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Individual and Joint Effects of Early-Life Ambient $PM_{2.5}$ Exposure and Maternal Prepregnancy Obesity on Childhood Overweight or Obesity

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Background: Although previous studies suggest that exposure to traffic-related pollution during childhood increases the risk of childhood overweight or obesity (COWO), the role of early life exposure to fine particulate matter (aerodynamic diameter $< 2.5\,\mu m$; $PM_{2.5}$) and its joint effect with the mother's prepregnancy body mass index (MPBMI) on COWO remain unclear.

Objectives: The present study was conducted to examine the individual and joint effects of ambient $PM_{2.5}$ exposures and MPBMI on the risk of COWO.

Methods: We estimated exposures to ambient $PM_{2.5}$ *in utero* and during the first 2 y of life (F2YL), using data from the U.S. Environmental Protection Agency's (EPA's) Air Quality System matched to residential address, in 1,446 mother–infant pairs who were recruited at birth from 1998 and followed up prospectively through 2012 at the Boston Medical Center in Massachusetts. We quantified the individual and joint effects of $PM_{2.5}$ exposure with MPBMI on COWO, defined as the child's age- and sex-specific BMI *z*-score $\geq$85th percentile at the last well-child care visit between 2 and 9 y of age. Additivity was assessed by estimating the reduced excess risk due to interaction.

Results: Comparing the highest and lowest quartiles of $PM_{2.5}$, the adjusted relative risks (RRs) [95% confidence intervals (CIs)] of COWO were 1.3 (95% CI: 1.1, 1.5), 1.2 (95% CI: 1.0, 1.4), 1.2 (95% CI: 1.0, 1.4), 1.3 (95% CI: 1.1, 1.6), 1.3 (95% CI: 1.1, 1.5) and 1.3 (1.1, 1.5) during preconception; the first, second, and third trimesters; the entire period of pregnancy; and F2YL, respectively. Spline regression showed a dose–response relationship between $PM_{2.5}$ levels and COWO after a threshold near the median exposure ($10.46\,\mu g/m^3$–$10.89\,\mu g/m^3$). Compared with their counterparts, children of obese mothers exposed to high levels of $PM_{2.5}$ had the highest risk of COWO [RR $\geq$2.0, relative excess risk due to interaction (RERI) not significant].

Conclusions: In the present study, we observed that early life exposure to $PM_{2.5}$ may play an important role in the early life origins of COWO and may increase the risk of COWO in children of mothers who were overweight or obese before pregnancy beyond the risk that can be attributed to MPBMI alone. Our findings emphasize the clinical and public health policy relevance of early life $PM_{2.5}$ exposure. https://doi.org/10.1289/EHP261

Introduction

The prevalence of childhood overweight and obesity (COWO) has reached alarmingly high levels in the past decade, surpassing 30% in the United States and in other developed countries [Ogden et al. 2014; World Health Organization (WHO) 2013]. COWO is associated with metabolic syndrome (Weiss et al. 2004), type 2 diabetes (Goran et al. 2003), and early signs of cardiovascular disease in childhood and adolescence (Lobstein et al. 2004). Furthermore, COWO is a major risk factor for chronic diseases in adulthood including overweight and obesity (The et al. 2010), stroke (Lawlor and Leon 2005), and premature death (Franks et al. 2010). Maternal overweight and obesity at conception, which occurs in one in two mothers in the United States (Kim et al. 2007; Vahratian 2009), is the leading risk factor for COWO (Reilly et al. 2005) and may reflect the interaction of genetic, lifestyle, and environmental risk factors shared within families as well as prenatal programming occurring *in utero* for increased susceptibility to overweight and obesity throughout life (Gillman 2005; Janesick and Blumberg 2012; Lawlor 2013; Romano et al. 2014).

The adverse effects of exposure to air pollution *in utero* on birth weight have been reported in multiple studies (Shah et al. 2011; Wang X et al. 1997). Recently, smoking and exposure to polycyclic aromatic hydrocarbons (PAHs) during pregnancy have been linked to overweight in offspring, suggesting that the effects of early life exposure to air pollution may persist into childhood and increase the risk of COWO (Oken et al. 2008; Rundle et al. 2012). Studies in the United States and China have shown an association between exposure to traffic-related pollution [particulate matter $\leq 10\,\mu m$ in diameter (PM_{10})] during childhood and increased BMI and odds of overweight or obesity in childhood or adolescence, but these studies did not include exposure during the prenatal period (Dong et al. 2014; Jerrett et al. 2010; Jerrett et al. 2014; McConnell et al. 2015). Exposure to $PM_{2.5}$ during the prenatal period has also been found to be associated with rapid postnatal weight gain in infants (Fleisch et al.

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2015), and similar findings have been reported in a rodent model (Wei et al. 2016), but until now, examination of the persistence of these prenatal effects into childhood has been limited to one recent study (Fleisch et al. 2017). In addition, modification of the effects of $PM_{2.5}$ by maternal overweight and obesity has not been assessed.

In this prospective cohort study, we sought to investigate the effects of early life exposure to ambient $PM_{2.5}$ on the risk of COWO and its joint effect with maternal prepregnancy overweight and obesity on COWO in the Boston Birth Cohort (BBC), a large prospective cohort of predominantly urban, low-income, minority mothers and their children living in Boston, MA.

