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Prenatal Particulate Air Pollution Exposure and Body Composition in Urban Preschool Children: Examining Sensitive Windows and Sex-specific Associations

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Abstract

Background—Evolving animal studies and limited epidemiological data show that prenatal air pollution exposure is associated with childhood obesity. Timing of exposure and child sex may play an important role in these associations. We applied an innovative method to examine sex-specific sensitive prenatal windows of exposure to PM_{2.5} on anthropometric measures in preschool-aged children.

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Methods—Analyses included 239 children born 37 weeks gestation in an ethnically-mixed lower-income urban birth cohort. Prenatal daily PM_{2.5} exposure was estimated using a validated satellite-based spatio-temporal model. Body mass index z-score (BMI-z), fat mass, % body fat, subscapular and triceps skinfold thickness, waist and hip circumferences and waist-to-hip ratio (WHR) were assessed at age 4.0±0.7 years. Using Bayesian distributed lag interaction models (BDLIMs), we examined sex differences in sensitive windows of weekly averaged PM_{2.5} levels on these measures, adjusting for child age, maternal age, education, race/ethnicity, and pre-pregnancy BMI.

Results—Mothers were primarily Hispanic (55%) or Black (26%), had 12 years of education (66%) and never smoked (80%). Increased PM_{2.5} exposure from 8–17 and 15–22 weeks gestation was significantly associated with increased BMI z-scores and fat mass in boys, but not in girls. Higher PM_{2.5} exposure from 10–29 weeks gestation was significantly associated with increased WHR in girls, but not in boys. Prenatal PM_{2.5} was not significantly associated with other measures of body composition. Estimated cumulative effects across pregnancy, accounting for sensitive windows and within-window effects, were 0.21 (95% CI=0.01–0.37) for BMI-z and 0.36 (95% CI=0.12–0.68) for fat mass (kg) in boys, and 0.02 (95% CI=0.01–0.03) for WHR in girls, all per µg/m³ increase in PM_{2.5}.

Conclusions—Increased prenatal PM_{2.5} exposure was more strongly associated with indices of increased whole body size in boys and with an indicator of body shape in girls. Methods to better characterize vulnerable windows may provide insight into underlying mechanisms contributing to sex-specific associations.

Keywords

prenatal exposure; particulate matter; child obesity; anthropometry; sensitive windows; sex difference

1. INTRODUCTION

Nearly one third of children in the United States (U.S.) are overweight or obese, a proportion that has more than doubled since 1980 (Ogden et al., 2016). While some data suggest that U.S. obesity rates are stabilizing, rates remain high in preschoolers (CDC 2013) and continue to show disparities for lower-socioeconomic status (SES) groups (Yanovski and Yanovski 2011). Moreover, correlated phenotypes in infants and toddlers, such as faster weight gain and higher body fat, predict later life obesity-related trajectories (Barker 2012; Taveras et al., 2009). For example, children who are obese are five times as likely as those who are not to be obese adults (CDC 2013). Moreover, obesity increases the risk of a number of physical and mental health disorders over the life course (Bogers et al., 2007; CDC 2013; Strazzullo et al., 2010). Such trends result in U.S. spending approaching nearly \$190 billion annually on obesity related healthcare expenses (Cawley and Meyerhoefer 2012). Identifying potentially modifiable risk factors is a research priority.

While current standards mandate prevention to start soon after birth (2010), research increasingly shows that programming of obesity begins prenatally (Sutton et al., 2016). Moreover, while attempts to curb childhood obesity have largely focused on physical

activity and diet, childhood obesity is likely influenced by a range of environmental factors beyond nutrition and exercise (Birch et al., 2011). Recent evidence points to a role for chemical environmental exposures in programming obesity (Vrijheid et al., 2016).

Emerging evidence specifically supports a role for particulate air pollution, a pro-oxidant environmental exposure, in obesity programming. Particulate air pollution has been increasingly linked to obesity and related phenotypes in animal models (Bolton et al., 2014). Oxidative stress (OS) plays a role in the generation and maintenance of an obesity phenotype in both isolated adipocytes and animals (Aroor and DeMarco 2014; De Marchi et al., 2013; Imhoff and Hansen 2010; Ye et al., 2015). Notably, obesity involves excess accumulation of adipose tissue, as well as dysregulation of glucose and lipid metabolism. Reactive oxygen species (ROS) promote adipogenic signaling pathways and disrupted adipogenesis (Atashi et al., 2015; Iyer et al., 2010). Moreover, recent prospective epidemiological data link early postnatal ambient pollution to child obesity (McConnell et al., 2015), and also link ambient pollution exposure, even below air quality guidelines, to glucose tolerance during pregnancy and food reward hormone dysregulation (Calderon-Garciduenas et al., 2015; Fleisch et al., 2014), both of which are identified intermediate pathways to offspring/child obesity (Hillier et al., 2007; Jastreboff et al., 2014; Kubo et al., 2014; Poston 2010).

