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Prenatal Ambient Particulate Matter Exposure and Longitudinal Weight Growth Trajectories in Early Childhood

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Abstract: Air pollution exposure during pregnancy has been associated with impaired fetal growth and postnatal weight gain, but few studies have examined the effect on weight growth trajectories. We examine the association between validated 1 km^2 resolution particulate matter (PM$_{2.5}$) concentrations, averaged over pregnancy, and sex-specific growth trajectories from birth to age six of participants in the Boston-based Children's HealthWatch cohort (4797 participants, 84,283 measures). We compared weight trajectories, predicted using polynomial splines in mixed models, between prenatal PM$_{2.5}$ above or below the median (9.5 μg/m^3), and examined birth weight as an effect modifier. Females exposed to average prenatal PM$_{2.5} \geq 9.5$ μg/m^3 had higher weights compared to females exposed to < 9.5 μg/m^3 throughout the study period (0.16 kg at 24 months, 0.61 kg at 60 months). In males, higher prenatal PM$_{2.5}$ exposure was associated with significantly lower weights after 24 months of age, with differences increasing with time (−0.17 at 24 months, −0.72 kg at 60 months). Associations were more pronounced among low birth weight (<2500 g) females, but did not differ by birth weight status in males. Our findings demonstrate the complex association between air pollution exposures and childhood weight trajectories and emphasize the importance of sex-stratified analyses.

Keywords: air pollution; PM$_{2.5}$; weight trajectories; in utero exposures; growth; childhood

1. Introduction

Evidence is accumulating that weight growth trajectories in utero and during early postnatal periods are predictive of childhood overweight and obesity [1,2]. Investigating when the onset of childhood overweight and obesity occurs is of interest to understand the etiology of childhood and adult obesity and to identify critical periods for intervention [2]. Early-life overweight and obesity are associated with a range of chronic adverse health outcomes later in life, such as type 2 diabetes,

coronary heart disease [3], and hypertension [4–8]. Although factors such as genetic susceptibility and nutrition are associated with overweight and obesity [9–11], the rapid rise of obesity implicates environmental risk factors as contributors to this trend [12]. Specific early-childhood growth trajectory phenotypes, such as the "thrifty phenotype" whereby catch-up growth follows fetal growth restriction, have been linked to adverse cardiometabolic outcomes in adulthood [13,14].

The vast majority of epidemiological studies to date associating prenatal ambient particulate matter with an aerodynamic diameter of 2.5 microns ($PM_{2.5}$) and weight have focused almost exclusively on weight outcomes (birth weight, raw weight, body mass index (BMI), adiposity) measured cross-sectionally [15,16]. Modelling weight as a longitudinal outcome—growth trajectories—is a more informative measure than weight modelled as a cross-sectional outcome to understand steps on the causal pathway between early-life air pollution exposure and morbidities later in life. Few studies have investigated the link between prenatal ambient air pollution exposure and infant and early-childhood growth trajectories [17–22].

Using electronic health records (EHRs) and surveys administered to obtain detailed maternal and child demographic information, we investigated the association between prenatal $PM_{2.5}$ exposure and weight growth trajectories from birth to age six years in the Boston-based Children's HealthWatch (CHW) cohort. We assessed exposure using concentrations from spatially and temporally resolved $PM_{2.5}$ predictions at 1 km^2 resolution at maternal residence. Based on previous evidence associating prenatal $PM_{2.5}$ and traffic exposure with low birth weight (LBW), we hypothesize a significant association between prenatal $PM_{2.5}$ exposures and weight growth rates in our study population.

2. Materials and Methods

2.1. Study Population

We identified the study population from participants who enrolled in the CHW at the Boston Medical Center between 1 January 2008 and 31 December 2015. The CHW is an ongoing, sentinel surveillance study that gathers clinical and interview data from primary care sites or emergency department (ED) visits [23]. Institutional review board (IRB) approval (protocol number H-34069) was obtained from Boston University Medical Campus IRB prior to data collection and participants provided informed consent.

At primary care or ED visits, trained CHW interviewers surveyed caregivers accompanying children younger than 48 months in a private setting. The survey covers multiple domains, including demographic and socioeconomic characteristics, breastfeeding practices, smoking status, child health status, and information about material hardship—including housing, food, and energy insecurity. Respondents were excluded if the interviewee was not the primary caregiver, if they did not speak English or Spanish, were not knowledgeable about the child's household, had been interviewed previously that year, lived out of state, or did not consent to participate. Caregivers of critically ill or injured children were not approached.