Methods

Study Population

The study population included mother–infant pairs participating in the BBC, a prospective cohort established in 1998 at the Boston Medical Center (BMC) using rolling enrollment. BMC serves an ethnically diverse community of patients who primarily reside in an urban setting, and the birth cohort is enriched for preterm birth and low birth weight by recruiting at a ratio of approximately one preterm to two full-term births. Multiple births and newborns with major birth defects were excluded. Detailed data collection and measurement methods for clinical and sociodemographic variables have been published previously (Kumar et al. 2008; Wang X et al. 2002). Briefly, recruitment occurred 24–72 h after birth, and written informed consent was obtained from all participating mothers. At this time, data on clinical and social variables were collected via participant interview or extraction from medical records using a structured questionnaire developed for the BBC. These data included birth weight, sex of the baby, season of delivery, maternal age at delivery, race/ethnicity, education level, smoking status before and during pregnancy, diabetes history, marital status, parity, household income, and current and previous residential addresses. Gestational age was assessed based on the date of the last menstrual period as well as on the results of early ultrasound (<20 wk gestation). Breastfeeding was assessed by a questionnaire administered during postnatal follow-up, and the majority of study mothers answered this question before the child reached the age of 2. The study protocol was approved by institutional review boards at the BMC and at the Johns Hopkins Bloomberg School of Public Health.

Since 2003, all children enrolled in the BBC who were intended to receive primary care at the Boston Medical Center were eligible to participate in a postnatal follow-up study. Of the 2,891 children followed up, 1,446 were included in this analysis. As depicted in a flow chart (Figure S1), reasons for exclusion from the analysis were birth date later than November 2012 ($n=84$), primary care received outside BMC ($n=630$), lack of available $PM_{2.5}$ exposure data ($n=438$), maternal underweight ($n=73$), and lack of MPBMI ($n=9$); children who completed at least one follow-up well-child visit after 9 y of age ($n=211$) were also excluded.

Assessment of Maternal and Childhood Overweight and Obesity

Children's height and weight were measured by pediatric medical staff during annual well-child care visits per standard clinical procedure and were documented in the electronic medical records at the BMC (Wang G et al. 2016). For children younger than 2 y, the recumbent length was measured as the height (Rifas-Shiman et al. 2012), and for children 2–9 y, the staff measured the child's height while the child was standing without shoes. The weights of all children were measured using a pediatric scale. BMI was calculated as the weight divided by height squared (kilograms per meter squared). BMI-z, defined as the number of standard deviations by which a child differed from the mean BMI of children of the same age and sex, was calculated using the SAS Program for the 2000 CDC Growth Charts provided by the Centers for Disease Control and Prevention (CDC) 2011). Childhood overweight was defined as a BMI-z score $\geq$85th percentile and $<$95th percentile, and childhood obesity was defined as a BMI-z score $\geq$95th percentile. Because the length of follow-up and the number and frequency of annual well-visits varied by participant, COWO was defined as childhood overweight or obesity between ages 2 and 9 y based on the last recorded BMI-z score.

Maternal prepregnancy body mass index (MPBMI) was calculated as weight in kilograms divided by height in meters squared based on the mother's height and weight before pregnancy, collected from maternal questionnaire interviews and electronic medical records. MPBMI was categorized into 3 groups: BMI from 18.5 to 24.9 kg/m^2 (normal weight), BMI from 25.0 to 29.9 kg/m^2 (overweight) and BMI ≥ 30.0 kg/m^2 (obesity).

Ambient $PM_{2.5}$ Exposure Assessment

We assigned individual $PM_{2.5}$ exposure values to mothers (for periods of pregnancy) and children (for the first 2 y after birth) based on the Euclidean minimum distance from the air pollution monitoring sites to the mother's residential address, which was converted from the physical address at street level using the PROC GEOCODE procedure of SAS 9.4 (SAS Institute Inc.) and matched to the nearest monitor using ArcGIS 10.2 (Esri). We imposed no limits on the distance between participants and monitors. Only data from monitors with at least one measurement per week for $>75.0\%$ of the study period were included in the final analyses. A map of the study area depicting the locations of subjects relative to monitor locations has been published elsewhere (Nachman et al. 2016). Exposure periods were defined based on the gestational age of the infant at birth and were divided into 6 phases: preconception (90 d before pregnancy), the first trimester (day 1 to day 90 of pregnancy), the second trimester (day 91 to day 180 of pregnancy), the third trimester (day 181 of pregnancy to birth), the whole pregnancy (day 1 of pregnancy to birth), and the first 2 y of life (F2YL) (the first 2 y after birth). Exposure to $PM_{2.5}$ was assessed for each individual participant as the geometric mean of the daily ambient $PM_{2.5}$ concentration during a given exposure period of interest. Daily $PM_{2.5}$ concentration data were obtained from the monitor closest to the participant's date-specific address. If a participant moved, daily data from the monitor closest to the new address were used starting on the date of the move. Quartiles of exposure were determined separately for each pregnancy period from the distribution of individual participant exposures during that period. Exposure was categorized by quartile and as a continuous variable for analyses of individual effects of $PM_{2.5}$ and as a dichotomous variable for the analysis of joint effects of $PM_{2.5}$ and MPBMI on COWO.

Statistical Analyses

Population characteristics for children with COWO and for their controls were compared as follows. Continuous variables such as gestational age, birth weight, and others were described as the median (first quartile, third quartile), and the Mann-Whitney U-test was applied to compare the differences between the two groups because the distributions were skewed. Chi-squared tests were used to compare and describe the differences of the proportion of categorical variables between the two groups.

