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Postnatal exposure to $PM_{2.5}$ and weight trajectories in early childhood

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Background: Inconsistent evidence has assessed the impact of air pollution exposure on children's growth trajectories. We investigated the role of 90-day average postnatal fine particulate matter ($PM_{2.5}$) exposures by estimating the magnitude of effects at different ages, and the change in child weight trajectory by categories of exposure.

Methods: We obtained weight values from electronic health records at each hospital visit (males = 1859, females = 1601) from birth to 6 years old children recruited into the Boston-based Children's HealthWatch cohort (2009–2014). We applied mixed models, adjusting for individual and maternal confounders using (1) varying-coefficient models allowing for smooth non-linear interaction between age and $PM_{2.5}$, (2) factor-smooth interaction between age and $PM_{2.5}$ quartiles. Additionally, we stratified by sex and low birthweight (LBW) status (≤2500 g).

Results: Using varying-coefficient models, we found that $PM_{2.5}$ significantly modified the association between age and weight in males, with a positive association in children younger than 3 years and a negative association afterwards. In boys, for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ we found a 2.6% increase (95% confidence interval = 0.8, 4.6) in weight at 1 year of age and a −0.6% (95% confidence interval = −3.9, 2.9) at 5 years. We found similar but smaller changes in females, and no differences comparing growth trajectories across quartiles of $PM_{2.5}$. Most of the effects were in LBW children and null for normal birthweight children.

Conclusions: This study suggests that medium-term postnatal $PM_{2.5}$ may modify weight trajectories nonlinearly in young children, and that LBW babies are more susceptible than normal-weight infants.

Keywords: Children's weight trajectories; Fine particulate matter; Low-income families; Postnatal exposure; Varying coefficient models

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Children's HealthWatch (CHW) health- and individual-level data are highly regulated and have IRB and HIPAA administration placed on them by the source institution. Our data use agreements will prohibit us from distributing the data to other parties. To gain access to CHW data, the collaborator must file a request including a proposed research plan to the original institution. Part of the code is in the Supplemental Digital Content (SDC); http://links.lww.com/EE/A166, and the full code will be made available through a request to the corresponding and first authors as well as to the CHW representatives.

SDC *Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.environepidem.com).*

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Introduction

Outdoor air pollution is a well-documented risk factor for human diseases,[1,2] contributing to around 7.6% of global deaths in 2016. Air pollution is also the largest environmental cause of disease and premature death of children worldwide.[3–6] Its harmful effects vary by specific subpopulations, for example by age, sex, genetics, behavior, and socioeconomic conditions, leading to a severe disproportionate disease burden.[6–11]

Children's first years of life are a uniquely sensitive developmental epoch of rapid body and brain growth that establishes the foundation for future physical, socioemotional, and cognitive health. The rapid development that occurs in early childhood enhances children's vulnerability to social and environmental stressors, such as housing instability,[12] temperature extremes,[13] infections,[14] and air pollution exposure.[15] Children

What this study adds

This is the first study to investigate the role of postnatal 90-day average $PM_{2.5}$ exposures in determining sex-specific growth trajectories in early childhood, with the goal to estimate the sensitive time periods when childhood growth may be most affected by postnatal exposures, and the change in child weight trajectory by categories of exposure. In a Boston-based children's cohort from low-income families, using varying coefficient models we found that continuous medium-term $PM_{2.5}$ might lead to increased weight in early ages, with stronger effects in males, and with LBW children especially vulnerable. We also found that $PM_{2.5}$ quartiles do not modify weight trajectories. Identification of time periods during childhood when growth may be most affected by exposures is essential to target measures of prevention.

may, in fact, be more susceptible to air pollution effects because they spend more time outdoors and breathe faster.

Various studies have found a link between prenatal and postnatal ambient particulate matter with an aerodynamic diameter of 2.5 μm ($PM_{2.5}$) and several adverse health outcomes in children, including lower birthweight,[16–18] higher newborn blood pressure,[19–21] asthma risk,[22,23] preterm birth,[24] and weakened lung function[25] among others. While, to our knowledge, no studies have examined postnatal exposure to $PM_{2.5}$ and children's growth trajectories, unhealthy childhood longitudinal weight-related outcomes have been associated with pre- and postnatal air pollution exposure, but results are inconsistent. Two studies found that higher PM_{10} was longitudinally associated with lower weight[26] and lower body mass index (BMI),[27] and others found that increases in NOx[28] and NO_2[29] lead to children's excessive BMI growth. There is a larger evidence base of studies investigating the link between prenatal air pollution exposure and childhood growth trajectories, but again the results are inconsistent.[30–32]

These previous studies have some limitations that should be addressed to appropriately understand if air pollution affects body weight in early childhood. While most prior studies examined the effects of prenatal air pollution on growth trajectories, only a few have focused on postnatal exposure. The studies that examined prenatal exposure assigned the same trimester averages exposure before birth to each longitudinal weight measurement. Similarly, postnatal exposure was assigned mostly based on only one point in time. Because early childhood is a time of rapid change in children's bodies, the strength of the association between air pollution exposure and weight likely changes over different periods of growth, and the effect of exposure on children's weight might vary across childhood. Postnatal exposure measured at each weight/age measurement addresses this issue. In addition, previous studies used exposure measurements obtained from ground monitors, leading to possible exposure misclassification, or using land-use regression models, which provided limited temporal variability in exposure. Finally, several methods have been applied to model growth trajectories as the non-linear relationship between age and weight[33–35]; most used parametric models or linear splines with specified age knots, but no study has used penalized splines, which is a semiparametric regression approach that does not require the investigator to assume a prior shape on the trajectory of growth.

The present study aimed to build on our study[30] in the Children's HealthWatch Boston cohort, where we found that prenatal high $PM_{2.5}$ concentrations may influence weight trajectories in early childhood. Specifically, we evaluated the role of time-varying postnatal 90-day average $PM_{2.5}$ exposure, as estimated by a spatio-temporal exposure model, on sex-specific growth trajectories in early childhood. First, we identified the sensitive time periods when childhood growth may be most affected by postnatal exposures, which is essential to effectively target measures of prevention in young children. To this end, we evaluated the non-linear interaction between age and $PM_{2.5}$ on weight with time-varying coefficient models, after adjusting for growth trajectories. Second, to replicate the results of previously published studies, we assessed the change in child weight trajectory by categories of exposure by estimating an interaction between a smooth effect of age and categorical exposure defined by $PM_{2.5}$ quartiles. We applied these models to all children combined, stratified by sex and by birthweight status.