Ambient air pollution effects likely begin *in utero*. In pregnant women, inhaled particles translocate from the lungs via the blood to other organs including the placenta (MohanKumar et al., 2008). Particulate matter can also invoke a chronic inflammatory process in the mother's lung resulting in systemic inflammation and consequent placental OS (Liu et al., 2016). Our group and others have linked *in utero* air pollution exposure with low birth weight, a potential predecessor of overweight/obesity in later life (Bell et al., 2007; Kloog et al., 2012; Lakshmanan et al., 2015; Padula et al., 2012).

Prospective human studies examining the association between prenatal traffic-related air pollution exposure and childhood obesity remain sparse. Rundle et al. linked prenatal exposure to polyaromatic hydrocarbons (PAHs) to obesity in children assessed at ages 5 and 7 years (Rundle et al., 2012). Fleisch et al. showed that prenatal exposure to fine particulate matter was associated with more rapid postnatal weight gain in 6-month-old infants (Fleisch et al., 2015). This group also demonstrated a link between proximity to major roadways at birth (<50 meters) and fat mass at both early- and mid-childhood (median 3.3 and 7.7 years of age) (Fleisch et al., 2016). Lavigne et al. showed that increased exposure to air pollution during pregnancy was associated with higher levels of umbilical cord blood adiponectin, which regulates glucose and fatty acid breakdown in the developing fetus, and may contribute to obesity in later childhood (Lavigne et al., 2016).

Notably, existing studies of prenatal air pollution effects on childhood obesity have considered subjective assignment of exposure timing, such as air pollution exposure in a certain trimester or averaged over the entire pregnancy or over a certain length of time before pregnancy. This makes it difficult to compare the results across studies as well as to better delineate the critical windows affecting fetal programming. Clinically defined trimesters do not necessarily correspond to relevant vulnerable periods of body growth.

Measuring exposure in an arbitrarily defined susceptibility window that does not overlap with periods of physiological vulnerability may lead to underestimated or even missed associations (Wilson et al., 2017a). In addition, animal data demonstrate sex-specific vulnerability to prenatal oxidant injury (Minghetti et al., 2013), which has been linked to both air pollution and infant growth (Sun et al., 2009). Recent analyses from our group combined advanced statistical methods with highly temporally resolved exposure data to more objectively identify susceptibility windows and enhance the power to detect associations and identify vulnerable groups (i.e., effect modification) (Chiu et al., 2016; Hsu et al., 2015). These analyses demonstrated sex-specific and time-varying associations of prenatal air pollution exposure on asthma and neurodevelopmental outcomes in children, but to our knowledge, this has not yet been examined for early childhood growth indicators.

We leveraged data on daily exposure to particulate matter with a diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) measured over gestation and applied advanced statistical methods to more precisely identify the sensitive windows of time-varying prenatal $\text{PM}_{2.5}$ exposure effects on anthropometric measurements in preschool-aged children from an ethnically mixed lower-SES inner city population. We also examined effect modification by child sex.

2. MATERIALS AND METHODS

Participants were from the Asthma Coalition on Community, Environment and Social Stress (ACCESS) project, a pregnancy cohort originally funded to recruit 500 mother-child pairs to examine independent and interactive effects of early life stress and physical toxins on childhood respiratory health (Wright et al., 2008). Between August 2002 and January 2007, English- or Spanish-speaking pregnant women (≥ 18 years old) receiving care at Brigham & Women's Hospital (BWH), Boston Medical Center (BMC), and affiliated community health centers were enrolled (at 28.4 ± 7.9 weeks gestation). Seventy-eight percent (78%) of women receiving prenatal care, who were approached by research staff on select clinic days, were eligible and agreed to enroll. There were no significant differences on race/ethnicity, education, and income between women enrolled and those who declined. A total of 455 women gave birth to a live born infant and continued follow-up. Supplemental funding was obtained to assess anthropometry in children aged 3 to 5 years; of $n=358$ children age-eligible for this initiative, $n=277$ completed anthropometry assessments at age 4.0 ± 0.7 years of age. Among these children, $n=30$ were born <37 weeks, and $n=8$ did not have prenatal $\text{PM}_{2.5}$ data (i.e., did not have accurate addresses during pregnancy), resulting in $n=239$ available for analysis. Those included in analyses did not differ significantly from those not included in analyses based on key covariates including race/ethnicity, maternal age at enrollment, maternal educational status, maternal pre-pregnancy weight, prenatal smoking, child's birth weight or gestational age. Procedures were approved by the human studies committees at BWH and BMC. Mothers provided written consent in their preferred language.