We estimated the individual and joint effects of pre- and postnatal ambient $PM_{2.5}$ exposures and MPBMI on either COWO or BMI-z using multivariable generalized linear models (GLMs). Given that the outcome COWO is common, raising concerns that the odds ratio would overestimate risk and interactions, associations between the contributing variables of interest and COWO (dichotomous, where $y = 1$ indicates COWO) were quantified by relative risk using a "modified Poisson" model, a log10-linked linear model of the probability of COWO, which uses sandwich error estimation to produce robust standard errors (Zou 2004). All models of the independent effects of $PM_{2.5}$ exposure during preconception, during the first, second, and third trimesters, during the whole pregnancy, and during F2YL were performed in the following two ways: with exposure as a categorical variable (quartiles) and as a continuous variable [scaled to interquartile range (IQR)]. For models of the joint effects of $PM_{2.5}$ exposure and MPBMI, $PM_{2.5}$ was binary, with high exposure defined as greater than the median exposure for the exposure period, and MPBMI was a three-level categorical variable with normal-weight mothers as the reference group. Two product interaction terms, for the interaction of $PM_{2.5}$ with maternal overweight and for the interaction of $PM_{2.5}$ with maternal obesity, were used to evaluate interaction on a multiplicative scale; joint significance of both interaction terms was determined using the Wald test. In addition, additivity of effects was evaluated by modeling the relative risk due to interaction (RERI) using the method of variance estimates recovery (MOVER) method (Zou 2008). A RERI of 0 indicates no interaction. We adjusted for the following potential confounders known to be associated with childhood weight gain: maternal age at delivery, race/ethnicity, education level, smoking status during pregnancy, diabetes, marital status, household income per year, MPBMI, season of delivery, preterm birth, birth weight, and breastfeeding. All covariates were categorical, and values were grouped according to the categories presented in Table 1 with missing data for each covariate treated as a separate category. Owing to the low rate of exclusive breastfeeding in the study population (5.0%), breastfeeding was treated as a dichotomous variable indicating any breast milk; thus, the breastfed group predominantly comprised children with a mixed diet of both breast milk and formula. We did not include child age and sex in the final regression models because the BMI-z score was age- and sex-specific.

In addition, we examined the possibility of a nonlinear relationship between $PM_{2.5}$ exposure and risk of COWO nonparametrically with restricted cubic splines (Durrleman and Simon 1989). We tested for nonlinearity using the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms (http://www.hsph.harvard.edu/donna-spiegelman/software/). We also conducted the following sensitivity analyses to ensure the robustness of the results:

Table 1. Characteristics of mother-infant pairs of the participants.

Variables[a]	Children without COWO ($n = 832$)	Children with COWO ($n = 614$)	p-value
Maternal age at delivery, years	27.4 (22.7, 32.7)	28.8 (24.0, 34.0)	0.001
Maternal prepregnancy body mass index, kg/m^2			<0.001
Normal weight (18.5–24.9)	439 (52.8)	218 (35.5)	
Overweight (25.0–29.9)	232 (27.9)	202 (32.9)	
Obesity ($\geq$30.0)	161 (19.4)	194 (31.6)	
Maternal race/ethnicity, number (%)			0.523
Hispanic	146 (17.5)	106 (17.3)	
White	49 (5.9)	30 (4.9)	
African/African American	533 (64.1)	425 (69.2)	
Other	102 (12.3)	53 (8.6)	
Missing	2 (0.2)	0 (0.0)	
Maternal education, number (%)			0.718
Middle school or below	287 (34.5)	211 (34.4)	
High school	307 (36.9)	213 (34.7)	
College or above	230 (27.6)	182 (29.6)	
Missing	8 (1.0)	8 (1.3)	
Married (mother), number (%)	556 (66.8)	402 (65.5)	0.837
Continued smoking during pregnancy (mother), number (%)	87 (10.5)	73 (11.9)	0.792
Gestational diabetes mellitus, number (%)	30 (3.6)	37 (6.0)	0.002
Born in United States (mother), number (%)	354 (42.5)	230 (37.5)	0.141
Parity, number (%)			0.808
0	350 (42.1)	251 (40.9)	
1 +	481 (57.8)	363 (59.1)	
Missing	1 (0.1)	0 (0.0)	
Season at delivery, number (%)			0.485
Spring (March to May)	194 (23.3)	124 (20.2)	
Summer (June to August)	210 (25.2)	164 (26.7)	
Autumn (September to November)	220 (26.4)	160 (26.1)	
Winter (December to February)	208 (25.0)	166 (27.0)	
Low birth weight (birth weight <2500 g)[birth weight less than 2500 grams]	263 (31.6)	133 (21.7)	<0.001
Preterm[b], number (%)	251 (30.2)	163 (26.5)	0.132
Gestational age, weeks	38.6 (36.3, 39.9)	38.9 (36.7, 40.0)	0.030
Birth weight, g	2925.0 (2357.5, 3350.0)	3152.5 (2595.0, 3595.0)	<0.001
Age of child at last follow-up			
Median (Q1,Q3)	6.6 (4.0, 8.9)	7.7 (5.4, 9.2)	<0.001
Mean ± SD	6.3 ± 2.5	7.2 ± 2.2	<0.001
Boys (child), number (%)	408 (49.0)	315 (51.3)	0.395
Breastfeeding	546 (65.6)	380 (61.9)	0.104

Notes: Continuous data are described as median (1st quartile, 3rd quartile), and the Mann-Whitney U test was applied to compare the differences between groups because their distribution was skewed. COWO, childhood overweight or obesity; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.
[a]Underweight, normal weight, overweight and obesity are defined as maternal BMI <18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–29.9 kg/m^2, and $\geq$30 kg/m^2, respectively.
[b]Preterm is defined as gestational age <37 wk.

individual and joint effects of $PM_{2.5}$ and MPBMI on COWO stratified by child's age, by warm and cold season, or within subgroups living within 10 km or 5 km of a monitor.