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Data and methods

Study population

Our study population included, for the years 2009–2014, participants from the Boston site of Children's HealthWatch, an ongoing five-city sentinel surveillance study investigating associations between socioeconomic hardships and the health of young children and their caregivers (https://childrenshealthwatch.org/). Trained research assistants administered surveys to caregiver-child dyads seeking medical care in the emergency department (ED) at Boston Medical Center.[36] Eligibility criteria included child age ≤48 months; residency in Massachusetts; caregiver ability to speak English or Spanish; respondent living in the child's household; and consenting to be interviewed.[36] Caregivers of critically ill or injured children were not approached, nor were those interviewed within the previous six months. Institutional review board approval was obtained from Boston University Medical Campus Institutional review board before data collection and renewed annually.

For this study, we included information from the Children's HealthWatch survey on history of breastfeeding and caregiver's characteristics. Maternal variables consisted of age (years), self-identified race/ethnicity (Hispanic, Black non-Hispanic, White non-Hispanic, other/multiple races), BMI (kg/m^2), nativity (US born or Immigrant), educational attainment (less than high school, high school or General Educational Development graduate, postsecondary education), smoking status in the last 5 years (yes/no), and household food security status.[37–39]

In addition, we matched the Children's HealthWatch survey with children's electronic health records (EHR), based on medical record number, date of interview, sex, and date of birth. For each visit from the EHR, we extracted the child's residential address, date of birth, age (months), sex, weight (kilograms), birthweight (grams), gestational age (weeks), and visit type (inpatient, outpatient, ED). EHR missing values for gestational age and birthweight were imputed using the Children's HealthWatch survey data. We did not have adequate measurements of height, as heights are sometimes not recorded in the EHR or are often inaccurate due to time constraints, effort, or equipment needed to adequately measure height in the clinical setting. To mirror clinical usage, we also computed the weight-for-age z-scores as applied previously by Gamliel et al.,[40] and previously used in Children HealthWatch publications.

Exposure

We used concentrations of $PM_{2.5}$ obtained from a spatio-temporal hybrid model[41] already applied in similar settings[42,43] that provides daily exposure estimates at a spatial resolution of 1 km^2 grid. This model incorporates satellite Aerosol Optical Depth data, ground monitors, spatial predictors, such as population and traffic density, as well as temporal predictors, such as meteorological data. Model performance was validated by 10-fold cross-validation, which indicated negligible bias (slope of observed versus predicted observations = 0.99) and high spatio-temporal accuracy (out-of-sample $R^2 = 0.87$)[41] of the resulting exposure estimates.

We geocoded children's addresses obtained from the EHR (96.2%) to parcel MASSGIS 2019 and the remaining addresses

to ArcGIS Online World Geocoding Service. Of all addresses listed in the EHR, we excluded 0.15% geocoded as Locality, PostLoc, and Postal level, and 1% which did not match to any address. We calculated $PM_{2.5}$ moving average over a 90-day period before each visit and assigned it to the relevant geocoded current address at each visit.

Sample selection

After merging data from the Children's HealthWatch survey, EHR and $PM_{2.5}$, our dataset included 4,755 caregiver-child dyads with a total of 120,728 child EHR visits. Because we hypothesized that exposure-related variation in weight during the first months after birth is likely due to prenatal rather than postnatal exposure, we excluded child EHR visits within the first 6 months of age (n = 28,189). Since our analyses focused on early childhood, we also excluded child EHR visits after 72 months of age (n = 6,695). We then excluded observations with: missing weights, implausible weight values based on the CDC definition,[44] missing data for other covariates, and 0.04% of hospital visits with $PM_{2.5}$ above 30 $\mu g/m^3$, leaving a final dataset with 48,381 child EHR visits corresponding to 3,460 mother-child dyads.

Statistical analyses

We applied generalized additive mixed models to investigate the impact of time-varying 90-day average $PM_{2.5}$ on weight in early childhood through two main model specifications. First, to identify the sensitive time periods when childhood growth may be most affected by postnatal exposures, we applied a varying coefficient model to evaluate the nonlinear interaction between age and $PM_{2.5}$, adjusting for growth trajectories. Second, to identify whether exposure to different levels of $PM_{2.5}$ modifies weight trajectories, we applied a factor-smooth interaction model, which included an interaction between a potentially nonlinear effect of age and categories of $PM_{2.5}$ on childhood weight measurements. We applied each of these models to all children combined and separately for males and females because of prior evidence of sex differences in body composition, growth patterns, and air pollution susceptibility.[8,45–47] In addition, we ran stratified analyses by low birthweight (LBW, birthweight <2500 g) and normal birthweight (NBW, birthweight ≥2500 g), which previous studies suggested to be a potential effect modifier of the relationship between air pollution and growth trajectories.[26,30,48]

In both varying coefficient models and factor-smooth interaction models, we log-transformed the outcome measurements, weight (in kg), because of the right-skewed nature of the original distribution, resulting in a normal distribution of the residuals. All models included a random intercept for each child and a random slope for child's age, to account for longitudinal correlation among repeated weight measurements taken on the same child and to capture each child's deviation from the average trajectory.[49,50]

We selected the covariates a priori based on the literature on children's weight-related measures shown to be biologically related to childhood postnatal weight, or as confounders of the association between weight and $PM_{2.5}$.[18,26,30] In all models, we adjusted for maternal age, BMI, educational attainment, race/ethnicity, nativity, smoking, and child's gestational age. We also included the number of visits for each child as we hypothesized that the higher the number of visits the worse the child's health condition might be, which in turn could affect their growth trajectory. To adjust for seasonality, we included sine and cosine terms of date of birth. We used a penalized spline term to model the non-linear relationship between the continuous covariates and the outcome.[51] We modeled the weight trajectory with a penalized spline of child's age, which flexibly fit the non-linear relationship between age and weight.