2.2. Linking EHR and CHW Survey Data

As shown in Figure 1 and Figure S1, we linked CHW survey data to EHRs and to $PM_{2.5}$ predictions. We matched CHW surveys to the EHR based on date of the child's CHW interview, gender, date of birth, and medical record number. EHR data coverage included births until 31 December 2015, resulting in an EHR data range from 2005 to 2015. Birth weight and weight (kg) at each visit were extracted from the EHR, as well as address at each visit, age at each visit (months), gestational age (weeks), primary diagnosis for admission (ICD-10 code), child sex, child date of birth, and visit type (inpatient or outpatient). Missing EHR gestational age (42%) and birth weight (42%) data were imputed using CHW survey data. Correlation coefficients between the two data sources were 0.97 for birth weight and 0.95 for gestational age. We used the EHR value if CHW survey and EHR values differed.
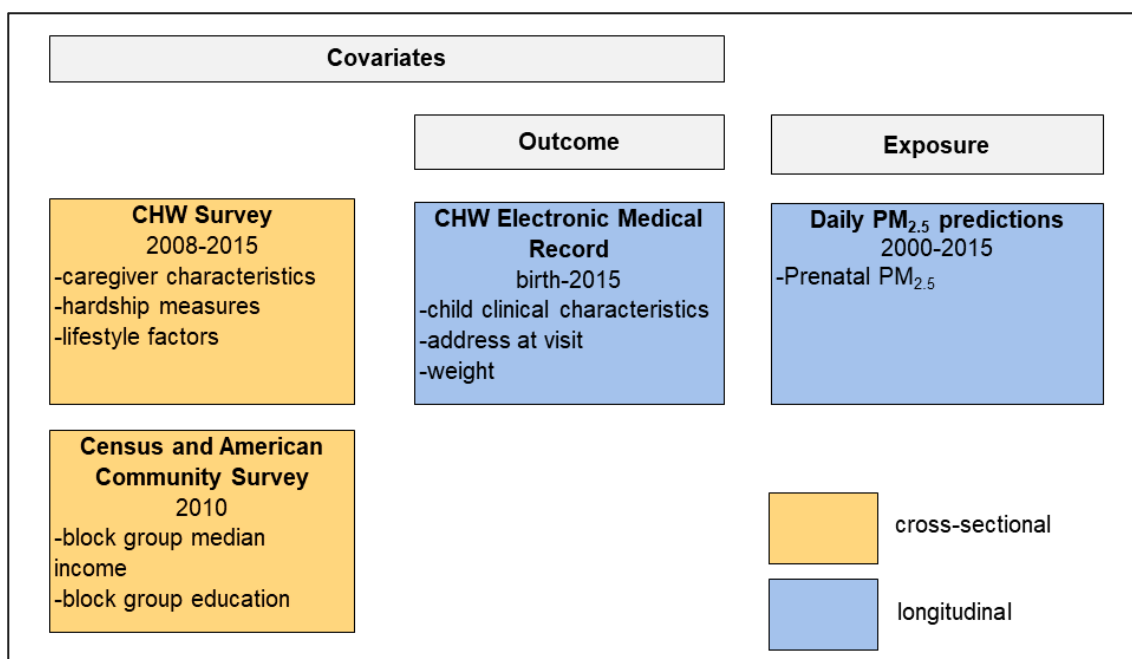
Figure 1. Data sources linked to create final analytical dataset for growth trajectory analysis. CHW: Children's HealthWatch; $PM_{2.5}$: particulate matter with an aerodynamic diameter of 2.5 microns.

2.3. Weight Outcome Data and Analytical Sample Selection

Of 100,712 visits, 84,283 visits included weight measurements. Only participants with two or more weight measurements over the study period were included in the study. We excluded visits with missing weight data, if exact weight measurements were repeated between visits, if an address was missing, could not be geocoded, or Boston Medical Center was listed as the address. Biologically implausible weight values, defined as a sex-specific weight-for-age z score of less than -6 or more than 5, were also dropped from analyses, as recommended by the Centers for Disease Control and Prevention [24]. This process yielded a final analytical sample of 4797 caregiver/child dyads with over 70,369 visits (Figure S1).

In the final sample, 28%, 64%, and 8% of weight measurements were from ED, outpatient, and inpatient visits, respectively. We used weight measurements from all visit types as our dependent variable, and performed a sensitivity analysis excluding inpatient weights.

2.4. Exposure Assessment

Geocoding. We geocoded addresses recorded on the medical record to the corresponding residential parcel [25]. Of all addresses listed in the EHR, 0.8% were either missing or listed as a P.O. Box. Of the remaining addresses that were included in the geocoding process, 98% were matched to a residential address. We linked geocoded addresses at each visit to predicted $PM_{2.5}$ data and several other spatial covariates, discussed in more detail below.

Prenatal ambient $PM_{2.5}$. Details of the validated 1-km^2 resolution $PM_{2.5}$ prediction model can be found in Kloog et al. (2014). Briefly, this modeling approach used a combination of aerosol optical depth (AOD) satellite data retrieved using the multi-angle implementation of atmospheric correction (MAIAC) algorithm, land use and meteorological variables, and daily ambient monitor $PM_{2.5}$ concentrations to calculate daily $PM_{2.5}$ predictions on a 1-km^2 grid between 2000 and 2015 [26]. The daily ambient $PM_{2.5}$ monitoring data were obtained from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) database, which includes ground monitoring sites located in urban, suburban, and rural areas across the United States, and from the Interagency Monitoring

of Protected Visual Environments (IMPROVE) network, which includes monitors located in national parks and other federal lands.