All tests were two-sided, and $p < 0.05$ was considered to be significant. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc.). Figures were drawn with SAS 9.4 and SigmaPlot® for Windows version 12.5 (Build 12.5.0.38, Systat Software Inc.).

Results

Population Characteristics

The prevalence of COWO in 1,446 children in the study population was 42.46% (41.36% for boys and 43.57% for girls). The mean age of assessment of COWO (i.e., the last well-child visit on record) was 6.70 y (median: 7.10 y). Among mothers, 54.56% were overweight or obese before pregnancy (30.01% overweight and 24.55% obese). More than 90% of the subjects lived within 12 km of a monitor. A majority (66.25%) of the women in the study were African/African American, and 28.49% were college graduates or above. The prevalence of maternal diabetes mellitus (DM) including type 1, type 2, or gestational DM was 9.96% (5.33% for type 1 or type 2 DM, 4.63% for gestational DM). Breastfeeding was practiced by 63.37% of the mothers.

When comparing population characteristics by COWO status (Table 1), mothers of COWO children were more likely to be older at delivery, to be overweight or obese, to have gestational diabetes, and to be African/African American. Children with COWO, compared with those without COWO, tended to have higher birth weights and were less likely to be classified as low birth weight.

Ambient $PM_{2.5}$ exposures in the study population peaked in 2002 and then decreased slightly over the remainder of the study period (Figure S2). Individual exposures during the different prenatal and postnatal periods studied were correlated (Spearman ρ: 0.35–0.89) (Table S1). The highest correlations were between the period of the whole pregnancy and trimester 1, trimester 3, and F2YL (Spearman ρ = 0.86, 0.85, 0.89, respectively). Of the total variability in exposures among subjects, 7.27% was attributable to monitor site, and 92.73% was attributable to variability within subjects assigned to the same monitor (i.e., differences in dates of exposure).

Individual Association between MPBMI and COWO or Childhood BMI-z score

The risk of COWO was significantly increased in children of overweight [relative risk (RR) = 1.3 (95% CI: 1.2, 1.6)] and obese [RR = 1.6 (95% CI: 1.3, 1.8)] mothers compared with the risk of COWO in children of normal-weight mothers after adjusting for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marital status, household income per year, season of delivery, preterm birth, birth weight, and breastfeeding (Table 2). In addition, when the relationship between COWO and MPBMI was assessed as a continuous variable, the risk of COWO increased significantly by 30% with each unit increase in MPBMI [RR = 1.3 (95% CI: 1.1, 1.4)]. In additional analyses, childhood BMI-*z* score was also positively associated with MPBMI (Table S2).

Individual Association between $PM_{2.5}$ Exposure and COWO or Childhood BMI-z score

Compared with the lowest quartile of $PM_{2.5}$, the third and fourth quartiles of prenatal and postnatal $PM_{2.5}$ exposures were significantly associated with increased risk of COWO in all six exposure periods [with the exception of the RR for the fourth quartile in the first trimester and the third quartile in the second trimester ($p = 0.065$ for both)] after adjusting for the abovementioned potential confounders (Table 2). The effect estimates were similar across the six exposure periods. In addition, the risk of COWO was significantly increased for each IQR increase in maternal ambient $PM_{2.5}$ exposure in the five exposure periods excluding preconception [RR = 1.1 (95% CI: 1.0, 1.2) for the first trimester, 1.1 (95% CI: 1.0, 1.2) for the second trimester, 1.1 (95% CI: 1.0, 1.2) for the third trimester, 1.1 (95% CI: 1.0, 1.2) for the whole pregnancy, and 1.1 (95% CI: 1.0,1.2) for F2YL]. Based on multivariable spline regression models, the risk ratio increased monotonically following a threshold with increasing $PM_{2.5}$ in an exposure–response relationship pattern at each exposure period examined (Figure 1). Based on the modeled exposure–response curves, the effect of $PM_{2.5}$ exposure on COWO was strongest during the second trimester compared with the other periods of exposure. BMI-*z* score as a continuous outcome was also significantly increased when comparing the highest and lowest quartiles of $PM_{2.5}$ exposure in all exposure periods except the first trimester, for which the relationship was positive but not statistically significant (Table S2).

In sensitivity analyses, estimated associations between the risk of COWO or childhood BMI-*z* score and ambient $PM_{2.5}$ exposure remained positive but were not significant with stratification by age group (Table S3). Associations remained positive with stratification by cool or warm season but were slightly higher in the warm season and remained significant for the fourth quartile in some but not all exposure periods (Table S4). Our findings were consistent with the main results when the analysis was limited to participants within 10 km or 5 km of a monitor (Tables S5 and S6).

Joint Associations between $PM_{2.5}$ Exposure and MPBMI on COWO or BMI-z score

The risk of both COWO and childhood BMI-*z* score was significantly increased with maternal overweight or obesity and exposure to ambient $PM_{2.5}$ during all exposure periods examined (Tables 3 and S7, Figure 2). The largest effects (RR ≥ 2.0) were observed among children whose exposure to $PM_{2.5}$ was in the high category ($PM_{2.5} \geq$ median) and whose mothers were obese at the time of conception. Among mothers who were obese at conception (MPBMI ≥ 30), the risk of COWO rose by 11–35% (depending on the exposure period) for those with high $PM_{2.5}$ exposure (≥ median) compared with those with low $PM_{2.5}$ exposure (< median) in the same MPBMI stratum. Product interaction terms were not significant. RERI estimates for the joint effect of high $PM_{2.5}$ exposure and MPBMI ≥ 30 on COWO exceeded zero for all exposure periods except for the third trimester. However, the 95% CIs all included zero; thus, RERI was not significant for any time period.

