-scores at 20 and 34 weeks. These outcomes reflect the impact of $PM_{2.5}$ on fetal growth during early, mid-, and late pregnancy, respectively.

2.4. Covariate measurement

All women underwent interviews during the first and third trimesters of pregnancy to collect data on sociodemographic and behavioral characteristics via interviewer-administered questionnaires. Potential confounders were informed by prior knowledge and a directed acyclic graph. We adjusted models for the following variables: maternal age (continuous [years]), maternal and paternal education (primary, secondary, and university), cohabitation (living with father/not living with father), parity (0, 1, and $\geq$2), alcohol use (at least one drink per week/fewer than one drink per week) and smoking (self-reported active smoking at 12 and/or 32 weeks gestation) during pregnancy, fetal sex (female/male), social class, and pre-pregnancy body mass index (BMI). Social class was classified based on the highest of either maternal or paternal occupation during pregnancy according to the 1994 Spanish National Occupation Codes and assessed as a ternary measure of low (IV + V for skilled, semi-skilled, and unskilled manual workers), middle (III for other non-manual workers and manual worker supervisors), and high (I + II for managers, technicians, and associate professionals) (Domingo-Salvany et al., 2000). Self-reported pre-pregnancy BMI (kg/m^2) was classified as underweight (BMI $\leq$18.49), normal (BMI 18.50–24.99), overweight (BMI 25.0–29.99), and obese (BMI $\geq$30.0). We also adjusted for the child's birth season as a proxy for potential seasonal trends, including trends in ambient temperature.

2.5. Statistical analysis

Among the 2462 women with complete fetal growth data, women missing exposure (n = 22) and covariate (n = 112) data were excluded for a final sample size of 2328 women. All covariate data were summarized using percentages. Gestational period-specific exposure metrics (i.e., $PM_{2.5}$ averaged across gestational weeks 1–11, 12–19, and 20–33) were summarized using the median, 25th, and 75th percentiles.

To address our primary goal to evaluate susceptible windows of exposure to $PM_{2.5}$ on fetal growth, we applied distributed lag non-linear models, a flexible approach that utilizes a bi-dimensional space of functions, called a cross-basis, to simultaneously model the exposure- and lag-response relationships (Gasparrini, 2011) and addresses the limitation of assessing exposure averaged across relatively large periods of time. Distributed lag non-linear models allow for the estimation of potentially non-linear variations in the dimensions of predictor intensity and lag. In our study, average weekly $PM_{2.5}$ exposures were used when fitting these models. A linear exposure-response function was specified and a natural cubic spline was specified for the lag-response function in the cross-basis of the models. Fitting a spline function of time in the models allows us to capture long-term trends in the data (Bhaskaran et al., 2013). The number and placement of knots in the splines were determined through evaluation of multiple models with varying numbers of knots; the final model was selected based on the Akaike information criterion (AIC) (Gasparrini, 2014). The placement of knots for splines in the 10 models with the lowest AIC and for each fetal growth outcome are shown in Supplementary Material, Tables S1, S2, and S3. We evaluate the estimated weekly $PM_{2.5}$ exposure that corresponded to one less than the gestational week of the growth trajectory of interest (i.e., we evaluated $PM_{2.5}$ exposures during gestational weeks 1 through 11 with 12-week growth trajectories, 1 through 19 with 20-week growth trajectories, and 1 through 33 with 34-week growth trajectories). Distributed lag non-linear models were fit using the Bayesian hierarchical model framework via the integrated nested Laplace approximation (Gómez-Rubio, 2020). Further, to account for potential heterogeneity in study characteristics between regions, an independent and identically distributed Gaussian random effect for study region was included in the model framework (Lowe et al., 2021). The percentage change in fetal growth associated with a 5 $\mu g/m^3$ unit increase in $PM_{2.5}$ exposure during a given week of gestation was estimated. Susceptible windows of exposure were identified as those weeks

in which 95% credible intervals (CrIs) excluded the null; cumulative effects (β_{cum}) were calculated by aggregating effects across lags when susceptible windows were identified in adjacent weeks.