We assigned $PM_{2.5}$ to the geocoded addresses at birth using the closest 1 km^2 grid centroid. We calculated average $PM_{2.5}$ concentration over the prenatal period, which we estimated using date of birth and gestational age (in weeks). We categorized prenatal $PM_{2.5}$ as a bivariate variable above and below the median (9.5 µg/m^3) and as tertiles in a sensitivity analysis because of the non-linear association with weight.

2.5. Covariates

We assigned block group-level covariates from American Community Survey (ACS) 2006–2010 5-year summary data to each geocoded address. Linked covariates included median block group household income and percent with less than a high school degree (both continuous).

Individual covariates collected from the EHR included number of moves within the study period (continuous), child's birth weight (binomial categorized at > 2500 grams), child's gestational age (continuous and binomial categorized at > 37 weeks), child sex, and birth date.

We obtained the following covariates from the CHW survey: year of enrollment, caregiver BMI (underweight, normal weight, overweight, obese), caregiver race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), breastfed during pregnancy (yes/no), caregiver smoking status in the past five years (yes/no), caregiver immigration status (U.S.-born, yes/no) and caregiver educational attainment (no schooling or some high school, high school, postsecondary), a composite measure of food, energy, and housing insecurity (referred to herein as "cumulative hardship") [27], and mother's age at birth (derived from child date of birth and mother's age at CHW enrollment date).

2.6. Growth Trajectories Model

To estimate associations between average prenatal $PM_{2.5}$ and growth trajectories, we applied a mixed effects model. We ran all models separately for males and females because of evidence of sex differences in growth trajectories and air pollution susceptibility [11,28,29]. In the model, we adjusted for several covariates a priori known to be biologically related to childhood postnatal weight, or as confounders of the association between weight and $PM_{2.5}$. They include: caregiver race/ethnicity, cumulative hardship (categorical), child's gestational age (categorical), block group median household income (continuous), and caregiver immigration status. Our main model also included a random intercept for child and a random slope for age to account for repeated measurements within subject and to adjust for heterogeneity in trends over time [30,31]; this model allows for correlated repeated weight measurements and varying number of measures per child. This modeling approach has been shown to produce good model fit in this and several other cohorts [9,32–37].

To model the growth trajectories we first applied generalized additive mixed effect models, controlling for covariates described above, and used penalized splines for age to visually inspect the shape of the relationship between weight and age defining sex-specific growth curves, and weight and $PM_{2.5}$ [38].

To create a model that allows for a close approximation of the true growth function, we then used linear spline models with cubic polynomial terms for age. We used an iterative process to test combinations of one, two, three or four knot points at knot placements 3, 6, 9, 12, 18, 24, 36, and 40 months (number of participants with weight observations at different age ranges is shown in Supplemental Table S1). We explored two- and three- degree polynomial functions by adding linear, quadratic, and cubic terms to the model at the aforementioned knot points. We assessed model fit by comparing Akaike Information Criterion (AIC) and log-likelihood values between non-nested and nested models, respectively. Models for both sexes were the same and included a quadratic term, and cubic term, with knots at 6 and 12 months (Supplemental Table S2). We evaluated interactions between age terms and covariates using a likelihood ratio test.

We found that including interactions between covariates and age terms in the model provided a significantly (*p*-value < 0.05) better fit than simply including the covariates as main effects, suggesting that the effect of covariates varies over age. We also tested year of enrollment to test for time trend, but found that it did not improve model fit. In addition, we included in the model interaction terms between prenatal $PM_{2.5}$ and the age terms to allow the shape of the curve to differ between age groups.

The final model was:

$$\begin{aligned}
Y_{ij} = {} & B_0 + B_1 age_{ij} + B_2 age_{ij}^2 + B_3 age_{ij}^3 + B_4(age_{ij} - 6 months)^2 + B_5(age_{ij} - 12 months)^2 \\
& + B_6 exposure_i + B_{7-n} covariates_i + (B_n age_{ij} * (exposure_i + covariates_i)) \\
& + (B_n age_{ij}^2 * (exposure_i + covariates_i)) \\
& + (B_n age_{ij}^3 * (exposure_i + covariates_i)) + ((B_n(age_{ij} - 6 months)^2) * (exposure_i + covariates_i)) \\
& + (B_n(age_{ij} - 12 months)^2 * (exposure_i + covariates_i)) + b_{0i} + b_{1i} age_{ij} + e_{ij},
\end{aligned} \tag{1}$$

where Y_{ij} is weight for the ith subject at time j, $exposure_i$ is average prenatal $PM_{2.5}$ for the ith subject; $covariates_i$ are non-time-varying covariates for the ith subject, and b_{0i} and b_{1i} are the subject-specific random intercept and slope, respectively, for the ith subject.

To optimize interpretability of the model, we estimated predicted weight and associated 95% confidence interval at specified ages for the two levels of $PM_{2.5}$. We then computed the differences in weight between levels of $PM_{2.5}$ over the growth trajectory at the specified ages.

We tested effect modification by birth weight (< 2500 grams), as growth trajectories may differ by birth weight. The phenotype of low birthweight followed by catchup growth has been associated with a range of cardiometabolic outcomes [13,14,39].