Varying coefficient model

To estimate the impact of $PM_{2.5}$ at each age, we included in the model a non-linear interaction between the smooth function of age and linear term for $PM_{2.5}$, with a varying coefficient term. The model is as follows:

$$\log(\text{weight}) = b_{00} + b_{01*}(\text{age}) + f(\text{age}) + \beta(\text{age}) * PM_{2.5} + \text{covariates},$$

where the b_{00} and b_{01} are the random intercept and age slope for each child, respectively, f(age) is the penalized cubic spline of age representing the average potentially non-linear growth trajectory across all children in the analysis; $\beta(\text{age}) \times PM_{2.5}$ is the varying coefficient term that represents the non-linear interaction between $PM_{2.5}$ and age, as a function of age. The coefficient β(age) can be interpreted as the effect of $PM_{2.5}$ on weight at each specific value of age, given background nonlinear growth.

From this model, we extracted the coefficients from the varying coefficient term to obtain estimates and standard errors of the association of $PM_{2.5}$ on weight at 12, 24, 36, 48, and 60 months of age. We report the results as percent change in weight for 10 $\mu g/m^3$ increase in $PM_{2.5}$.

We tested the global significance of the interaction age- $PM_{2.5}$ using global *P* values from the varying coefficient models, with the null hypothesis being that the non-linear varying coefficient is 0 across all ages (H_0: $\beta(\text{age}) = 0$). We set the overall significance level to $\alpha = 0.05$ for all the analyses and estimated 95% confidence intervals (CIs) for each effect estimate.

Factor-smooth interaction model

We then examined whether weight trajectory varied according to categories of $PM_{2.5}$ exposure as defined by quartiles of the exposure distribution by including in the model an interaction term between the weight trajectory represented by the spline of age and $PM_{2.5}$ quartiles. In the model above we replaced $f(\text{age}) + \beta(\text{age}) \times PM_{2.5}$ with $f(\text{age}) \times PM_{2.5,k}$, where k = 1,2,3,4 represent $PM_{2.5}$ quartiles. The output of this model produces weight trajectories for each $PM_{2.5}$ quartile represented by the smooth function of the relationship between age and the logarithm of weight. These curves can be interpreted as the weight trajectory for the subjects exposed to each category of $PM_{2.5}$ concentration during the entire follow-up time.

All the analyses were performed using the mgcv package in R software (version 3.6.1). Because of the computational requirements of the models, we used bam which is an implementation of GAM for large datasets. The code for the models is reported in the Supplemental Digital Content, section 1; http://links.lww.com/EE/A166.

Sensitivity analyses

Because no previous study has shown a clear age threshold to delineate the separated effects of pre- and postnatal air pollution on weight, we repeated all the analyses using 3 and 12 months as follow-up starting points instead of 6 months. We used weight-for-age z-scores as an outcome to validate our findings with a measure typically used in clinical settings. Previous studies found an association between prenatal $PM_{2.5}$ and child weight or obesity. Therefore, we also ran the models for all children adjusting for prenatal $PM_{2.5}$ averaged over the full pregnancy period. We also adjusted for household food security in the model.

Finally, for the models using categories of $PM_{2.5}$, to compare our results with previously published studies, we ran additional analyses where instead of using a penalized spline for age, we used either a truncated polynomial or a natural cubic spline. In these models, we placed internal knots at 12 and 36 months.

(See Supplemental Digital Content, section 2; http://links.lww.com/EE/A166 for the R code).

Results

Table 1 details the study characteristics for both mothers and children. Both sexes were evenly represented between the 3460 children (males = 1859, females = 1601). Approximately 90% of the children were born to either a Black non-Hispanic or a Hispanic mother, 76% were breastfed and 88% were at healthy weight at birth. Mothers' average age was 29 years, and more than 30% reported a BMI that corresponds with obesity (BMI > 30 kg/m^2). Approximately 70% never smoked in the last 5 years and 77% obtained at least a high school diploma. Gestational age and birthweight were highly correlated (around 80%). Children had most of their visits before 40 months of age (third quartile—42 months). The number of visits varied markedly among children with the median number at 50, ranging between 2 and 400, and interquartile range (IQR) of 57. The median time difference between visits was 25 days with an IQR of 71 days. More than 67% of visits were recorded as outpatient, 30% at the ED and only 3% were inpatient. The median concentration of the 90-day average $PM_{2.5}$ was 8.4 μg/m^3 with an IQR of 1.7 μg/m^3, below the daily National Ambient Air Quality Standard.

Varying coefficient model results

Figure 1 presents estimates from the varying coefficient model for all children combined and by sex. The plots depict the relationship between weight and $PM_{2.5}$ as a smooth function of age, and each point on the curve represent the percent change in weight per 10 μg/m^3 increase in the 90-day average $PM_{2.5}$ at each age. Areas in which the CIs of the curve do not contain the zero line indicate the intervals of age with a significant association between weight and $PM_{2.5}$. Table 2 presents the percent change in weight for a 10 μg/m^3 increase in the 90-day average of $PM_{2.5}$ for selected ages, for boys and girls, and by birthweight status, obtained from the varying coefficient estimates plotted in Figures 1 and 2.

Across all children combined, Figure 1 shows that the non-linear relationship between weight and $PM_{2.5}$ is decreasing, with a positive association between weight and $PM_{2.5}$ in children less than 2 years old. The relationship became negative and nonsignificant after 30 months. As shown in Table 2, at 12 months, we found a 1.7% increase (95% CI = 1.0, 2.5) in weight for 10 μg/m^3 increase in $PM_{2.5}$, while at age 48 months, we found a -0.54% increase (95% CI = −1.67, 0.61) in weight. The plots show a similar descending patterns for both boys and girls (Figure 1). In boys, we found that $PM_{2.5}$ significantly modified the association between weight and age (*P*-value for interaction males <0.001; females 0.16). Specifically, we found a positive association between weight and $PM_{2.5}$ in children less than 2 years old, whereas in children older than 2 years, we found a nonsignificant negative association between these variables. For example, we found a 2.6% increase (95% CI = 0.8, 4.6) in weight at 1 year of age and a −0.6% (95% CI = −3.9, 2.9) at age 5 associated with a 10 μg/m^3 increase in $PM_{2.5}$ (Table 2). We found a similar pattern but with smaller associations in girls, with a suggestion of a positive association between weight and $PM_{2.5}$ at ages less than 2 years, becoming negative afterwards.