We conducted several secondary analyses. First, given sex differences in response to air pollution exposures and prenatal development (Bertin et al., 2015), we evaluated fetal sex-specific effects in two ways. First, we included an interaction term between the cross-basis in the distributed lag non-linear models and fetal sex. Here, an interaction between $PM_{2.5}$ and fetal sex was indicated if the deviance information criterion (DIC) for the interaction model was at least 2 units lower than the model without an interaction term and the widely applicable information criterion (WAIC) in the interaction model was at least 7 units lower than the model without an interaction term (Duncan and Mengersen, 2020). Second, we produced fetal sex-specific models to visually compare the shapes of the model curves for male and female fetuses. Second, we conducted a sensitivity analysis applying inverse probability weights (IPWs) to the distributed lag non-linear models to assess the impact of potential selection bias due to the loss of subjects missing fetal growth measurements (n = 173). Third, given our previous results regarding an association between NO_2 exposure and fetal growth (Whitworth et al., 2022), among the subset of women for whom NO_2 exposure data were available (n = 2104), we conducted sensitivity analyses adjusting for this co-exposure (operationalized as averaged weekly exposure) through the addition of a second cross-basis in the distributed lag non-linear models representing the NO_2 response function. Finally, to demonstrate potential differences in identification of susceptible windows of exposure using more traditional methods, general linear models were adopted within the integrated nested Laplace approximation to evaluate associations between $PM_{2.5}$ exposure averaged across each exposure period and each fetal growth parameter during early, mid-, and late pregnancy. These models were mutually adjusted for exposure during different pregnancy periods (Wilson et al., 2017). Specifically, for early pregnancy growth outcomes, we examined exposure averaged across weeks 1–11; for mid-pregnancy growth outcomes, we examined exposure averaged across weeks 1–11 and weeks 12–19; for the late pregnancy growth outcomes, we examined exposure averaged across weeks 1–11, weeks 12–19, and weeks 20–33. Effect estimates and 95% CrIs for these models are presented as a percentage change in fetal growth per 5 $\mu g/m^3$ increase in average $PM_{2.5}$ exposure over a given exposure period.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.0.4 (R Core Team, Vienna, Austria).

3. Results

3.1. Participant characteristics

The maternal, paternal, and fetal characteristics of the participants are summarized in Table 1. Most women were 30–34 years of age (42.40%). Overall, 41.32% of the mothers and 44.33% of the fathers had a secondary level of education, and 40.72% of mothers were classified in the low social class category. More than half of the women had pre-pregnancy BMI classified as normal (69.03%), and 26.55% were overweight or obese. The majority of women in the present study were primiparous (56.49%). Approximately one-third of women reported smoking during pregnancy (31.70%), and 8.93% of women reported at least one alcoholic drink per week during their pregnancy. There were some differences in the sociodemographic characteristics between women recruited from different study regions (Supplementary Material, Table S4). For example, while 25.82% of women in Asturias were ≥35 years at recruitment, the proportion of women recruited from other study regions ranged from 14.66 to 18.72%. Compared with women from the other three study regions, more women in Gipuzkoa had a university-level of education and were classified in the high social class category. A total of 41.08% of women from Valencia self-reported smoking during pregnancy compared with 28.40% of women in Asturias, 22.82% of women in Sabadell, and 30.48% of women in Gipuzkoa. The median (25th-75th percentiles) of the average $PM_{2.5}$ exposure during gestational weeks 1–11, 12–19, and 20–33 was 14.72 (12.63–16.73), 14.52 (12.62–16.71), and 14.53 (12.43–16.51) $\mu g/m^3$, respectively.

Table 1
Maternal, paternal, and fetal characteristics of 2328 INMA participants, 2003–2008.

Characteristics	n (%)
Maternal age (years)	
< 25	166 (7.13)
25–29	749 (32.17)
30–34	987 (42.40)
≥ 35	426 (18.30)
Maternal education	
Up to primary	561 (24.10)
Secondary	962 (41.32)
University	805 (34.58)
Paternal education	
Primary	823 (35.35)
Secondary	1032 (44.33)
University	473 (20.32)
Social class	
Low	947 (40.72)
Middle	620 (26.63)
High	760 (32.65)
Cohabitation	
Living with father	2294 (98.54)
Not living with father	34 (1.46)
Pre-pregnancy BMI (kg/m^2)	
Underweight (≤18.49)	103 (4.42)
Normal (18.50–24.99)	1607 (69.03)
Overweight (25.0–29.99)	436 (18.73)
Obese (≥30.0)	182 (7.82)
Parity	
0	1315 (56.49)
1	859 (36.90)
≥ 2	154 (6.62)
Smoking during pregnancy	
No	1590 (68.30)
Yes	738 (31.70)
Alcohol use during pregnancy	
< 1 drink per week	2120 (91.07)
≥ 1 drink per week	208 (8.93)
Fetal sex	
Female	1129 (48.50)
Male	1199 (51.50)
Child's birth season	
Spring	571 (24.53)
Summer	558 (23.97)
Autumn	542 (27.58)
Winter	557 (23.93)

3.2. Identification of weekly susceptible windows of $PM_{2.5}$ exposure on fetal growth

Fig. 1 shows the results from the distributed lag non-linear models (see corresponding effect estimates and 95% CrIs in Supplementary Material, Tables S5, S6, and S7). Although the shape of these models indicated negative associations between $PM_{2.5}$ exposure and each fetal growth parameter in early pregnancy, there was no evidence of any specific susceptible windows (Fig. 1, A). In mid-pregnancy (Fig. 1, B), we identified that $PM_{2.5}$ exposure during gestational weeks 1–2 was associated with increased EFW growth (β_{cum} = 0.44%, 95% CrI = 0.22%, 0.66%) while weeks 7–19 were associated with reduced EFW growth (β_{cum} = −1.17%, 95% CrI = −1.59%, −0.75%). As with EFW, we observed a susceptible window of exposure during the first two gestational weeks on mid-pregnancy AC growth (β_{cum} = 0.30%, 95% CrI = 0.18%, 0.42%), while $PM_{2.5}$ exposure during weeks 6–9 was associated with decreased AC growth in mid-pregnancy (β_{cum} = −0.35%, 95% CrI