2.7. Sensitivity Analyses

We performed a sub-analysis including mother's BMI (underweight, normal, overweight, obese) at study enrollment as a model covariate given literature showing that maternal and paternal weight are associated with childhood growth and obesity outcomes [9–11]. This analysis was conducted within a subset of the study population (63%) as the remaining participants were missing biological mother's BMI. We also performed a sensitivity analysis excluding all subjects born <37 weeks gestation and a separate analysis excluding inpatient weights [40].

We report results as mean difference in weight (kg) between above and below median prenatal $PM_{2.5}$ concentrations using *t*-tests, reported separately for males and females. All statistical tests were 2-tailed and a *p*-value of < 0.05 is used to denote statistical significance. Statistical analyses were conducted using R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

We present characteristics of the study population stratified by child sex in Table 1. The CHW cohort is an ethnically diverse, low-income population. Cohort participants were 50% non-Hispanic black and 35% Hispanic, 43% had a post-secondary degree, and 42% of mothers enrolled were immigrants to the United States. The average block group median household income was $43,792 and $43,442 (United States Dollar) for males and females respectively, which was lower than the state average of $70,114. The median mother's age at delivery was 27 years (± 6.3). Average prenatal $PM_{2.5}$ was approximately normally distributed across the population. The mean prenatal $PM_{2.5}$ concentrations were similar between males (9.6 ± 1.2, range: 6.5–14.0 µg/m^3) and females (9.5 ± 1.2, range: 6.3–14.1 µg/m^3).

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Table 1. Characteristics of 4797 children and their caregivers enrolled in the Boston, Massachusetts based Children's HealthWatch Cohort, 2008–2015.

Child Characteristics		
	Males (*n* (%))	**Females (*n* (%))**
Total	2603 (100)	2194 (100)
Birth weight (g) (% missing: 1.6 males, 1.1 females)		
<2500	292 (11.4)	289 (13.3)
>=2500	2269 (88.6)	1881 (86.7)
Gestational age (% missing: 0.4 males, 0.4 females)		
<37 weeks	411 (15.9)	309 (14.1)
>= 37 weeks	2181 (84.1)	1876 (85.9)
Breastfed During Pregnancy (% missing: 0.8 males, 0.6 females)		
Yes	1999 (77.4)	1688 (77.4)
No	584 (22.6)	492 (22.6)
Cumulative hardship (% missing: 12.7 males, 11.6 females) [a]		
0 hardships	806 (35.5)	655 (33.8)
1–3 hardships	1288 (56.7)	1121 (57.8)
>3 hardships	179 (7.9)	163 (8.4)
Number of overall visits (inpatient and outpatient)		
mean ± SD	14.8 ± 14.9	14.5 ± 14.1
Block group median income ($)		
mean ± SD	43,792.4 ± 22,003.7	43,442.3 ± 22,424.0
Self-reported caregiver characteristics		
Marital status (% missing: 0.5 males, 0.4 females)		
Married	933 (36.0)	782 (35.8)
Not married	1657 (64.0)	1403 (64.2)
Ethnicity (% missing: 1.2 males, 1.0 females)		
Hispanic	919 (35.7)	766 (35.3)
Black, non-Hispanic	1294 (50.3)	1099 (50.6)
White, non-Hispanic	222 (8.6)	191 (8.8)
Other	137 (5.3)	116 (5.3)
Education (% missing: 0.5 males, 0.3 females)		
Less than high school	611 (23.6)	524 (24.0)
High school graduate	853 (33.0)	723 (33.0)
Post-secondary	1125 (43.5)	941 (43.0)
Country of birth [b] (% missing: 0.8 males, 0.3 females)		
U.S.-born	1484 (57.5)	1266 (57.9)
Not U.S.-born	1099 (42.6)	921 (42.1)
Smoked in last 5 years (% missing: 4.1 males, 2.9 females)		
Yes	618 (24.8)	562 (26.4)
No	1879 (75.3)	1568 (73.6)
Age at child's birth		
Mean ± SD	26.8 ± 6.3	27.0 ± 6.3

Note: SD, standard deviation; [a] Refers to biological mother; [b] Score derived from questions about housing, energy, and food insecurity.

Supplemental Figure S2 displays the plot of the penalized spline model with a smooth term for model age in the model for weight, for males and females. As expected, both males and females have an exponential rate of growth in the first few months of life, which slows and becomes linear around 12 months of age, consistent with U.S. growth curve trends [41].

Supplemental Table S3 presents observed weights and estimated weights in the study population compared to the U.S. reference population weights from ages 0 to 72 months. Overall, models produced values close to observed weights. Cubic polynomial models slightly overestimated weight between 12 and 24 months for males, and slightly underestimated weights after 48 months for females. Observed

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weights in the study population were lower than the U.S. population during the early infancy period (0–3 months) but were higher at all other ages.