The results of our evaluation of the joint effect of $PM_{2.5}$ and MPBMI on COWO and BMI-*z* score by stratified analysis were robust to additional stratification by age group, by cool and warm season, and by distance from a monitor in sensitivity analyses (Table S8, Table S9, Table S10 and Table S11, respectively).

Discussion

To the best of our knowledge, this is the first report to examine the joint effect of MPBMI and ambient $PM_{2.5}$ exposure during pregnancy and F2YL on COWO and childhood BMI-*z*. Ours findings suggest that exposure to $PM_{2.5}$ prenatally and during F2YL is an independent risk factor for COWO. Although interactions and RERI were not significant in the present study, children of mothers who were obese at the time of conception and who

Table 2. Individual effects of maternal prepregnancy BMI and ambient $PM_{2.5}$ exposure on the risk of childhood overweight or obesity.

Variables	n	COWO Number (%)	Crude		Adjusted	
			RR (95% CI)	p-value	RR (95% CI)	p-value
Maternal BMI, kg/m^2[a]						
18.5–24.9 (Normal weight)	657	218 (33.2)	Reference	Reference	Reference	Reference
25.0–29.9 (Overweight)	434	202 (46.5)	1.4 (1.2,1.6)	<0.001	1.3 (1.2,1.6)	<0.001
≥30.0 (Obesity)	355	194 (54.6)	1.6 (1.4,1.9)	<0.001	1.6 (1.3,1.8)	<0.001
Per kg/m^2			1.3 (1.2,1.4)	<0.001	1.3 (1.1,1.4)	<0.001
Ambient $PM_{2.5}$, mg/m^3						
Preconception						
Q1 (4.48–8.85)	348	130 (37.4)	Reference	Reference	Reference	Reference
Q2 (8.86–10.59)	350	138 (39.4)	1.1 (0.9,1.3)	0.574	1.1 (0.9,1.3)	0.420
Q3 (10.59–12.36)	348	155 (44.5)	1.2 (1.0,1.4)	0.055	1.2 (1.0,1.4)	0.037
Q4 (>12.36)	348	163 (46.8)	1.3 (1.1,1.5)	0.012	1.3 (1.1,1.5)	0.011
Per IQR = 3.49 mg/m^3			1.1 (1.0,1.2)	0.110	1.1 (1.0,1.2)	0.134
First trimester						
Q1 (4.16–8.73)	353	136 (38.5)	Reference	Reference	Reference	Reference
Q2 (8.74–10.58)	353	130 (36.8)	1.0 (0.8,1.2)	0.641	1.0 (0.8,1.1)	0.597
Q3 (10.59–12.28)	353	169 (47.9)	1.2 (1.0,1.5)	0.013	1.2 (1.0,1.4)	0.021
Q4 (>12.28)	354	161 (45.5)	1.2 (1.0,1.4)	0.062	1.2 (1.0,1.4)	0.065
Per IQR = 3.58 mg/m^3			1.1 (1.0,1.2)	0.025	1.1 (1.0,1.2)	0.025
Second trimester						
Q1 (5.39–8.79)	357	143 (40.1)	Reference	Reference	Reference	Reference
Q2 (8.80–10.54)	358	123 (34.4)	0.9 (0.7,1.0)	0.116	0.9 (0.7,1.0)	0.113
Q3 (10.55–12.22)	356	168 (47.2)	1.2 (1.0,1.4)	0.056	1.2 (1.0,1.4)	0.065
Q4 (>12.22)	358	172 (48.0)	1.2 (1.0,1.4)	0.032	1.2 (1.0,1.4)	0.037
Per IQR = 3.42 mg/m^3			1.1 (1.0,1.2)	0.023	1.1 (1.0,1.2)	0.035
Third trimester						
Q1 (3.78–8.64)	354	131 (37.0)	Reference	Reference	Reference	Reference
Q2 (8.65–10.52)	355	137 (38.6)	1.0 (0.9,1.3)	0.663	1.0 (0.9,1.3)	0.607
Q3 (10.53–12.32)	355	164 (46.2)	1.2 (1.0,1.5)	0.014	1.2 (1.0,1.5)	0.012
Q4 (>12.32)	354	177 (50.0)	1.4 (1.1,1.6)	0.001	1.3 (1.1,1.6)	0.001
Per IQR = 3.64 mg/m^3			1.1 (1.0,1.2)	0.030	1.1 (1.0,1.2)	0.042
Whole pregnancy						
Q1 (5.88–8.80)	361	136 (37.7)	Reference	Reference	Reference	Reference
Q2 (8.81–10.66)	362	139 (38.4)	1.0 (0.8,1.2)	0.841	1.0 (0.9,1.2)	0.740
Q3 (10.67–11.93)	362	161 (44.5)	1.2 (1.0,1.4)	0.064	1.2 (1.0,1.4)	0.050
Q4 (>11.93)	361	178 (49.3)	1.3 (1.1,1.5)	0.002	1.3 (1.1,1.5)	0.002
Per IQR = 3.17 mg/m^3			1.1 (1.0,1.2)	0.017	1.1 (1.0,1.2)	0.041
F2YL						
Q1 (6.13–9.06)	361	136 (37.7)	Reference	Reference	Reference	Reference
Q2 (9.07–10.21)	362	135 (37.3)	1.0 (0.8,1.2)	0.916	1.0 (0.8,1.2)	0.994
Q3 (10.22–11.99)	362	165 (45.6)	1.2 (1.0,1.4)	0.032	1.3 (1.1,1.5)	0.010
Q4 (>11.99)	361	178 (49.3)	1.3 (1.1,1.5)	0.002	1.3 (1.1,1.5)	0.002
Per IQR = 3.01 mg/m^3			1.1 (1.0,1.2)	0.015	1.1 (1.0,1.2)	0.038