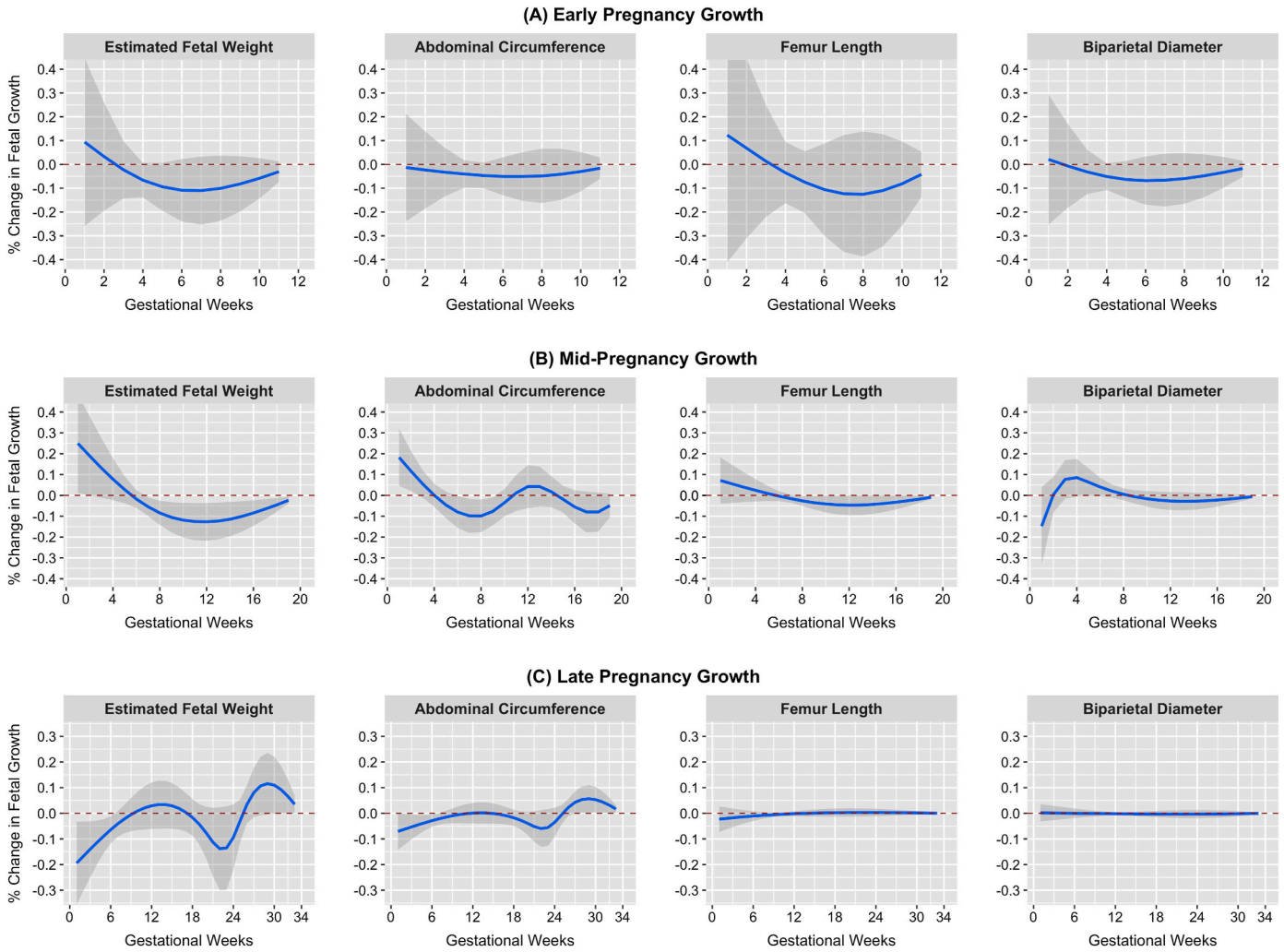

Fig. 1. Associations between weekly prenatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) and percentage change in estimated fetal weight, abdominal circumference, femur length, and biparietal diameter during (A) early (first 12 weeks of gestation), (B) mid- (12–20 weeks of gestation), and (C) late (20–34 weeks of gestation) pregnancy. Models were adjusted for maternal age, maternal and paternal education, social class, cohabitation, pre-pregnancy BMI, parity, smoking and alcohol use during pregnancy, child's birth season, fetal sex, and account for heterogeneity between regions. The x-axes represent gestational weeks, and the y-axes represent the percentage change in fetal growth. The solid lines represent the estimated values from the fitted distributed lag non-linear models, and the shaded areas represent 95% CrI around the estimate for each gestational week. The gestational weeks where the 95% CrI excludes null value (dotted horizontal line) were identified as susceptible windows of exposure.