Figure 2 shows estimated childhood weight trajectories by levels of prenatal $PM_{2.5}$ exposure below the median and above the median, and the weight trajectory of the general U.S. population for comparison, from birth through 72 months. Among males, above-median prenatal $PM_{2.5}$ exposure results in growth trajectories that are significantly lower compared to the below-median prenatal $PM_{2.5}$ exposure group from 2–6 years of age. The model predicts a 0.17 kg lower weight at 24 months and 0.72 kg lower weight at 60 months. We see an association in the opposite direction among females, where above-median prenatal $PM_{2.5}$ is associated with significantly higher weights at all ages, with the exception of birth weight. The greatest difference in weight was at 72 months, where high exposure groups had weights 0.64 kg higher than low exposure groups (Table 2).
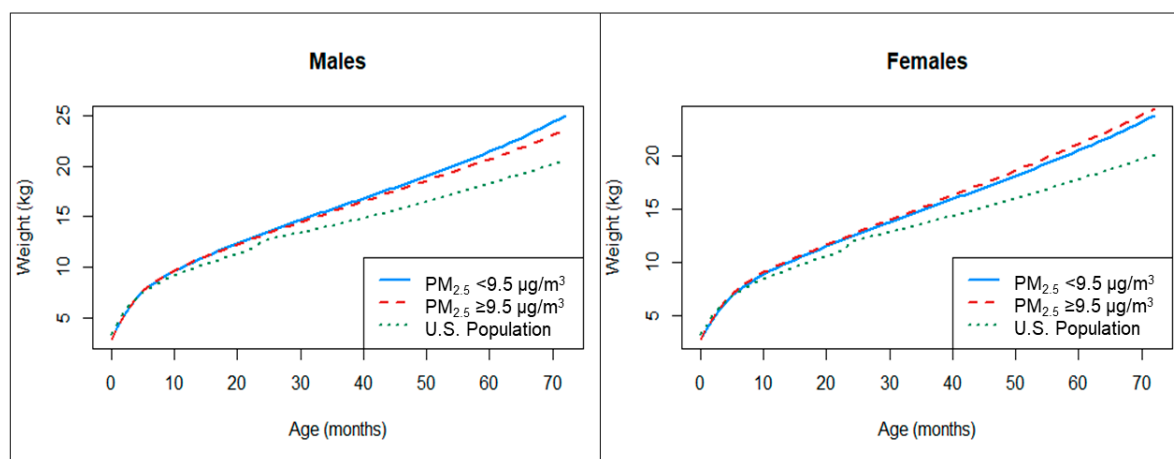
Figure 2. Predicted weight (kg) over age (months) by levels of average prenatal $PM_{2.5}$. Note: Models adjusted for: age, age^2, age^3, quadratic spline terms at 6 and 12 months, gestational age, ethnicity, education, U.S.-born, cumulative hardship, and block group median income.

In a sensitivity analysis, mother's BMI at enrollment was associated with weight in all male prenatal $PM_{2.5}$ models. Male babies of underweight mothers have statistically significantly lower weights compared to those from normal BMI mothers (−0.47, $p = 0.0013$), but not for female babies. The direction and magnitude of effects were similar when compared to a model that omitted BMI. We found similar results to our main analysis when we categorized $PM_{2.5}$ into tertiles, with similar growth curves between the second and third tertiles of $PM_{2.5}$ and lower rates of growth for those at or below the first tertile (data not shown, but available upon request). We restricted to full-term births (>37 weeks) and to outpatient weight measurements only, finding similar magnitude and direction of effect for male and female models (data not shown, but available upon request).

Results for polynomial age models for prenatal $PM_{2.5}$, stratified by low birth weight (LBW, <2500 g) and non-low birth weight (>=2500 g), are presented in Figure 3, and Tables S4 and S5. As with the unstratified sample, estimated weights for males were significantly higher for the lower prenatal $PM_{2.5}$ group in the non-LBW group, after 24 months. Absolute weight differences were more pronounced in the non-LBW group as compared to the LBW group (e.g., 0.82 kg in non-LBW vs. 0.39 kg in LBW at 60 months). Among females, differences between high and low $PM_{2.5}$ exposure groups were greater among LBW compared to non-LBW females. Among LBW females, the above-median prenatal $PM_{2.5}$ group had 0.24 kg greater weight at 6 months of age and 3.31 kg greater weight at 72 months compared to below-median $PM_{2.5}$.

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Table 2. Mean predicted weight (kg) by prenatal PM$_{2.5}$ category.