Notes: Adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, marriage status, prepregnancy BMI, diabetes, annual household income, season of delivery, preterm birth, birth weight, and breastfeeding. BMI, body mass index; CI, confidence interval; COWO, childhood overweight or obesity; F2YL, first 2 y of life; IQR, interquartile range; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3, Q4, quartile 4; RR, relative risk.
[a]Not adjusted for mother's prepregnancy BMI; mothers with BMI <18.5 kg/m^2 were excluded.

were in the upper 50th percentile of exposure during prenatal and postnatal periods were at least twice as likely to be overweight or obese between 2 y and 9 y than children of mothers with MPBMI in the normal range and with $PM_{2.5}$ exposure below 50th percentile.

Interaction on the multiplicative scale was not observed in any period of exposure examined. Furthermore, we found no quantitative evidence of supra-additivity because the 95% CIs for the RERI included 0 for every exposure period (Table 3). However, $PM_{2.5}$ exposure that exceeded the period-specific median was associated with increased risk of COWO in all MPBMI strata. These findings suggest that reduction of $PM_{2.5}$ exposure may reduce risk of COWO in children of mothers with MPBMI in the normal, overweight, and obese ranges. Although our findings do not show that MPBMI modifies the relationship between $PM_{2.5}$ and COWO, children of mothers with obesity at the time of conception who were also exposed to $PM_{2.5}$ concentrations above the median of 10.46–10.89 $\mu g/m^3$ were at higher risk of COWO than children of mothers with one of these risk factors alone. Given the high prevalence of obesity among women of reproductive age in the United States and in other developed countries (>30%) (Ogden et al. 2014; WHO 2013) and the associated risk of COWO for their offspring, reduction of $PM_{2.5}$ exposure during the prenatal and postnatal periods may be an important consideration in reducing COWO in this high-risk subpopulation.

Comparison across studies of air pollution and adiposity in children is complicated by differences in study design and in the exact air pollutants and outcomes examined, but consistent with our findings, a body of literature suggests that exposure to air pollutants may contribute to increased adiposity early in life and that these effects persist with age. A significant association between particulate matter ≤10 μm in diameter (PM_{10}) and COWO was reported in a large, multicity cross-sectional study of children 2–14 y living in China between 2006 and 2008 (Dong et al. 2014). In a cohort of 3,318 children in California who were followed up throughout late childhood and adolescence, those living closest to roadways at 10 y had a significantly higher BMI at age 18 than children living farther away from roadways, and the effect increased synergistically with joint exposure to roadway pollution and secondhand tobacco smoke (Jerrett et al. 2010; McConnell et al. 2015).