= −0.50%, −0.21%). Although attenuated, a similarly shaped curve was observed for the associations between weekly $PM_{2.5}$ exposures and mid-pregnancy FL as for EFW, with a susceptible window of exposure identified during gestational weeks 7–19 (β_{cum} = −0.43%, 95% CrI = −0.64%, −0.21%). Lastly, we observed that $PM_{2.5}$ exposure during gestational weeks 5–6 was marginally associated with increased mid-pregnancy BPD growth (β_{cum} = 0.10%, 95% CrI = 0.05%, 0.16%). With regards to fetal growth during late pregnancy (Fig. 1, C), we observed a susceptible window of $PM_{2.5}$ exposure for reduced EFW growth during gestational weeks 1–6 (β_{cum} = −0.77%, 95% CrI = −1.07%, −0.47%), while $PM_{2.5}$ exposure during weeks 29–33 (β_{cum} = 0.42%, 95% CrI = 0.20%, 0.64%) was associated with increased EFW growth. In addition, a similar pattern was found for AC, with gestational weeks 1–7 (β_{cum} = −0.32%, 95% CrI = −0.46%, −0.18%) identified as a susceptible window of exposure for reduced AC growth in late pregnancy. As with EFW, we also observed a susceptible window of exposure to $PM_{2.5}$ during the end of the period (weeks 27–33) associated with increased late pregnancy AC growth (β_{cum} = 0.30%, 95% CrI = 0.16%, 0.44%). No evidence of specific susceptible windows of exposure to $PM_{2.5}$ on FL and BPD growth in late pregnancy were observed.

Our results were unchanged after applying IPWs to the distributed lag non-linear models (data not shown). No evidence of sexually dimorphic differences in sensitive windows of exposure to $PM_{2.5}$ on fetal growth was identified based on our comparison of model fit between models with and without an interaction term between the cross-basis and fetal sex. However, visual inspection of the fetal sex-specific model results (Supplementary Material, Figs. S1, S2, and S3) did reveal some differences in patterns of effect and windows of susceptibility to $PM_{2.5}$ between male and female fetuses. For example, suggested negative associations between $PM_{2.5}$ exposure and decreased early fetal growth for AC and BPD appear to be primarily influenced by female fetuses. Additionally, windows of susceptibility to $PM_{2.5}$ on mid-pregnancy EFW and FL appear isolated to female fetuses. Similarly, associations between $PM_{2.5}$ exposure and late EFW and AC growth also appear in female but not male fetuses. In addition, adjustment for weekly prenatal NO_2 exposure resulted in wider credible intervals, the direction and strength of the associations between $PM_{2.5}$ exposure and each fetal growth parameter remained similar (Supplementary Material, Fig. S4).