When we stratified by birthweight, we found that most of the association is attributable to LBW children (Figure 2), with a decreasing trend that mirrors the unstratified analysis, although

Table 1.

Characteristics of 3460 caregiver-child dyads, weight measurements and exposure by children's sex in the Children's HealthWatch cohort, Boston (2009–2014).

	All children		Males		Females	
	N (%)	Mean (SD)	N (%)	Mean (SD)	N(%)	Mean (SD)
Maternal characteristics						
Age (years)		28.8 (6.6)		28.8 (6.6)		28.8 (6.7)
BMI (kg/m^2)		28.5 (7.1)		28.6 (7.4)		28.2 (6.7)
Maternal nativity						
US born	2172 (62.8)		1167 (62.8)		1005 (62.8)	
Immigrant	1288 (37.2)		692 (37.2)		596 (37.2)	
Maternal race/ethnicity						
Black non-Hispanic	2058 (59.5)		1113 (59.9)		945 (59.0)	
Hispanic	97 (28.3)		522 (28.1)		457 (28.5)	
White non-Hispanic	338 (9.8)		182 (9.8)		156 (9.7)	
Other/multiple races	85 (2.4)		42 (2.3)		43 (2.7)	
Education						
College graduate/Master's/Tech School	1622 (46.9)		876 (47.1)		746 (46.6)	
High school graduate or General Educational Development	696 (20.1)		379 (20.4)		317 (19.8)	
Some high school or less	1142 (33.0)		604 (32.5)		538 (33.6)	
Ever smoked in the last 5 years						
Yes	953 (27.5)		502 (27.0)		451 (28.2)	
No	2507 (72.5)		1357 (73.0)		1150 (71.8)	
Child characteristics						
Weight (kg)		13.9 (5.1)		14.1 (4.9)		13.5 (5.3)
Gestational age (weeks)		38.0 (3.2)		37.8 (3.2)		38.2 (3.0)
Breastfeeding						
Yes	2641 (76.3)		1419 (76.3)		1222 (76.3)	
No	819 (23.7)		440 (23.7)		23.7 (23.7)	
Food security						
Yes	2339 (67.6)		1277 (68.7)		1062 (66.3)	
No	1121 (32.4)		582 (31.3)		539 (33.7)	
Birthweight status						
≤2500 g	439 (12.7)		223 (12.0)		216 (13.5)	
>2500 g	3021 (87.3)		1636 (88.0)		1385 (86.5)	
Exposure						
PM2.5—90 days average		8.5 (1.4)		8.5 (1.4)		8.5 (1.4)

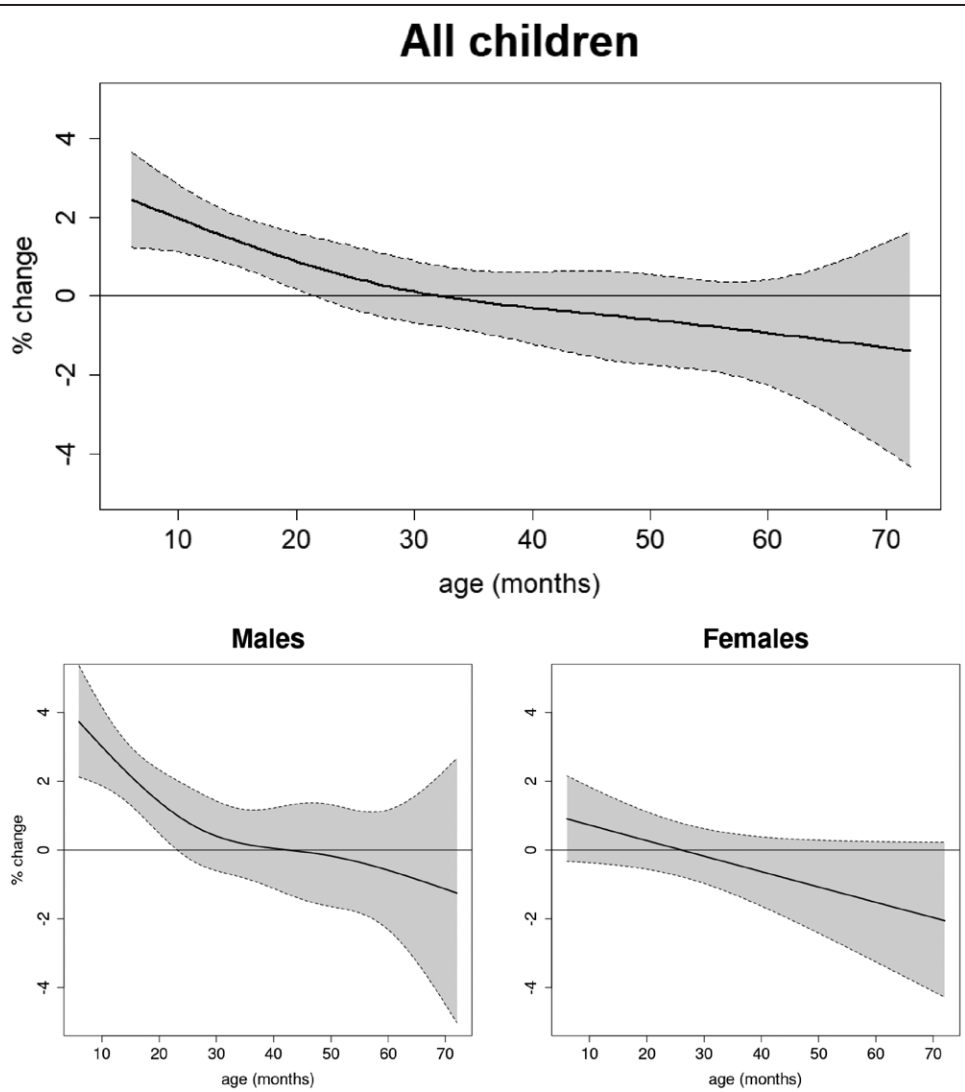

Figure 1. Associations between time-varying 90-day $PM_{2.5}$ averages and children's weight as smooth function of age estimated from the time-varying coefficient model (solid line) for all children combined and by sex. Panels depict the smoothing function derived from the varying-coefficient term representing the interactions between the concentrations of $PM_{2.5}$ and age. Estimates are computed as % change in weight for an increase of 10 μg/m^3 of $PM_{2.5}$ concentrations at each value of age. Confidence bands (dashed lines) represent the 95% pointwise CI for the change in weight. Areas in which both dashed bands (upper and lower) fall above or below the zero line indicate intervals of age values with a significant association between $PM_{2.5}$ exposure and weight.

more clearly for boys. The results are prevalently null for normal birthweight boys and girls. In boys, in the first 24 months of life, $PM_{2.5}$ is positively associated with weight which became negative after 60 months of age. The shape of the relationship differed in the LBW girls with a negative association that became significant around 48 months of age. For example, in boys we found a 7.98% (95% Cl: 5.67, 10.36) increase in weight at 12 months, and a 0.68% (95% Cl: –2.42, 3.87) increase in weight at 48 months.