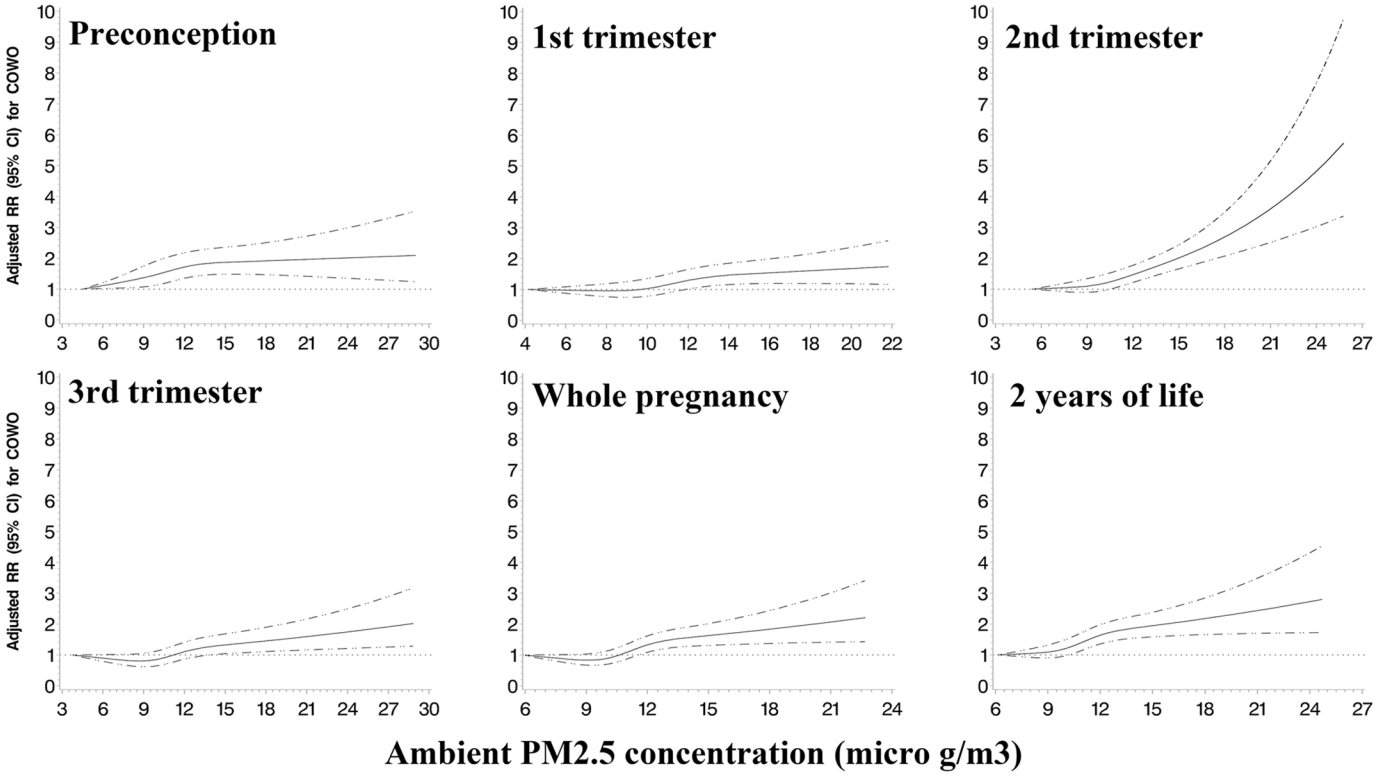

Figure 1. Associations of early-life exposure to ambient $PM_{2.5}$ with the risk of childhood overweight or obesity based on spline regression models. All estimates are adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marriage status, body mass index before pregnancy, household income per year, season of delivery, preterm birth, breastfeeding, and birth weight. COWO, childhood overweight/obesity; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.

The effects of prenatal exposure to $PM_{2.5}$ on birth outcomes has been studied extensively (Shah et al. 2011; Wang et al. 1997; Xu et al. 1995), but studies of postnatal outcomes are less common. In a study of the effect of prenatal exposure to air pollution on adiposity, Fleisch et al. (2015) reported that the highest quartile of neighborhood traffic density was significantly associated with an increase in weight-for-length gain [$\beta = 0.25$ units (95% CI: 0.01, 0.49)] and with higher odds of $\geq$95% weight-for-length [OR = 1.84 (95% CI: 1, .11, 3.05)] at age 6 mo. In the same study, $PM_{2.5}$ exposure was also positively associated with these two outcomes, but the association did not reach significance. In a follow-up study of cardiometabolic health indicators in the same cohort, distance to a major roadway at the time of birth was inversely associated with BMI-*z* in early and mid-childhood; no association was found for prenatal $PM_{2.5}$ exposure and BMI-*z* in early and mid-childhood. Prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) during pregnancy was strongly associated with obesity at 5 y [RR = 1.79 (95% CI: 1, .09, 2, .96), $n = 422$] and at 7 y [RR = 2.26 (95% CI: 1, .28, 4.00), $n = 341$)] in a study population that was demographically very similar to ours (Rundle et al. 2012), although unlike $PM_{2.5}$, PAHs are thought to act primarily via a hormonal mechanistic pathway.

The mechanism by which $PM_{2.5}$ affects overweight and obesity is not well understood, but studies conducted in rodents show that $PM_{2.5}$induces inflammatory responses in visceral adipose tissue (de Melo et al. 2015; Sun et al. 2009; Xu et al. 2010). Another rodent study reported increased inflammation of the epididymal fat pad in male rats exposed to unfiltered polluted air in Beijing *in utero* compared with those exposed to filtered air, suggesting that a proinflammatory mechanistic pathway may underlie associations between maternal air pollution exposure and risk of COWO in offspring (Wei et al. 2016). Notably, the second trimester is a critical period of development for white adipose tissue (Gesta et al. 2007).

The main strengths of this study are its prospective design and the follow-up of our study population from birth through childhood, which facilitated examination of the long-term effects of early-life exposures to $PM_{2.5}$ and maternal overweight or obesity on adiposity in childhood. In addition, the use of medical records, structured questionnaires, and quality assurance protocols such as the clinical protocol for collection of child height and weight data ensured high-quality exposure, outcome, and covariate data. Postnatal confounding variables that were controlled for in the study included breastfeeding, age, and sex; the last two were controlled by the use of age- and sex-specific BMI-*z* scores. However, there may be residual confounding from prenatal and postnatal variables that were not accounted for in the model.

Moderate to strong correlations between exposures during different prenatal and postnatal periods limited our ability to examine the effects of a specific period of exposure while controlling for exposure during other periods. To avoid collinearity, we examined each exposure period in a separate single-period model. Period-specific risk ratios may reflect the effects of chronic exposure or exposure during other prenatal or postnatal periods.

Restriction of our study to a single city limits the generalizability of our findings to other geographic locations or to other populations with different social and demographic makeups. Generalizability may also be limited by the high prevalence of preterm birth and of low birth weight in the BBC compared with the general population because low birth weight is a risk

Table 3. Joint effect of maternal prepregnancy BMI and $PM_{2.5}$ exposure on the risk of childhood overweight or obesity.