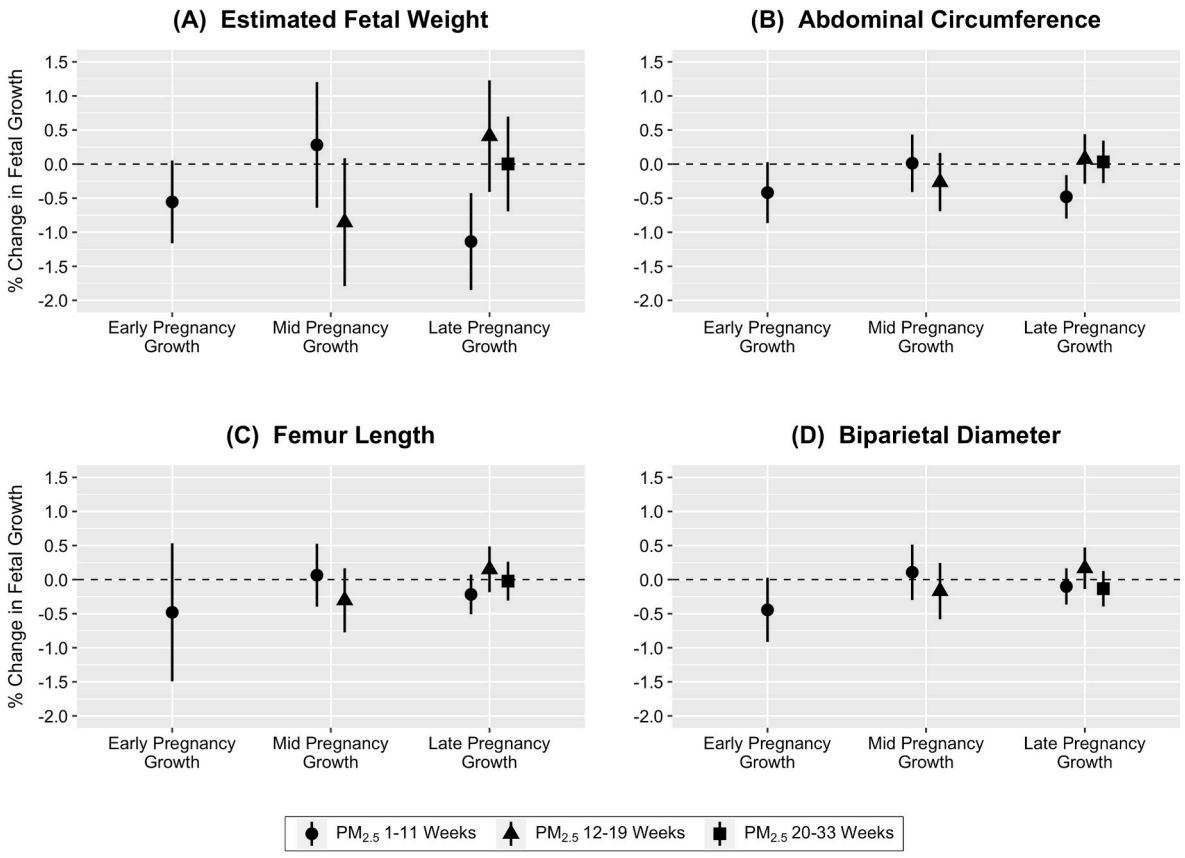

Fig. 2. Associations between prenatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) averaged across multi-week pregnancy periods and percentage change in (A) estimated fetal weight, (B) abdominal circumference, (C) femur length, and (D) biparietal diameter during early (first 12 weeks of gestation), mid- (12–20 weeks of gestation), and late (20–34 weeks of gestation) pregnancy, mutually adjusted for exposure during each period. Models were adjusted for maternal age, maternal and paternal education, social class, cohabitation, pre-pregnancy BMI, parity, smoking and alcohol use during pregnancy, child's birth season, fetal sex, and account for heterogeneity between regions. The y-axes represent the percentage change in fetal growth. The dotted horizontal lines represent the null value.

3.3. Associations between $PM_{2.5}$ exposure averaged across pregnancy periods and fetal growth

The associations of prenatal $PM_{2.5}$ exposure averaged across different pregnancy periods with fetal growth during early, mid-, and late pregnancy are shown in Fig. 2 (see corresponding effect estimates and 95% CrIs in Supplementary Material, Table S8). We observed reductions in early pregnancy growth for EFW (β = −0.55%, 95% CrI = −1.16%, 0.05%), AC (β = −0.42%, 95% CrI = −0.87%, 0.03%), and BPD (β = −0.44%, 95% CrI = −0.91%, 0.03%) in relation to $PM_{2.5}$ exposure averaged across gestational weeks 1–11, although none of these estimates were statistically significant. Little evidence of associations between period-averaged $PM_{2.5}$ exposure and mid-pregnancy growth was observed, although exposure during weeks 12–19 was marginally associated with reduced EFW during this period (β = −0.85%, 95% CrI = −1.79%, 0.09%). $PM_{2.5}$ exposures during the first eleven weeks was associated with reduced growth in EFW (β = −1.14%, 95% CrI = −1.85%, −0.43%) and AC (β = −0.48%, 95% CrI = −0.80%, −0.16%) in late pregnancy.

4. Discussion

Our study implemented distributed lag non-linear models to explore temporally refined (weekly) susceptible windows of exposure to $PM_{2.5}$ on longitudinally-measured fetal growth trajectories, which addresses a gap in the literature regarding not only the influence of the timing of $PM_{2.5}$ exposure on fetal growth but also the influence of $PM_{2.5}$ exposure on the growth of specific fetal body segments. The assessment of susceptible windows of exposure revealed a few consistent patterns, including a window of sensitivity to exposure during gestational weeks 29–33 and 27–33 on increased late pregnancy growth for both EFW and AC, respectively. We also applied more 'traditional' metrics of exposure averaged across multi-week periods. Although this method provided some consistent results with the distributed lag non-linear models, the use of exposures averaged across multi-week periods obscured the biologically plausible finding regarding increased growth in late pregnancy.

Several previous epidemiologic studies have utilized fetal biometry to address limitations in the use of birth anthropometry to understand the association between exposure to $PM_{2.5}$ and fetal growth. For example, a study conducted in North East Scotland (Clemens et al., 2017) found that a 5 μg/m^3 increase in $PM_{2.5}$ concentrations was associated with reductions in z-scores of FL, AC, and BPD during the third trimester. Additionally, this study utilized annual $PM_{2.5}$ exposures estimated at the maternal residential postal code which may not reflect individual exposure levels nor inform temporal variability. Two Chinese studies (Cao et al., 2019; Lin et al., 2020) observed negative associations between $PM_{2.5}$ exposure aggregated from conception to the time of each ultrasound measurement and several measures of fetal growth, including EFW, AC, FL, and BPD. In a study of Shanghai women, Shao et al. (2020) reported reductions in AC and FL at gestational week 24 were associated with a 10 μg/m^3 increase in $PM_{2.5}$ exposure averaged during the first and second trimesters. However, women in these Chinese studies experienced $PM_{2.5}$ exposure levels higher than women in the United States (US) and Europe (average range from approximately 30 to 80 μg/m^3) and thus, may not be generalizable and directly comparable to our results. In addition, in a study of women who resided in

Eastern Massachusetts, Leung et al. (2022) observed that a 5 μg/m^3 increase in $PM_{2.5}$ exposure averaged across the first 16 gestational weeks was associated with reduced AC and BPD z-scores measured during the routine anatomy scan during the second trimester (before 24 weeks of gestation). While these previous results support the hypothesis that $PM_{2.5}$ exposure is related to impaired fetal growth, they have relied on exposures aggregated across relatively large periods of pregnancy, or the entire gestational period and thus, were unable to evaluate specific windows of sensitivity to exposure at different time points during pregnancy.