Factor-smooth interaction model results

In Figure 3, we present the weight trajectories by quartiles of postnatal $PM_{2.5}$ exposure, estimated with penalized spline terms, for all children combined and stratified by sex. We did not find differences in growth trajectories by different levels of $PM_{2.5}$ for all children combined and by sex.

When in addition we stratified by birthweight status (Figure 4), we found differences among the weight trajectories and $PM_{2.5}$ levels only among LBW children. In the LBW subgroup, we found small differences in the trajectories after 60 months of age. The direction of the association was different for males and females for concentrations above the third quartile (>9.3 μg/m^3).

In sensitivity analyses, we found that changing the starting point for the follow-up from 6 months to 3 or 12 months did not modify the results. Similarly, neither the inclusion of household food security nor the specification of an autocorrelation structure altered the associations between $PM_{2.5}$ and weight (data not shown). Using weight-for-age z-scores as an outcome did not change the results of the varying coefficient model for all children combined and by sex (Supplemental Digital Content eFigure 1; http://links.lww.com/EE/A166). Similarly, adjusting for prenatal $PM_{2.5}$ in the models did not change the results (Supplemental Digital Content eFigure 2; http://links.lww.com/EE/A166).

Finally, we found that the models for the weight trajectories specified using the truncated polynomial or natural cubic splines were consistent with our main models with penalized splines (Supplemental Digital Content eFigures 3 and 4; http://links.lww.com/EE/A166).

Discussion

To the best of our knowledge, this is the first study to explore the role of time-varying postnatal $PM_{2.5}$ as an effect modifier on sex-specific growth trajectories and to examine the non-linear

Table 2.

Percent change in weight for 10 μg/m³ increase in 90 days average $PM_{2.5}$ for selected ages during growth, predicted from the varying coefficient model, in the Children's HealthWatch cohort, Boston (2009–2014).

	Overall	Birtweight ≤ 2500	Birtweight > 2500
	% change (95% CI)	% change (95% CI)	% change (95% CI)
All children			
At 12 months	1.74 (1.00, 2.47)	3.14 (1.50, 4.81)	0.82 (0.09, 1.56)
At 24 months	0.53(–0.26, 1.32)	1.11 (–0.13, 2.36)	0.49 (–0.07, 1.04)
At 36 months	–0.16(–0.95, 0.63)	–0.89 (–2.26, 0.51)	0.15 (–0.47, 0.78)
At 48 months	–0.54(–1.67, 0.61)	–2.84 (–4.74, –0.90)	–0.18 (–1.07, 0.72)
At 60 months	–0.94(–2.26, 0.41)	–4.76 (–7.31, –2.14)	–0.51 (–1.74, 0.73)
Males			
At 12 months	2.65 (1.68, 3.63)	7.98 (5.67, 10.36)	0.73 (–0.24, 1.71)
At 24 months	0.90 (–0.11, 1.94)	–0.53 (–2.90, 1.91)	0.58 (–0.15, 1.31)
At 36 months	0.14 (–0.87, 1.16)	0.02 (–2.39, 2.49)	0.43 (–0.40, 1.26)
At 48 months	–0.12 (–1.57, 1.36)	0.68 (–2.42, 3.87)	0.28 (–0.90, 1.47)
At 60 months	–0.59 (–2.32, 1.17)	–3.49 (–6.94, 0.09)	0.13 (–1.50, 1.78)
Females			
At 12 months	0.63 (–0.39, 1.68)	–2.03 (–4.74, 0.77)	1.0 (–0.17, 2.20)
At 24 months	0.09 (–0.69, 0.88)	0.77 (–2.45, 4.10)	–0.08 (–1.38, 1.24)
At 36 months	–0.45 (–1.34, 0.46)	1.58 (–5.30, 2.28)	–0.09 (–1.40, 1.23)
At 48 months	–0.98 (–2.25, 0.30)	–5.0 (–9.23, –0.58)	–0.02 (–1.90, 1.90)
At 60 months	–1.52 (–3.25, 0.25)	–8.15 (–13.28, –2.72)	–1.15 (–3.33, 1.07)

Models adjusted for sine and cosine of date of birth, type of visit, number of visits, gestational age, mother's age, nativity, BMI, education attainment, race/ethnicity, and smoking status in the last 5 years.

interaction between age and postnatal $PM_{2.5}$ on early childhood weight. In a Boston cohort of children from families with low income, we found that the impact of exposure decreases with age, mostly in males, with a positive association in children younger than 2 years old, and reversing direction as children age, turning negative around 2–3 years of age. We also found that high and low levels of $PM_{2.5}$ do not modify weight trajectories. In addition, we found that most of the identified association was attributable to LBW status, and sex differences in the shape of the effect.

While the results from the two models may seem contradictory, in fact they investigate the effect of $PM_{2.5}$ on children's growth from two different angles. The nonlinear interaction in the varying coefficient model specifically shows how weight varies with continuous $PM_{2.5}$ concentration at each age, therefore indicating during which periods in early life the child's body is more affected by pollution. The second model, which has been previously applied in the literature in relation to prenatal exposure, presents instead how child weight trajectories change for different categories of the exposure. This latter model is less flexible because it categorizes pollution, reducing the variability of the continuous exposure to four categories.