2.1 Prenatal $\text{PM}_{2.5}$ Exposure

As described previously (Chiu et al., 2016), we used a validated hybrid satellite based spatio-temporal prediction model to estimate each woman's prenatal exposure to $\text{PM}_{2.5}$, an

index of ambient pollution from traffic and other sources, based on residence over pregnancy (i.e., at enrollment and updated if they moved). In brief, the model combines the aerosol optical depth (AOD) data derived by Moderate Resolution Imaging Spectroradiometer (MODIS) at a 10 km spatial resolution with traditional land-use regression (LUR) predictors to yield residence-specific estimates of daily $PM_{2.5}$, as detailed elsewhere (Kloog et al., 2011). The model was run using day-specific AOD data were calibrated against ground monitor-based $PM_{2.5}$ measurements derived from 78 monitoring stations covering New England and incorporated traditional LUR terms (traffic density, point sources, etc) and meteorological variables (temperature, wind speed, visibility, elevation, distance to major roads, percent of open space, point emissions and area emissions). The relationship between AOD and $PM_{2.5}$ was calibrated daily using data from grid cells with both AOD values and monitor data using mixed models with random slopes for day, nested within regions. If the AOD data was not available for certain locations due to metrological conditions such as cloud coverage or snow, the predictions at these locations were imputed by fitting the model with a thin plate spline of latitude and longitude and a random intercept for each cell. The R^2 of “out of sample” ten-fold cross validation for daily values were 0.83 for days with AOD and 0.81 for days without AOD data. We then calculated weekly averaged $PM_{2.5}$ levels for each week over pregnancy for each participant to reduce potential noise caused by day-to-day $PM_{2.5}$ variation and autocorrelations.

2.2 Anthropometric Measurements

2.2.1 Body mass index (BMI)—Children’s height while standing was measured without shoes (to nearest 0.1 cm) using a portable stadiometer (Shorr Productions, Olney, MD) and weight was measured (to nearest 0.1 kg) in light clothing using a calibrated portable electronic scale (Seca model 881; Seca Corporation, Hanover, MD). BMI (kg/m^2) was calculated as weight divided by square of height. BMI z-scores were calculated based on sex- and age- specific normative U.S. data using the Centers for Disease Control (CDC) 2000 growth chart (CDC 2000).

2.2.2 Bioimpedance—Bipolar bioelectrical impedance was used to estimate fat mass (kg), fat free mass (kg), and percent body fat using the BIM4 bio-impedance analyzer (Impedimed, Queensland, Australia) which has been validated in young children (Rush et al., 2013).

2.2.3 Skinfold thickness—Subscapular (SS) and triceps skinfold (TS) thicknesses (mm) were measured using Harpenden skinfold calipers and standard techniques (Oken et al., 2005); the sum (SS + TS) and ratio (SS:TS) were also calculated.

2.2.4 Waist and hip circumferences—Waist circumference was measured midway between the lowest rib and the top of the iliac crest at end expiration and hip circumference (to nearest 0.1 cm) over the great trochanters using a measuring tape (Hoechstmass Balzer GmbH, Sulzbach, Germany). Waist-to-hip ratio (WHR) was calculated by dividing waist circumference by hip circumference.

2.3 Covariates

Maternal age, race/ethnicity, and educational status were ascertained at enrollment; information about child's sex, date of birth, gestational age at birth, and birth weight were obtained by medical record review. Women's pre-pregnancy BMI (kg/m^2) was calculated from height and pre-pregnancy weight reported at enrollment. An internal validation study comparing self-report and measured height and weight available in 121 women assessed early in pregnancy (<10 weeks gestation) showed good agreement across all levels of height and weight (Wright et al., 2013). We calculated length of gestation using last menstrual period, and sex-specific birth weight for gestational age z-scores were calculated based on the U.S. national reference (Lakshmanan et al., 2015; Oken et al., 2003).

2.4 Statistical Analysis

Analyses included 239 mothers and their singleton children born at 37 weeks gestation. In order to identify sensitive windows for the effects of prenatal $\text{PM}_{2.5}$ in relation to anthropometric outcomes, we applied a distributed lag model (DLM) (Gasparrini et al., 2010; Zanobetti et al., 2000). Using a constrained DLM, we estimate the time-varying association for each participant's weekly exposures throughout the gestational period and anthropometric outcomes. Significant sensitive exposure windows were identified as weeks during pregnancy with a statistically significant association as previously described (Chiu et al., 2016; Hsu et al., 2015).