Similar to Shao et al. (2020) and Leung et al. (2022), we observed associations between $PM_{2.5}$ exposure in several gestational weeks during early pregnancy (i.e., gestational weeks 1–7) and decreased AC growth in late pregnancy. While Shao et al. (2020) indicated that $PM_{2.5}$ exposures during each trimester were associated with reduction of FL measured at both weeks 24 and 36, we did not observe associations between $PM_{2.5}$ exposures and late pregnancy FL growth. Additionally, Leung et al. (2022) reported that $PM_{2.5}$ exposure averaged across the first 16 gestational weeks was associated with decreased BPD measured during the routine anatomy scan, while we found a marginal association between $PM_{2.5}$ averaged across weeks 1–11 and reduced early pregnancy BPD growth, and no association was observed with mid-pregnancy BPD. A direct comparison between the studies from Shao et al. (2020) and Leung et al. (2022) and ours is difficult given differences in the timing of assessment of both exposure and fetal biometry; moreover, these previous studies analyzed fetal size while we analyzed fetal growth trajectories. To date, we are aware of only one Chinese study that has employed distributed lag non-linear models to examine associations of exposure to $PM_{2.5}$ on a growth-related outcome (Wu et al., 2018). This study found exposure to $PM_{2.5}$ during weeks 27–33 was associated with decreased birth weight, and exposure in weeks approximately 20–25 was (not statistically significantly) associated with increased birth weight. Although this study did not directly assess fetal growth as an outcome and evaluated extremely high levels of change in $PM_{2.5}$ exposure (about per 55 μg/m^3) that are not relevant to Western countries, it supports the necessity of refining exposure assessments due to the differential effects of air pollution exposures on birth weight (and by extension, fetal growth) during periods that do not align with traditionally defined time periods (e.g., trimesters).

Our study identified multiple susceptible windows of $PM_{2.5}$ exposure associated with delayed fetal growth. Several biological mechanisms have been implicated in this association, including systemic oxidative stress, inflammation, and vascular and placental dysfunction, which lead to the inhibition of transplacental nutrient exchange (Kannan et al., 2007; Liu et al., 2016; Veras et al., 2008). Reduced placental vascularization may also explain differential influences of air pollution on fetal growth during different time periods in gestation. The placenta is more vulnerable to air pollution during the first trimester, and early placental insults may lead to delayed effects, including pregnancy complications (Hettfleisch et al., 2017). This delayed effect has been confirmed in Griffin et al.'s findings that dysregulated placentation and angiogenesis led by maternal infections in early pregnancy (before 20 weeks of gestation) may result in changes in umbilical blood flow during the third trimester (Griffin et al., 2012). In addition, different body parts may be differently influenced by air pollution as time, duration, and intensity of exposure may selectively affect the maturation of different body segments (Selevan et al., 2000). For example, brain development is critical in the early to mid-pregnancy periods (Salihagić Kadić and Predojević, 2012; Selevan et al., 2000); therefore, measuring head growth only during late pregnancy may not be informative. Lastly, growth velocities vary by organ system. While AC marks growth in subcutaneous fat and abdominal organs and has relatively stable growth velocity throughout pregnancy (Ohuma et al., 2021), FL and BPD are indicators of fetal skeleton growth with the highest growth velocities around 16–20 gestational weeks, followed by rapid decrease in growth velocity until term. This may coincide with our finding of a sensitive window of exposure to $PM_{2.5}$ for reduced FL growth in mid but not late pregnancy. Further, the brain-sparing effect – a fetal adaptive reaction for brain development to placental insufficiency (Roza et al., 2008; Swanson et al., 2009) may possibly explain the limited evidence of susceptible windows of exposure to $PM_{2.5}$ on BPD in our study.