No previous study examined the nonlinear interaction between $PM_{2.5}$ and age on childhood weight using varying coefficient models. This approach, which includes an interaction term between two continuous variables, flexibly allows estimation of the magnitude of the impact of $PM_{2.5}$ at each age, and therefore identification of the time periods during childhood when growth may be most affected by postnatal exposures. Thus, there are no other studies that are directly comparable to ours. Nevertheless, a few studies have investigated longitudinal child weight measurements as a measure of growth using time-varying exposure. A Korean cohort of children[26] found a negative association between time-varying postnatal exposure to PM_{10} measured from monitoring stations and children's weight. Similar to our results, they found greater vulnerability in LBW children. The PM_{10} concentrations in this study were substantially higher than in our study. Other studies that examined longitudinal growth used different outcomes (such as BMI or BMI z-score) in older cohorts,[52] or used different exposures such as NO_2[29] and annual average daily traffic.[28,53] Similar to our study these studies found increases in weight in males compared to females.[52] In these studies, pollution was measured once during the follow-up, while our continuous postnatal exposure allowed us to look at air pollution effects throughout childhood and not just at a point in time, leading to a better understanding of the effects of air pollution on growth by age.

This is also the first study to examine postnatal $PM_{2.5}$ as an effect modifier of age on childhood weight and is therefore not directly comparable to other studies. While we did not find differences in growth trajectories by quartiles of postnatal $PM_{2.5}$ exposure, in our previous investigation using Children's HealthWatch data prenatal $PM_{2.5}$ and growth trajectories,[30] we found differences in childhood weight trajectories between levels of prenatal $PM_{2.5}$ exposure. This different finding could be due to the different impact of prenatal versus postnatal time-varying exposures. Similarly, we found that these associations were different by sex and by LBW status. Other studies assessing prenatal effects on childhood growth found null,[31] negative,[32] and positive[54] effects. In line with our findings, some of these studies[26,30,48] found differences by sex, with stronger effects in males compared to females.

Inhalation of PM pollution before birth was found to adversely affect child weight by increasing inflammatory potential of fetal adipose tissue,[55–57] which may prime children for greater weight or adiposity later in life.[58,59] Toxicological studies, in fact, point to the inflammatory effects of air pollution,[60] suggesting that PM concentrations may increase adiposity as well as lead to metabolic dysfunctions,[61] and that exposure to particulate matter may induce downregulation of brown adipose genes and upregulation of white adipose genes, suggesting a path for obesity.[62,63]

Possible differences by sex were previously highlighted in epidemiological settings[48] and can be explained by biological sex differences in body composition and growth patterns, and clear sex differences in the distribution of adiposity.[47] Gender-specific differences may also be due to social and cultural differences in the ways in which males and females interact with their physical and social environments.[64]

We also found differences by birthweight status, with most of the effect in LBW children. LBW is a leading cause for perinatal morbidity and mortality[65–67] and is a known risk factor for neurological and developmental adverse outcomes in childhood and adulthood.[68,69] Several studies found an association between air pollution and LBW.[16,70–73] Our rate of LBW is higher than the national average.[74] However, given that we have a sample that includes predominantly women of color,