To examine effect modification by child sex, we estimated the interaction of prenatal $\text{PM}_{2.5} \times \text{sex}$ using Bayesian distributed lag interaction models (BDLIMs) as recently detailed elsewhere (Wilson et al., 2017b). In brief, BDLIM extends the traditional constrained DLM framework for critical windows to more fully account for effect modification - in our case, by child sex. The constrained DLM assumes that boys and girls either have the same sensitive window and within-window effect or that they have both different windows and different within-window effects. In contrast, BDLIM partitions the DLM into shape and scale components, which allows the additional possibilities of boys and girls having the same sensitive window but different within-window effect or the same within-window effect but different sensitive windows. The BDLIM for child i ($i=1, \dots, n$) who is sex j ($j=1$ for female and $j=0$ for male) is $E(Y_i) = a_j + \beta_j \sum_{t=1}^T w_{jt} X_{it} + Z_i^T \gamma$, where a_j is a fixed sex-specific intercept, β_j is the regression coefficient characterizing the sex-specific association between weighted $\text{PM}_{2.5}$ exposure and anthropometric outcome, $\sum_{t=1}^T w_{jt} X_{it}$ is the weighted exposure, and $Z_i^T \gamma$ is the covariate regression term. BDLIM partitions the time-varying association between exposure and outcome into two components: 1) the weights, w_{jt} , that identify critical windows of susceptibility and 2) the coefficients, β_j , that identify the magnitude of the within-window effects. When the weights are constant over time in both groups, BDLIM is equivalent to a model with mean exposure over pregnancy interacted with child sex. When the weights vary by time, the model identifies time periods with greater weight (i.e., potential sensitive windows) that will graphically appear as a bump during which exposure is significantly associated with the respective anthropometric indicators. This data-driven approach automatically determines whether the w_{jt} and β_j are the same or

different for each group based on the likelihood of each pattern of heterogeneity. In other words, the BDLIM is able to identify the best fit pattern of effect modification by sex among the four patterns: 1) boys and girls have the same weights (shape of distributed lag function) and the same coefficients (within window effect or scale); 2) boys and girls have the same weight (windows) function but different coefficients; 3) boys and girls have different weights but the same coefficients; 4) and boys and girls have both different weights and coefficients. The association between exposure and outcome was then estimated under the effect modification pattern that is best supported by the data. Deviance information criterion (DIC) was used to determine the best fitting model with optimal parameters (e.g., number of knots and degrees of freedom used) and whether the weights and effects were different across sex (Wilson et al., 2017b).

The BDLIM incorporates the data from all exposure time points simultaneously and assumes that the association between the outcome and exposure at a given time point varies smoothly as a function of time while controlling for exposure at all other time points. It also yields an estimate of a cumulative effect across all time points (in our case, across the entire pregnancy) accounting for both the sensitive windows and the strength of within-window associations for each sex group, by calculating the sum of $\beta_j \times w_{jt}$ for each time point.

Standard controls (maternal age, child's sex, child's age at anthropometric assessment) as well as potential confounders (maternal race/ethnicity, education, pre-pregnancy BMI) were included in analyses. We also conducted sensitivity analyses additionally adjusting for postnatal daily PM_{2.5} levels predicted by the spatio-temporal model averaged over the first 2 years of life and perinatal smoking, as well as birth weight for gestational age z-score, a potential pathway variable. All analyses were implemented in *R* statistical software (v3.3.1, Vienna, Austria).

3. RESULTS

3.1 Participant characteristics

Most mothers were ethnic minority (55% Hispanic, 26% African American), had 12 years of education (66%), and never smoked (80%) (Table 1). Table 2 summarizes the distribution of child anthropometry measurements and prenatal PM_{2.5} exposure by sex. Prenatal PM_{2.5} levels were similar for boys and girls and there were no significant sex differences in terms of maternal age at enrollment, race/ethnicity, education, pre-pregnancy BMI, and smoking status or child's birth weight for gestational age z-score or age at anthropometry assessment (Tables 1–2).

3.2 Identification of sensitive windows and sex-specific associations

When examining the association between prenatal PM_{2.5} exposure over gestation and anthropometry using DLMs in the sample as a whole, only the calculated index, WHR, was significantly associated with exposure at 2–22 weeks gestation (Supplemental Materials, Figure S1). However, examining the interaction between prenatal PM_{2.5} and child's sex in relation to anthropometric outcomes using BDLIMs revealed significant sexually-dimorphic associations in several indices (Figures 1–3). When interpreting the figures, “sensitive