Prenatal PM$_{2.5}$ Group	Birth	3 Months	6 Months	12 Months	18 Months	24 Months	36 Months	48 Months	60 Months	72 Months
Males (*n* = 2244; weight measurements = 32,405)										
<9.5 µg/m^3 [a]	3.00 (2.94, 3.06)	6.17 (6.11, 6.22)	8.09 (8.03, 8.15)	10.25 (10.17, 10.32)	11.86 (11.78, 11.96)	13.33 (13.22, 13.44)	15.98 (15.81, 16.14)	18.55 (18.34, 18.78)	21.44 (21.16, 21.72)	24.99 (24.62, 25.36)
≥9.5 µg/m^3 [a]	3.02 (2.95, 3.09)	6.17 (6.11, 6.23)	8.14 (8.07, 8.21)	10.29 (10.21, 10.37)	11.77 (11.68, 11.87)	13.16 (13.04, 13.28)	15.71 (15.54, 15.88)	18.16 (17.94, 18.38)	20.72 (20.44, 21.00)	23.60 (23.25, 23.94)
Δ	−0.02	0.01	−0.05	−0.04	0.09	0.17	0.27	0.39	0.72	1.39
p-value [b]	0.70	0.99	0.30	0.41	0.17	0.04	0.02	0.01	0.0003	<0.00001
Females (*n* = 1931; weight measurements = 27,148)										
<9.5 µg/m^3 [a]	2.95 (2.88, 3.02)	5.58 (5.52, 5.64)	7.36 (7.30, 7.42)	9.52 (9.45, 9.60)	11.05 (10.96, 11.15)	12.48 (12.35, 12.60)	15.11 (14.93, 15.30)	17.71 (17.45, 17.97)	20.52 (20.19, 20.83)	23.79 (23.35, 24.23)
≥9.5 µg/m^3 [a]	2.98 (2.91, 3.06)	5.71 (5.64, 5.78)	7.55 (7.48, 7.61)	9.70 (9.62, 9.79)	11.21 (11.11, 11.30)	12.64 (12.51, 12.76)	15.41 (15.22, 15.58)	18.18 (17.93, 18.41)	21.13 (20.83, 21.43)	24.42 (24.05, 24.81)
Δ	−0.03	−0.13	−0.19	−0.19	−0.15	−0.16	−0.29	−0.47	−0.61	−0.64
p-value [b]	0.50	0.006	0.0001	0.001	0.03	0.07	0.03	0.01	0.01	0.03

Note: All estimates are from polynomial mixed models adjusted for: age, age^2, age^3, quadratic spline terms at 6 and 12 months, gestational age, ethnicity, education, U.S.-born, cumulative risk and block group median income; Δ = absolute difference in weight between low and high exposure categories (kg). [a] Values are mean estimated weights in kg (95% CIs); [b] *p*-values for difference between low and high exposure categories.
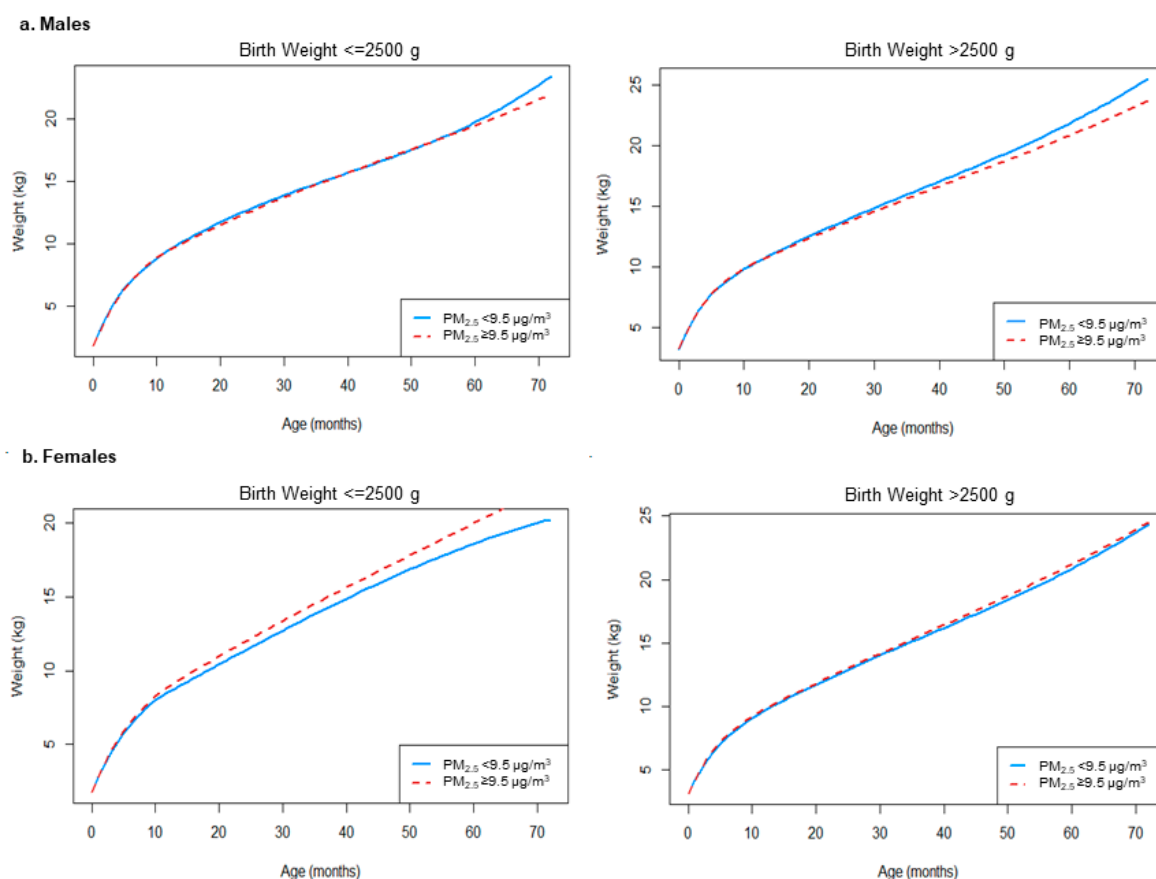
Figure 3. Predicted weight (kg) over age (months) by levels of average prenatal $PM_{2.5}$, stratified by birth weight categories for (**a**) males and (**b**) females. Note: Models adjusted for: age, age^2, age^3, quadratic spline terms at 6 and 12 months, gestational age, ethnicity, education, U.S.-born, cumulative risk, and block group median income