Though not identified in the 'traditional' analysis of $PM_{2.5}$ exposure averaged across pregnancy periods, the application of distributed lag non-linear models identified several positive associations between $PM_{2.5}$ and fetal growth. Notably, we found that $PM_{2.5}$ exposure during weeks 29–33 and 27–33 was associated with increased late pregnancy growth for EFW and AC, respectively. We recently published similar positive patterns between exposure to NO_2 during weeks in the second and third trimesters and increased late pregnancy EFW, AC, and BPD growth (Whitworth et al., 2022). Studies from other groups also report similar findings with respect to PM_{10} exposure and increased birth anthropometry (Lamichhane et al., 2018) and fetal growth (van den Hooven et al., 2012; Zhao et al., 2018). A study conducted in the Netherlands (van den Hooven et al., 2012) showed that women exposed to third (30.6–33.6 μg/m^3) and highest (>33.6 μg/m^3) quartile levels of PM_{10} averaged across pregnancy was associated with an increase EFW growth during weeks 20–24 compared to those with the lowest quartile (<28 μg/m^3). Additionally, in a large study of Chinese women, Zhao et al. (2018) reported that the risk of over-growth (classified as z-scores of growth >97th centile) in FL and head circumference increased by about 20% for women exposed to more than 150 μg/m^3 of PM_{10} averaged from conception to ultrasound examination compared to those with PM_{10} less than 150 μg/m^3. Recently, exposure to $PM_{2.5}$ has also been implicated to increased risk of macrosomia in a nationwide study of Chinese women (Chen et al., 2020). One possible mechanism for the effect of increased late pregnancy growth is that the levels of adipokines such as leptin and adiponectin in the placenta may be influenced by exposure to air pollution such as $PM_{2.5}$ and NO_2 in late pregnancy (Alderete et al., 2018; Lavigne et al., 2016), followed by various metabolic actions in utero, leading to abnormal fetal weight gain in late pregnancy (Alderete et al., 2018). Another hypothesis is related to intrauterine catch-up growth, such that exposure to several air pollutants ($PM_{2.5}$, PM_{10}, SO_2, O_3, and NO_2) induces delayed growth in early pregnancy following by a period of growth acceleration in late pregnancy (Shao et al., 2020). Given the emerging evidence related to prenatal air pollution exposure in postnatal catch-up growth (Fleisch et al., 2015; Starling et al., 2020), additional studies are needed to clarify the mechanisms underlying the effect of air pollution exposure in rapid catch-up growth during late pregnancy.

Although our analysis comparing model fit between models with and without an interaction term did not support fetal sex differences in susceptible periods of exposure to $PM_{2.5}$ on fetal growth, visual comparison of fetal-sex specific models did suggest sex differences, with many findings appearing only among female fetuses. The previous literature regarding the sexually-dimorphic impacts of $PM_{2.5}$ exposure on fetal growth has been mixed with Leung et al. (2022) and Clemens et al. (2017) reporting no fetal sex differences in associations between exposure to $PM_{2.5}$ and fetal growth. However, a systematic review of the effect of infant gender on associations between air pollution and varied pregnancy outcomes indicated evidence that female infants were more susceptible to air pollution with regard to low birth weight, though the number of studies included was limited (Ghosh et al., 2007). To our knowledge, ours is the first study to investigate the impact of fetal sex on susceptible periods of exposure to $PM_{2.5}$ on fetal growth trajectories. Future studies utilizing large sample sizes and from diverse populations should investigate this question further and animal studies would help to better inform potential mechanisms through which sexually-dimorphic impacts of air pollution on fetal growth may occur.

The use of distributed lag non-linear models in our study allowed us to identify more refined critical periods of exposure than traditional statistical models using exposure windows corresponding to relatively wide exposure windows (e.g., trimesters) (Wilson et al., 2017). There

were several instances where the analyses of $PM_{2.5}$ exposure averaged across pregnancy periods were inconsistent with the analyses of weekly susceptible windows of $PM_{2.5}$ exposure. Most notably were the above-mentioned positive associations between $PM_{2.5}$ exposure during weeks 27–33 and late pregnancy growth in EFW and AC. These biologically plausible associations were obscured when exposures were averaged across weeks 20–33 (the period in which late pregnancy growth was also measured). These findings clearly demonstrate that the use of traditional exposure metrics may not align with periods of fetal vulnerability and may mask the identification of windows of sensitivity. The use of distributed lag non-linear models has additional advantages. For example, linear models do not allow for simultaneous modeling of the temporal and intensity components of the lagged exposure (Gasparrini et al., 2010, 2017). Also, issues regarding multiple comparisons may be eliminated when simultaneously modeling lag-exposure-outcome relationships using the cross-basis structure inherent in distributed lag non-linear models (Gasparrini and Armstrong, 2013; Gasparrini et al., 2010). The distributed lag non-linear models also revealed increased mid-pregnancy growth in EFW, AC, and BPD associated with $PM_{2.5}$ exposure in the first several weeks of pregnancy, though the credible intervals for these estimates were wide. We are unaware of any biologically plausible mechanism to support these findings. It is possible that they are due to chance or the linearity constraints at the boundary knots in the natural cubic splines used in the models. Additionally, the present study may be susceptible to potential live-birth bias if fetuses who were particularly susceptible to $PM_{2.5}$ exposure were unobserved due to pregnancy loss (Goin et al., 2021; Leung et al., 2021; Liew et al., 2015). The magnitude of this bias likely depends on several factors, including the mechanism of selection (Goin et al., 2021; Leung et al., 2021). Given the observed associations between $PM_{2.5}$ exposure and pregnancy loss (Gaskins et al., 2019; Zhang et al., 2019), live birth bias may contribute, at least in part, to the unexpected protective associations observed in our study.