windows” graphically appear as a bump during which exposure is significantly associated with the respective outcome. Analyses revealed a significant association between higher PM_{2.5} exposure in early-to-mid pregnancy (8–17 weeks of gestation) and higher BMI z-scores in boys, but not in girls (Figure 1). Higher PM_{2.5} levels in mid-pregnancy (15–22 weeks of gestation) were significantly associated with increased fat mass among boys, but not in girls (Figure 2). On the other hand, a significant association between higher PM_{2.5} levels and increased WHR among girls with a sensitive window spanning 10–29 weeks gestation was seen, whereas the association was only suggestive in boys (Figure 3). We did not find statistically significant sensitive prenatal windows for the remaining anthropometric measurements. For the respective outcome measurements with identified significant sex-specific sensitive exposure windows, the BDLIM analysis found that effect modification by sex was attributable to difference in the magnitude of the within-window association (i.e., β_j) between boys and girls, while the window (i.e., w_{jt}) was not different between the two sexes (the normalized posterior density was 0.56, 0.98, and 0.97 for BMI-z, fat mass, and WHR models, respectively, which can be interpreted as a probability that the model with a common window but different magnitudes was the best fitting pattern of effect modification).

3.3 Cumulative effects across pregnancy accounting for sensitive windows

In order to further assess the associations over the entire pregnancy while accounting for time-varying associations, we also estimated the cumulative effects accounting for sensitive windows and within-window associations identified by BDLIMs (Table 3). The estimated cumulative effects of prenatal PM_{2.5} exposure (per $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}) were significant for BMI-z (0.21, 95% CI=0.003–0.37) and fat mass (0.36, 95% CI=0.12–0.68) in boys, but not in girls. The estimated cumulative effect of prenatal PM_{2.5} was significant for WHR among girls (0.02, 95% CI=0.01–0.03) and only suggestive in boys (0.006, 95% CI=–0.0001–0.014).

3.4 Sensitivity analyses

Finally, sensitivity analyses additionally including postnatal PM_{2.5} levels, perinatal smoking, and birth weight for gestational age z-scores in the models showed similar sex-specific patterns for significant associations as in our main analyses (Supplemental Materials, Figures S2–S4 and Table S1).

4. DISCUSSION

These data add to a sparse literature linking *in utero* traffic-related air pollution exposure and early childhood body composition in two significant ways. First, this is the first study to leverage weekly address-specific PM_{2.5} exposure estimates and Bayesian distributed lag interaction models to examine time-varying effects in a data driven fashion rather than assigning *a priori* exposure time periods arbitrarily (e.g., averaged over a certain length of time before birth or using clinically defined trimesters) in order to more definitively identify sensitive windows for effects on child growth. In addition, the use of BDLIM allowed us to directly examine the time-varying interaction by sex and estimation of cumulative effects across the pregnancy accounting for both sensitive windows and within-window effects. Our

data suggested that increased exposure to PM_{2.5} in early to mid-pregnancy was associated with increased fat mass and higher BMI z-scores among boys. Among girls, higher exposure to PM_{2.5} from early-to-mid pregnancy was associated with increased WHR.

More refined estimation of the sensitive time windows in which air pollution has the greatest impact may enhance our insight into underlying mechanisms as well as the etiology of sex-specific effects on child growth. Oxidative stress is one of the leading hypothesized mechanisms that may be operating between prenatal particulate air pollution and early growth outcomes. Particulate air pollution may result in increased placental or fetal oxidative stress and related DNA damage or inflammation, which may inhibit nutrient transfer from mother to fetus and disrupt programming of the fetal metabolic system, thereby disrupting fetal growth (Fleisch et al., 2015; Kannan et al., 2006). Excess fetal oxidative stress or inflammation resulting from air pollution exposure could also induce fetal or infant adipose tissue inflammation and hypertrophy, which may be related to excessive weight gain (Sun et al., 2009). Increased oxidative stress could also induce neuroinflammation and central nervous system effects, which may be linked to disrupted satiety signals (Bolton et al., 2014).

Further, these analyses also found that the sensitive windows for prenatal exposure to PM_{2.5} may be sex specific. While prior human data are not available, animal studies have demonstrated sex-specific associations between prenatal air pollutants and offspring growth outcomes. In a rodent study, Bolton et al. (Bolton et al., 2012) found that adult male offspring born to pregnant mice exposed to diesel exhaust weighed 12% more compared to those born to non-exposed pregnant mice, whereas there was no difference seen in female offspring. These investigators also found that female offspring born to pregnant mice exposed to diesel exhaust gained 340% more weight following a high fat diet compared to those born to non-exposed pregnant mice; no such differences were found in male offspring. Other research suggested that sex hormones contribute to sex differences induced by pro-inflammatory triggers such as air pollution (Melcangi et al., 2008). For example, a study in rodents found that estrogens may have anti-inflammatory properties mediated by cytokine expression (Shivers et al., 2015).