4. Discussion

We found differences in weight growth trajectories between levels of prenatal $PM_{2.5}$ exposure in a racially and ethnically diverse population. Males exposed prenatally to $PM_{2.5}$ greater than the median (9.5 $\mu g/m^3$) had lower weights after 24 months of age compared to less-exposed groups. In contrast, over the growth trajectory (birth to age 6), female weights were greater for higher $PM_{2.5}$ prenatal exposure, which was driven by the positive relationship between $PM_{2.5}$ and weight in LBW females.

Exposure to ambient air pollution such as particulate matter is a ubiquitous and modifiable risk factor. Inhalation of $PM_{2.5}$ during pregnancy can interfere with fetal growth via oxidative stress (OS), intrauterine inflammation, endothelial function, and altered mitochondrial function [42–44]. These biological processes may alter trophic mechanisms that control growth throughout the life course [4].

The existence of sex-specific differences in the association between prenatal $PM_{2.5}$ and growth trajectories is consistent with the broader literature on air pollution and birth outcomes, albeit with considerable variation in the magnitude and direction of effect. Overall, more studies have reported increased susceptibility to in utero $PM_{2.5}$ exposure among males compared to females [28,45–47]. In a systematic review, females were more commonly found to be at higher risk of LBW, but in a re-analysis of data from four studies, males were at higher risk of LBW in the presence of high prenatal $PM_{2.5}$ [45]. Ebisu and Bell (2012) reported a 3.2% (95% CI: 0.8, 5.6%) lower relative risk of LBW per IQR increase of $PM_{2.5}$ elemental carbon in females compared to males [46]. The opposite effect was found in a pregnancy cohort located in Krakow: males had 188.6 g lower birth weight in the fourth compared to the first quartile of prenatal $PM_{2.5}$ [47].

The literature is sparse with reference to prenatal outdoor ambient air pollution exposure and sex-specific differences in measures of weight later in childhood. Chiu et al. (2017) found that 1 μg/m^3 increase in prenatal-average $PM_{2.5}$ was associated with a 0.36 kg (95% CI: 0.12-0.68) increase in fat mass for males, but not females, and an increase in waist to hip ratio in females at four years of age [48]. Animal and human studies have demonstrated that prenatal $PM_{2.5}$ exposure can induce sex-specific epigenetic modifications in leptin methylation, which is associated with adult metabolic disorders [49,50]. Sex-specific differences in energy metabolism and increased OS vulnerability in males have been found in animal studies, and may explain sex-specific differences found here [51].

Beyond the sex-specific effects, our findings are broadly consistent with a growing literature linking air pollution exposures with childhood growth [19,21,22,52]. In a Boston-area pregnancy cohort, Fleisch et al. (2015) found increased odds of weight-for-length > 95th percentile at 6 months of age in fourth quartile third-trimester $PM_{2.5}$ and distance to roadway < 50 m compared to the referent groups, though estimates were not statistically significant. In a follow-up study, children whose mothers lived < 50 m from a major roadway at the time of delivery had 2.1 kg (95% CI: 0.8, 3.5) greater total fat mass compared to children (median 7.7 years of age) living >=200 m [52]. Inconsistent with our findings, this same study found each interquartile range increase in one-year average $PM_{2.5}$ concentrations prior to each measurement occasion was associated with lower BMI-z score and total and truncal fat mass in mid-childhood (average 8 years of age) [52]. Investigators also examined trimester-specific associations, finding no association between third trimester $PM_{2.5}$ and BMI outcomes [21].

A Massachusetts birth cohort with similar demographic characteristics to our study found an increased risk of overweight (BMI z-score >= 85th percentile) and obesity (BMI z-score > = 95th percentile) at ages 2–9 years in the highest versus lowest quartile of average prenatal $PM_{2.5}$ exposure (OR = 1.3 (95% CI: 1.1, 1.6)) and postnatal $PM_{2.5}$ in the first two years of life (OR = 1.2 (95% CI:1.1, 1.5)) [18]. Jerrett et al. (2014) assessed associations between traffic density within 150 m of the home and longitudinal sex-specific BMI growth trajectories between the ages of 5 and 11 years of age, finding no significant association [15].