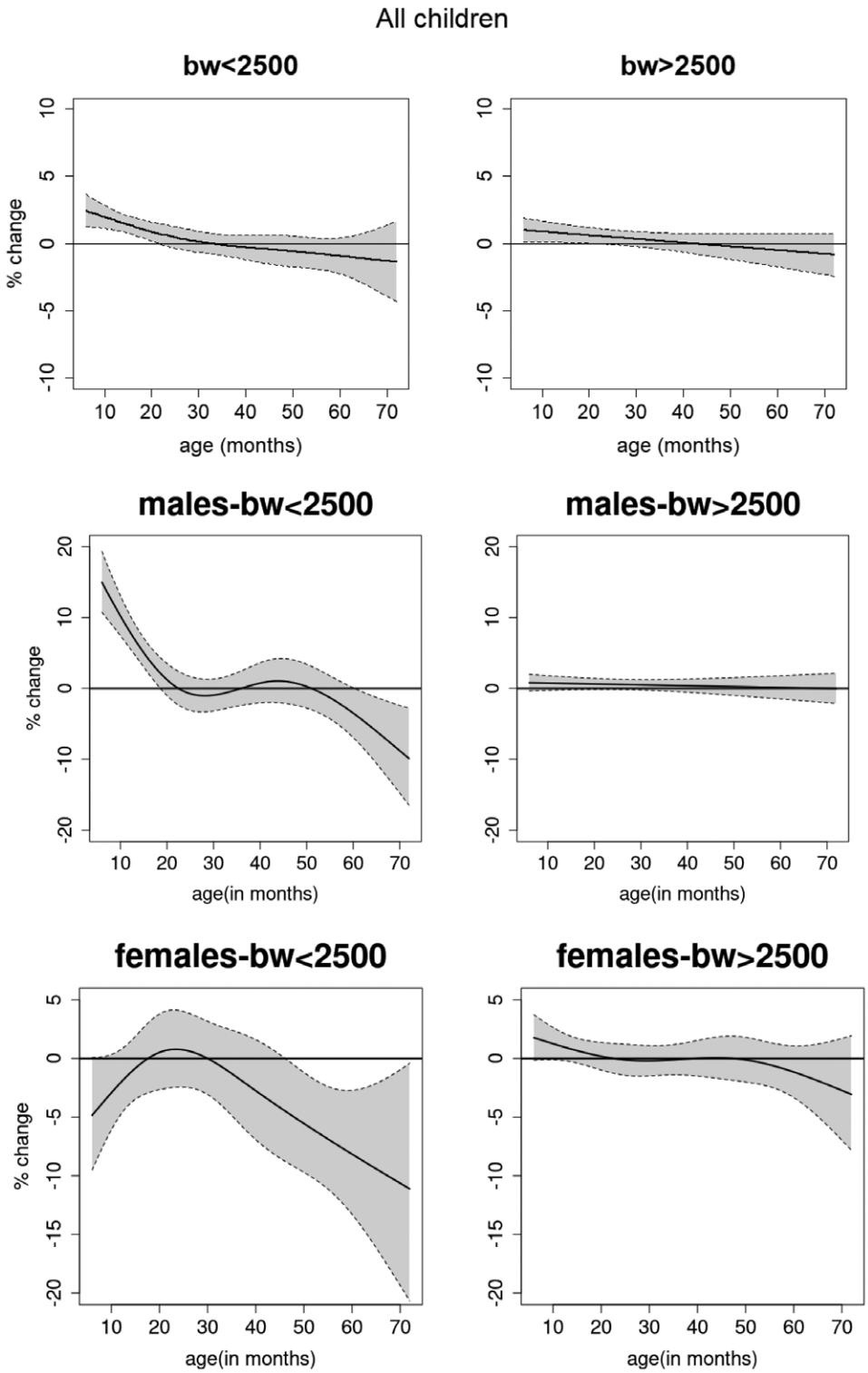

Figure 2. Associations between time-varying 90 days $PM_{2.5}$ averages and children's weight for all children combined and by sex as smooth function of age estimated from the time-varying coefficient model (solid line) by birthweight status (bw). Estimates are computed as % change in weight for an increase of 10 μg/m^3 of $PM_{2.5}$ concentrations at each value of age. Confidence bands (dashed lines) represent the 95% pointwise CI for the change in weight. Areas in which both dashed bands (upper and lower) fall above or below the zero line indicate intervals of age values with a significant association between $PM_{2.5}$ exposure and weight.

the rates reflect the higher LBW rates in those groups, in turn reflecting societal stressors that trigger more LBW.[75] No other study examined the sensitive time periods when childhood growth may be most affected by postnatal exposures, and the change in child weight trajectory by categories of exposure by birthweight status.

Our study has some limitations. There is potential for selection bias, as participants were selected from a pool of caregivers of young children seeking health care in a hospital ED. Children identified in EDs may present worse overall health. Being from families with lower incomes, children may be more vulnerable to the negative effects of $PM_{2.5}$ exposures. Reporting bias may

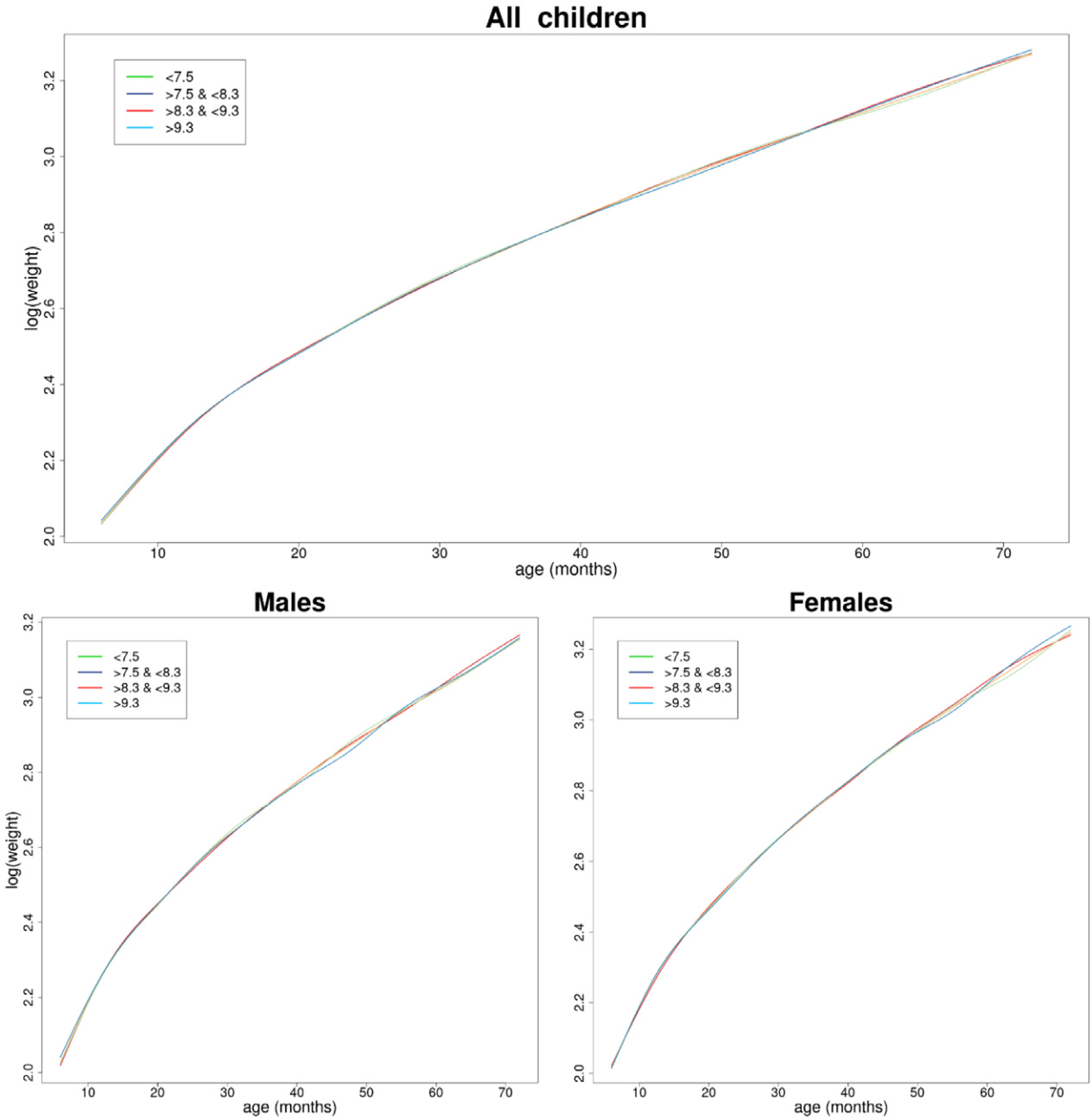

Figure 3. Predicted weight trajectories from birth to 72 months of age (6 years) by quartiles of 90-day average $PM_{2.5}$ for all children combined and for males and females. Weight trajectories were modeled using penalized cubic splines; the models were adjusted for sine and cosine of date of birth, type of visit, number of visits, gestational age, and mother's characteristics, which is age, nativity, BMI, education attainment, race/ethnicity and smoking status in the last 5 years.

also occur if caregivers refrain from reporting the true extent of problems, but EHR data are available for external validation and reporting is unlikely to be differential based on exposures. The use of weight in kilograms as an outcome does not allow one to draw conclusions on possible effects on overall children's health. In addition, weight measurements might be incorrectly measured, resulting in nondifferential outcome misclassification. Our study population includes prevalently low-income, Black non-Hispanic or Hispanic mothers, therefore our results may not be generalizable to the US population age 0–6 years, though reflective of families of color with low incomes. While we focused on the 90-day average $PM_{2.5}$ exposure, there is no agreement in the literature regarding which exposure window is most important to understand the association between postnatal $PM_{2.5}$ and child growth. Future studies should examine which time window(s) is most relevant. Finally, despite the use of medium-term exposure being original, it might result in underestimation of the impact compared to the long-term effects often assessed in the previous literature.