To our knowledge, only one previous human study has examined the association between prenatal fine particulate matter and anthropometric outcomes in children. Fleisch et al. (Fleisch et al., 2016) found that proximity to major roadway at birth address (<50 m), a surrogate of traffic-related air pollution exposure, was associated with BMI-z score, waist circumference, and skinfold thickness in children aged at 3.3 years as well as at 7.7 years. On the other hand, this same study did not find statistically significant associations between prenatal black carbon or PM_{2.5} exposure averaged over the 3rd trimester and these measurements nor did they find effect modification by sex (Fleisch et al., 2016). While the methodology used to estimate participant's exposure to PM_{2.5} was the same in both studies, Fleisch et al. (Fleisch et al., 2016) assessed exposure in the 3rd trimester only, and thus it is difficult to directly compare the results with our study. Of note, in a recent simulation analysis, our group demonstrated that measuring exposure only in an arbitrarily defined susceptibility window during pregnancy may lead to missed associations (Wilson et al., 2017a). Moreover, the analytical approach used in the present study found that associations

between $PM_{2.5}$ and growth outcomes may be more significant in the 1st and 2nd trimester rather than later in pregnancy. This may also explain the discrepancy between the findings in the two studies, especially in terms of effect modification by sex.

A larger WHR reflects a type of body shape with excess weight around the waist (i.e., central or abdominal obesity, or “apple shape” obesity), whereas increased BMI or fat mass is more of an indicator for increased general body size (Bray and Bouchard 2014). The sex-specific findings in our study suggest that prenatal air pollution exposure may have a stronger association with increased body size in general among boys, whereas it may affect body shape among girls. The observed associations with body composition in these preschool-aged children may have long term health implications in a sex-specific manner. For example, a recent study of 8–16 year-old Hispanic children reported that the association between BMI and insulin resistance, a predictor of type-2 diabetes, was significantly stronger in boys compared to girls; on the other hand, the association between WHR and insulin resistance was significantly stronger in girls compared to boys (Qi et al., 2016). Of note, as the variability of WHR in children is generally small, the estimated effect size of prenatal exposure per unit at each time point on this indicator also likely to be small; however, we were still able to identify a sensitive window and sex difference in estimated cumulative effect over the pregnancy. Further studies are needed to replicate these results in early childhood, elucidate underlying mechanisms, and examine whether these associations are sustained over time. Longitudinal studies assessing air pollution exposures beginning *in utero* on growth trajectories over the life course will be most informative.

This study has notable strengths. We were able to leverage daily particulate air pollution data estimated by address-specific exposure for each woman over gestation, using a validated state-of-the-art hybrid spatio-temporal LUR model incorporating satellite-derived AOD measures (Kloog et al., 2011), to apply a data-driven advanced statistical approach to more objectively identify sensitive windows of prenatal $PM_{2.5}$ and more directly examine interactions by child sex. In addition, our study population consists of a lower-SES ethnically mixed inner-city population that is more likely to live in communities with higher traffic-related air pollution exposures as well as being at greater risk for childhood obesity. We also acknowledge some limitations. While we found significant interactions between prenatal $PM_{2.5}$ exposure and sex for BMI-z, fat mass, and WHR, we did not find statistically significant associations on other anthropometric measures, which may be due to our sample size. Also, while we were able to control for postnatal air pollution exposure as well as several factors known to be important for child growth, we did not have data on dietary or other parenting practices that may influence child growth. However, controlling for SES-related variables including education and race/ethnicity which are correlated with dietary intakes and parenting practices may in part account for these other factors. Finally, our results may be more generalizable to lower SES racial/ethnic minority populations. Larger studies examining sex-specific time-varying effects of prenatal particulate air pollution are thus warranted to corroborate these findings and consider additional confounders or moderators. Moreover, integrating epidemiological findings using analytic methods to more objectively identify sensitive windows with knowledge regarding developmental pathways and processes involved in prenatal programming of obesity that may be disrupted in these

time periods as summarized in recent reviews (Berry et al., 2013; Gesta et al., 2007; MacKay and Abizaid 2014) can better inform future mechanistic research in this area.