The exposure and outcome assessments and study population sociodemographic characteristics may explain some of the discrepancies between our study and other studies that have assessed prenatal $PM_{2.5}$ with weight trajectories. For instance, we used 1-km^2 $PM_{2.5}$ predictions, while Chiu et al. 2017 used measures from the nearest monitor, which may have decreased exposure variability and increased exposure measurement error. Other studies used BMI z-score and physiological measures of adiposity as their outcomes [18–20,48]. In the present study, we used raw-weights rather than z-scores to examine the true shape of the growth trajectory. Though McConnell et al. (2015) and Jerrett et al. (2014) found positive associations between postnatal near roadway pollution and traffic density with rates of BMI growth, their exposure metrics incorporated traffic density and meteorological conditions, averaged over the year of each measurement, whereas our study only considered $PM_{2.5}$.

Further, the CHW study population was more ethnically diverse and the prevalence of multiple hardships was higher as compared to the more ethnically homogenous and high-income Boston-area Project Viva cohort [19,21,52]. Inconsistencies may also be explained by our weaker measure of smoking (ascertained at the time of survey by asking whether caregiver smoked in the last 5 years), which is a predictor of weight. Greater cigarette smoke exposure and has been shown to have a synergistic effect with air pollution in increasing growth rates [20]. Further investigation is required to examine the role of other social determinants of health, such as housing conditions or food insecurity, acting independently or as modifiers of the association between ambient pollutants and weight gain. Using data from the CHW Boston site, we found that homelessness during pregnancy and average $PM_{2.5}$ during the second trimester were marginally associated with reduced birthweight, while participating in Women, Infants, and Children (WIC) programs was associated with increased birthweight [53]. A deeper comprehension of these stressors can help identify root causes and potential solutions to the childhood obesity challenge, and why obesity may persist into adulthood [54].

There are a number of limitations in this study that may also explain our findings. We did not have measures of maternal smoking during pregnancy, nutrition, and maternal pre-pregnancy BMI,

which are risk factors for childhood weight gain [9,55]. We attempted to control for these measures using a variable measuring smoking status during the past five years and maternal BMI at study enrollment. CHW does not collect information on diet, physical activity, and other environmental exposures that may be jointly associated with air pollution and weight gain, so there may be residual confounding in our analysis [56]. To address this concern, we controlled for both a measure of hardship, including food insecurity, and block group median income, both of which were associated with child growth in our models.

There are some limitations inherent in the use of an EHR for data ascertainment. Health providers may inconsistently record weight measurements, resulting in non-differential outcome misclassification. However, weight measurements recorded in EHRs were found to be prone to < 0.7% error from 0 to 5 years of age according to a large prospective cohort study using EHRs [57]. Lastly, many of the visits in early childhood are routine checkups, whereas visits later in childhood may be comprised of children with poorer health outcomes, and thus differential susceptibility to the effects of $PM_{2.5}$ exposure later in life.

In spite of these limitations, our study has several strengths. This study included a large sample size: 4797 participants, with 70,369 weight measurements. The analytical method used to model the appropriate function of weight for age allowed us to explore longitudinal differences in trajectories by levels of ambient air pollution exposure. This method further allowed us take full advantage of the EHR containing measurements collected at varying time points and frequencies, and to estimate change in slope during specified growth time periods. Using an EHR for epidemiological analyses is a novel and relatively inexpensive, source of longitudinal data ascertainment, allowing for many measurements and limited potential for recall and participation bias [58]. The CHW cohort is ethnically diverse, making our results more representative of vulnerable populations, which are understudied to date. Survey data collected by CHW also provided rich information for covariates on multiple hardships, immigration status and caregiver characteristics. Up-to-date parcel-level reference data used in the geocoding process also strengthened confidence in exposure assessment.

Our findings, and those of other studies examining early childhood weight trajectories, have multiple important public health implications. The associations in females are consistent with other risk factors implicated in the "thrifty phenotype" of low birthweight followed by rapid weight gain [2]. This phenotype has been linked to several morbidities in adulthood, including obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease [14]. Although the differences in weights between $PM_{2.5}$ levels were small, the ubiquity of air pollution exposure across the population implies that even low levels of $PM_{2.5}$ may shift population prevalence of excess weight gain over the life course. Differential weight trajectories, as noted here, have been shown to persist into late childhood and adulthood [11]. Our results point to a potentially susceptible period during which introduction of interventions known to promote healthy growth during the early childhood period could reduce the potential impacts of $PM_{2.5}$ on growth [59].

5. Conclusions

In conclusion, we found in our study that low-birth weight females may be at increased susceptibility for weight gain in early childhood when exposed to higher prenatal $PM_{2.5}$, with a significant inverse association among males. Studying growth trajectories, rather than attained measures of birth weight and BMI, provides an opportunity to understand susceptible phenotypes and periods of potential interventions. Because of the unique risk patterns found in the CHW population, additional studies are needed in a variety of different study populations and geographies to replicate our findings and to further explore the sex-specific differences found in this study. Future studies should also consider extending the follow-up period through adolescence and adulthood and the implications of specific growth trajectory phenotypes on adult morbidities, such as cardiovascular disease and diabetes.

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