This study's strengths include its focus on a large, sentinel, racially and ethnically diverse sample of families with a difficult-to-reach population of young children who have access to health care. The sentinel sample is a strength as a dynamic form of data collection designed to signal early trends and identify and monitor policy effects and disease burdens before they become widely prevalent, allowing timely interventions to be developed. In addition, because we used highly spatio-temporally resolved exposure linked to each participant's address at each visit we may have reduced the impact of exposure misclassification. The linkage with the EHR provided us with a large sample size with 3,460 children each with multiple measurements. Finally, we applied modern statistical methods suitable

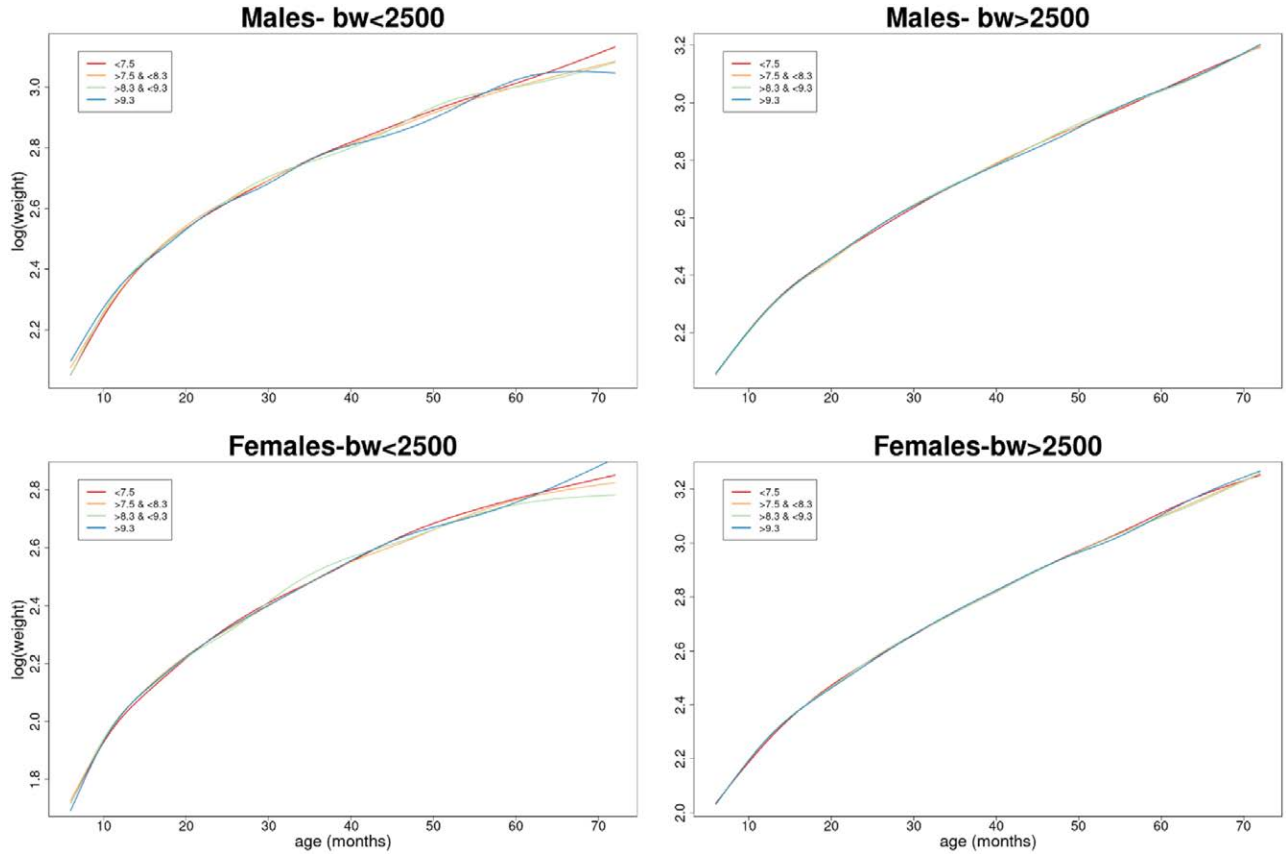

Figure 4. Predicted weight trajectories from birth to 72 months of age (6 years) by quartiles of 90-day average $PM_{2.5}$ for males and females and by birthweight status (bw). Weight trajectories were modeled using penalized cubic splines; the models were adjusted for sine and cosine of date of birth, type of visit, number of visits, gestational age, and mother's characteristics, which is age, nativity, BMI, education, race/ethnicity, and smoking status in the last 5 years.

for studying longitudinal cohorts with heterogeneity in the number of measurements and allowing for complex model terms. The application of generalized additive mixed models is advantageous because it allows us to flexibly model growth trajectories. To check for the consistency of our growth trajectories, we found similar results using two different specifications of the growth curves (truncated polynomial and natural cubic spline) that have been previously used in the literature. These functions were shown to have a greater predictive performance for growth in children with respect to simpler linear splines.[33]

In conclusion, our study extends the literature by focusing on the impact of $PM_{2.5}$ at each age of early childhood, pointing to the detrimental effects of air pollution on childhood growth. The joint investigation of growth trajectory and time-varying $PM_{2.5}$ exposure allowed us to identify the time periods during which child's growth is more susceptible to the impact of pollution exposure. Our findings suggest that in the first two years of life, medium-term $PM_{2.5}$ exposure may lead to increased weight, with stronger effects in males, and with most of the effect in LBW children. These results are relevant to low-income communities of color. Further studies are needed to replicate our findings in other geographies and nationally representative study populations. Future research should focus on other factors that either independently or in synergy with air pollution affect young children's growth to understand the implications of early exposure and possibly make the connection with lasting effects on health risks at older ages. Identifying these factors will aid in designing policies and interventions that can best support optimal child growth.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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