In summary, this study utilized a data-driven method to objectively elucidate sensitive windows and examined sex differences for the association between prenatal PM_{2.5} and body composition outcomes in early childhood. We found that increased prenatal PM_{2.5} exposure, particularly at early-to-mid pregnancy, may be more strongly associated with increased whole body size in boys, whereas it may be more strongly associated with an indicator of body shape (i.e., WHR) in girls. Advanced statistical methods combined with highly temporally resolved exposure data facilitates the more objective identification of susceptibility windows and enhances the ability to detect associations as well as to identify vulnerable groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AOD	aerosol optical depth
BDLIM	Bayesian distributed lag interaction model
BMI-z	body mass index z-score
CDC	Centers for Disease Control
DLM	distributed lag model
LUR	land-use regression
OS	oxidative stress
PAHs	polyaromatic hydrocarbons
ROS	reactive oxygen species
SES	socioeconomic status
SS	subscapular skinfold
TS	triceps skinfold
WHR	waist-to-hip ratio

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Highlights

- Implementation of a novel data-driven approach to objectively identify sensitive windows of prenatal PM_{2.5} on childhood anthropometry.
- Time-dependent associations and effect modification by sex were found based on different anthropometric indices.
- Understanding such sex difference in temporal associations may provide insights into underlying mechanisms.

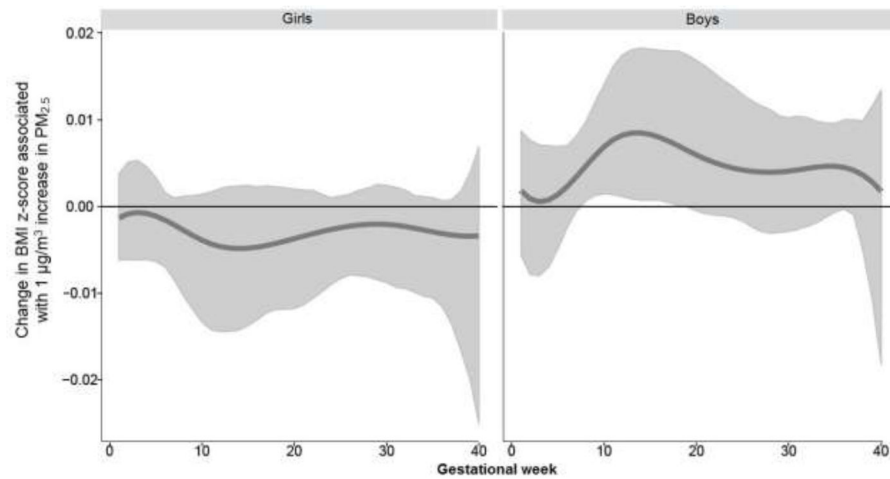


Figure 1. Associations between weekly PM_{2.5} levels over gestation and BMI-z: interaction by sex
 This figure demonstrates the association between PM_{2.5} exposure over pregnancy and BMI z-scores using BDLIM assuming week-specific effects. Models were adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, and child's age at anthropometric measurement. The y-axis represents the change in BMI z-scores corresponding to per µg/m³ increase in PM_{2.5}; the x-axis is gestational age in weeks. Solid lines show the predicted change in BMI z-score. Gray areas indicate 95% confidence intervals (CIs). A sensitive window is identified for the weeks where the estimated pointwise 95% CI (shaded area) does not include zero.

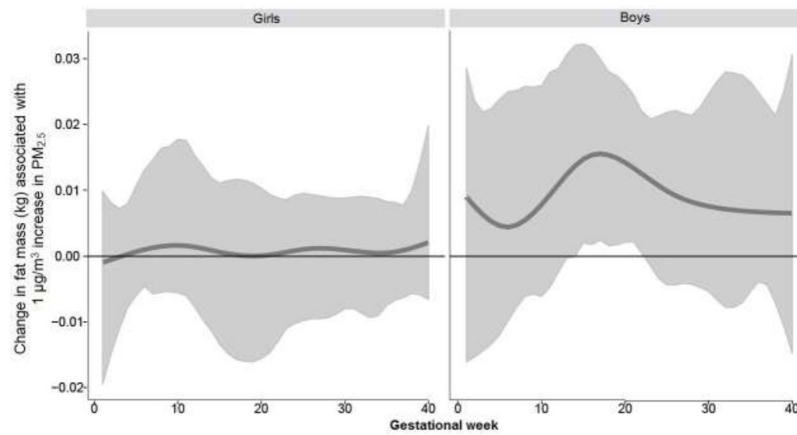


Figure 2. Associations between weekly $PM_{2.5}$ levels over gestation and fat mass: interaction by sex

This figure demonstrates the association between $PM_{2.5}$ exposure over pregnancy and fat mass (kg) using BDLIM assuming week-specific effects. Models were adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, and child's age at anthropometry measurement. The y-axis represents the change in fat mass corresponding to per $\mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$; the x-axis is gestational age in weeks. Solid lines show the predicted change in fat mass. Gray areas indicate 95% confidence intervals (CIs). A sensitive window is identified for the weeks where the estimated pointwise 95% CI (shaded area) does not include zero.