The assessment of $PM_{2.5}$ exposure in this study did not account for individual time-activity patterns and lacked information on exposures to indoor air pollutants; thus, may be susceptible to potential exposure misclassification. However, our exposure assessment did account for residential mobility during pregnancy, which improves the accuracy of estimating individual exposure levels compared to previous air pollution investigations. While it is possible that some measurement error may have been introduced in our air pollution models by using the ratio of measured PM_{10}:$PM_{2.5}$ to inform the temporal adjustment of $PM_{2.5}$ for some study regions, we accounted for between-region heterogeneity through the random effect in the statistical models. Furthermore, our study was unable to account for unmeasured factors such as ambient temperature. Although we attempted to control for temperature effects through the inclusion of birth season in our models, we recognize that season is an imperfect proxy of temperature. Potential measurement error in fetal biometry was limited because ultrasound measurements were conducted under a standard protocol by specialized obstetricians. Also, fetal growth z-scores were calculated based on longitudinal growth curves constructed using fetal biometry data measured from multiple ultrasounds and thus, the possible random error in modeling growth is diminished.

5. Conclusions

Our analysis of susceptible windows of exposure to $PM_{2.5}$ and fetal growth using data from a large prospective birth cohort in Spain provides evidence of the differential influences of prenatal $PM_{2.5}$ exposure on fetal growth. In particular, results of the distributed lag non-linear models revealed that $PM_{2.5}$ exposure during specific weeks of early and mid-pregnancy were associated with reduced mid- and late pregnancy EFW and AC growth, while $PM_{2.5}$ exposure during late pregnancy was associated with increased EFW and AC growth in late pregnancy. These analyses highlight the importance of refining exposure estimates in studying the associations of environmental exposure on adverse fetal growth given, as seen in our study, traditional exposure metrics may obscure the differential influences of exposure when aggregating exposure over broad periods and ignore fetal vulnerability on growth in specific periods and body segments. Further replication studies with refined exposure assessments are warranted to evaluate the windows of susceptibility to air pollution exposure to advance the understanding of the etiology of adverse fetal growth and rule out possibly spurious findings and to explore susceptible windows of exposure to other pregnancy outcomes that have been widely associated with air pollution, such as preterm birth. The evidence provided by this study not only supports the need to apply novel methods to enhance the understanding of the underlying mechanism of prenatal air pollution as a cause of adverse health effects in children but may also inform future public health interventions, such as those targeting community-wide reductions in air pollution levels, to further reduce the adverse effects of environmental factors on children.

Credit author statement

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Funding

This work was supported by grant R01ES028842 from the National Institutes of Health / National Institute of Environmental Health Sciences (NIH/ NIEHS); grants Red INMA G03/176, CB06/02/004; ISCIII-FEDER: PI03/1615, PI04/1509, PI04/1112, PI04/1931, PI04/2018, PI05/1079, PI05/1052, PI06/0867, PI06/1213, PI07/0314, PI09/02311, PI09/02647, PI11/01007, PI11/02591, PI11/02038, PI13/1944, PI13/2032, PI13/02429, PI14/00891, PI14/01687, PI16/1288, PI16/00118, PI17/00663, PI18/00909, PI18/01142, PI18/01237; Miguel Servet-FEDER CP11/00178, CP15/00025, CPII16/00051, CPII18/00018, and CP16/00128 from Instituto de Salud Carlos III, grant 1999SGR 00241 from Generalitat de Catalunya- CIRIT, grant FP7-ENV-2011 cod 282957 and HEALTH. 2010.2.4.5–1 from the EU Commission, Assistance Award No. R-82811201 from the Health Effects Institute, grant UGP 15-230, UGP-15-244, and UGP-15-249 from Generalitat Valenciana: FISABIO, grant 2005111093 from Alicia Koplowitz Foundation (2017), Department of Health of the Basque Government, grant DFG06/002 from the Provincial Government of Gipuzkoa, and annual agreements with the municipalities of the study area (Zumarraga, Urretxu, Legazpi, Azkoitia y Azpeitia y Beasain), Obra Social Cajastur/Fundación Liberbank, and Universidad de Oviedo. We also acknowledge support from the Spanish Ministry of Science and Innovation and the State Research Agency through the "Centro de Excelencia Severo Ochoa 2019–2023" Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program. KWW and ES were partially supported by the P30 Environmental Health Sciences Core Center grant P30ES030285 from the NIH/NIEHS and by funding from the NIH/National Institute on Minority Health and Health

Disparities (NIMHD) under Award Number P50MD015496. JI was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences.

Data sharing

Data are available upon reasonable request by contacting inma@proyectoinma.org. Information regarding the INMA Collaboration Policy is available here: https://www.proyectoinma.org/en/inma-project/inma-collaboration-policy/.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available upon reasonable request..

Acknowledgments

The authors would like to thank all participants in this study for their generous collaborative efforts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114628.

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