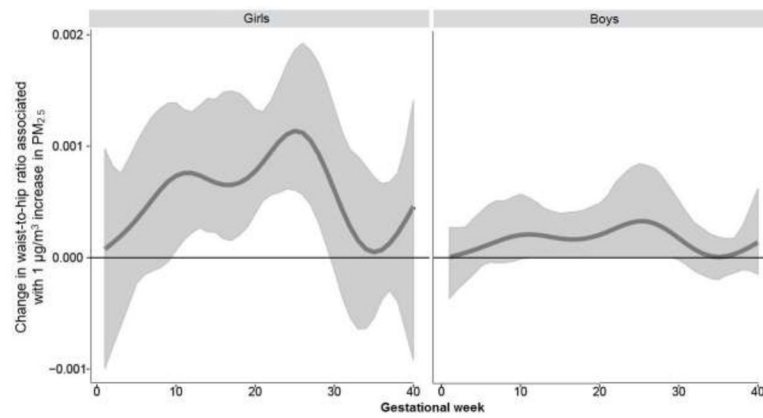


Figure 3. Associations between weekly $PM_{2.5}$ levels over gestation and waist-to-hip ratio: interaction by sex

This figure demonstrates the association between $PM_{2.5}$ exposure over pregnancy and waist-to-hip ratio using BDLIM assuming week-specific effects. Models were adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, and child's age at anthropometric measurement. The y-axis represents the change in waist-to-hip ratio corresponding to per $\mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$; the x-axis is gestational age in weeks. Solid lines show the predicted change in waist-to-hip ratio. Gray areas indicate 95% confidence intervals (CIs). A sensitive window is identified for the weeks where the estimated pointwise 95% CI (shaded area) does not include zero.

Table 1

ACCESS participant characteristics

	All children (n=239)		Girls (n=109)	Boys (n=130)
Race/Ethnicity (n, %)				
Black	61	25.5	30	31
Hispanic	132	55.2	61	71
White/Other	46	19.3	18	28
Maternal education (n, %)				
>12 yrs	81	33.9	40	41
12 yrs	158	66.1	69	89
Maternal smoking status (n, %)				
Never smoked	192	80.3	87	105
Smoked prenatally, but not postnatally	11	4.6	4	7
Did not smoke prenatally, but smoked postnatally	15	6.3	9	6
Smoked both pre- and postnatally	21	8.8	9	12
Maternal age at enrollment (yr; mean, SD)	28.1	5.8	28.7	27.6
Maternal pre-pregnancy BMI (kg/m²; median, IQR)	28.0	25.9–31.2	28.0	26.2–30.7
Child age at anthropometry measure (yr; mean, SD)	4	0.7	4	4
Birth weight for gestational age z-score (mean, SD)	-0.10	1.12	-0.20	1.07

Table 2

Anthropometry measurements and prenatal PM_{2.5} exposure levels by child sex

Variables	All children			Girls			Boys		
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Prenatal PM_{2.5} level (µg/m³)^a	10.7	9.9–11.4	10.8	10.0–11.5	10.6	9.8–11.4			
Body Mass Index (BMI)									
BMI z-score	0.50	-0.27–1.52	0.61	-0.30–1.48	0.44	-0.26–1.53			
Bioimpedance									
Fat mass (kg)	3.0	2.1–3.9	2.1	1.1–3.2	3.2	2.8–4.4			
Fat free mass (kg)	14	13–16	15	14–16	13	12–15			
% body fat (%)	17	13–21	11	6.5–16	19	17–22			
Skin fold									
Tricep skinfold (mm)	9.1	7.8–11.0	9.8	8.4–12.0	8.4	7.4–10.0			
Subscapular skinfold (mm)	6.2	5.2–7.8	6.8	5.6–8.6	5.8	5.0–7.0			
Waist and Hip Circumferences									
Waist circumference (cm)	52	50–56	53	50–57	52	49–55			
Hip circumference (cm)	56	52–59	56	52–60	55	52–59			
Waist-to-hip ratio	0.94	0.90–0.98	0.94	0.90–0.98	0.94	0.91–0.98			

^a Averaged over pregnancy

Estimated cumulative effects of prenatal PM_{2.5} exposure over gestation: accounting for time-varying interaction by sex, sensitive windows, and within-window effects identified by BDLIM^a

Table 3

<i>Anthropometry indices</i>	Girls		Boys	
	Cumulative Effect	95% CI	Cumulative Effect	95% CI
BMI z-score	-0.12	-0.37 0.03	0.21	0.003 0.37
Fat mass (kg)	0.03	-0.29 0.28	0.36	0.12 0.68
Waist-to-hip ratio	0.023	0.01 0.03	0.006	-0.0001 0.01

^aModels were adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, and child's age at anthropometric measurement; corresponding to per µg/m³ increase in PM_{2.5}.