Maternal BMI	$PM_{2.5}$ μg/m$^{3\xi}$	*n*	COWO Number (%)	Crude		Adjusted	
				RR (95% CI)	*p*-value	RR (95% CI)	*p*-value
Preconception	≥10.80						
Normal weight	No	325	85 (26.2)	1.0 (1.0,1.0)	Reference	1.0 (1.0,1.0)	Reference
Normal weight	Yes	312	124 (39.7)	1.5 (1.2,1.9)	<0.001	1.5 (1.2,1.9)	<0.001
Overweight	No	203	99 (48.8)	1.9 (1.5,2.3)	<0.001	1.8 (1.5,2.3)	<0.001
Overweight	Yes	215	91 (42.3)	1.6 (1.3,2.1)	<0.001	1.5 (1.2,1.9)	0.001
Obesity	No	170	84 (49.4)	1.9 (1.5,2.4)	<0.001	1.7 (1.4,2.2)	<0.001
Obesity	Yes	169	103 (60.9)	2.3 (1.9,2.9)	<0.001	2.3 (1.8,2.8)	<0.001
Interaction $PM_{2.5}$[a] Overweight				0.6 (0.4,0.8)	0.006	0.6 (0.4,0.8)	0.004
Interaction $PM_{2.5}$[a] Obesity				0.8 (0.5,1.2)	0.305	0.9 (0.6,1.3)	0.479
Interaction $PM_{2.5}$[a] Overweight + Obesity[a]				1.1 (0.7,1.5)	0.769	1.1 (0.8,1.6)	0.498
$RERI_{overweight}$ (95% CI) = –0.44(–1.52, –0.19)							
$RERI_{obesity}$ (95% CI) = 0.04 (–0.52, 0.31)							
1st trimester	≥10.81						
Normal weight	No	332	91 (27.4)	1.0 (1.0,1.0)	Reference	1.0 (1.0,1.0)	Reference
Normal weight	Yes	313	122 (39.0)	1.4 (1.1,1.8)	0.002	1.4 (1.1,1.7)	0.005
Overweight	No	198	88 (44.4)	1.6 (1.3,2.0)	<0.001	1.5 (1.2,1.9)	<0.001
Overweight	Yes	225	105 (46.7)	1.7 (1.4,2.1)	<0.001	1.6 (1.3,2.0)	<0.001
Obesity	No	176	87 (49.4)	1.8 (1.4,2.3)	<0.001	1.7 (1.3,2.1)	<0.001
Obesity	Yes	169	103 (60.9)	2.2 (1.8,2.8)	<0.001	2.1 (1.7,2.6)	<0.001
Interaction $PM_{2.5}$[a] Overweight				0.7 (0.5,1.1)	0.130	0.8 (0.5,1.2)	0.214
Interaction $PM_{2.5}$[a] Obesity				0.9 (0.6,1.3)	0.478	0.9 (0.6,1.3)	0.602
Interaction $PM_{2.5}$[a] Overweight + Obesity[a]				1.0 (0.7,1.4)	0.941	1.0 (0.7,1.4)	0.953
$RERI_{overweight}$ (95% CI) = –0.11 (–0.70, 0.06)							
$RERI_{obesity}$ (95% CI) = 0.03 (–0.49, 0.25)							
2nd trimester	≥10.75						
Normal weight	No	330	84 (25.5)	1.0 (1.0,1.0)	Reference	1.0 (1.0,1.0)	Reference
Normal weight	Yes	320	132 (41.3)	1.6 (1.3,2.0)	<0.001	1.6 (1.2,2.0)	<0.001
Overweight	No	205	94 (45.9)	1.8 (1.4,2.3)	<0.001	1.7 (1.3,2.2)	<0.001
Overweight	Yes	225	104 (46.2)	1.8 (1.4,2.3)	<0.001	1.7 (1.3,2.2)	<0.001
Obesity	No	180	88 (48.9)	1.9 (1.5,2.4)	<0.001	1.8 (1.4,2.2)	<0.001
Obesity	Yes	169	104 (61.5)	2.4 (1.9,3.0)	<0.001	2.3 (1.8,2.9)	<0.001
Interaction $PM_{2.5}$[a] Overweight				0.6 (0.4,0.9)	0.017	0.6 (0.4,1.0)	0.032
Interaction $PM_{2.5}$[a] Obesity				0.8 (0.5,1.2)	0.209	0.8 (0.6,1.2)	0.389
Interaction $PM_{2.5}$[a] Overweight + Obesity[a]				1.0 (0.7,1.4)	0.849	1.0 (0.7,1.5)	0.870
$RERI_{overweight}$ (95% CI) = –0.23 (–1.00, 0.00)							
$RERI_{obesity}$ (95% CI) = 0.04 (–0.54, 0.34)							
3rd trimester	≥10.75						
Normal weight	No	336	92 (27.4)	1.0 (1.0,1.0)	Reference	1.0 (1.0,1.0)	Reference
Normal weight	Yes	315	126 (40.0)	1.5 (1.2,1.8)	0.001	1.4 (1.1,1.8)	0.001
Overweight	No	198	86 (43.4)	1.6 (1.3,2.0)	<0.001	1.5 (1.2,1.9)	0.001
Overweight	Yes	225	114 (50.7)	1.9 (1.5,2.3)	<0.001	1.8 (1.4,2.2)	<0.001
Obesity	No	175	90 (51.4)	1.9 (1.5,2.4)	<0.001	1.8 (1.4,2.2)	<0.001
Obesity	Yes	169	101 (59.8)	2.2 (1.8,2.7)	<0.001	2.0 (1.6,2.5)	<0.001
Interaction $PM_{2.5}$[a] Overweight				0.8 (0.5,1.2)	0.256	0.8 (0.6,1.2)	0.338
Interaction $PM_{2.5}$[a] Obesity				0.8 (0.5,1.2)	0.251	0.8 (0.5,1.2)	0.301
Interaction $PM_{2.5}$[a] Overweight + Obesity[a]				0.9 (0.6,1.2)	0.433	0.9 (0.6,1.3)	0.496
$RERI_{overweight}$ (95% CI) = –0.04 (–0.55, 0.14)							
$RERI_{obesity}$ (95% CI) = –0.04 (–0.64, 0.20)							
Whole pregnancy	≥10.89						
Normal weight	No	335	93 (27.8)	1.0 (1.0,1.0)	Reference	1.0 (1.0,1.0)	Reference
Normal weight	Yes	322	125 (38.8)	1.4 (1.1,1.7)	0.003	1.4 (1.1,1.7)	0.007
Overweight	No	214	96 (44.9)	1.6 (1.3,2.0)	<0.001	1.5 (1.2,1.9)	<0.001
Overweight	Yes	220	106 (48.2)	1.7 (1.4,2.2)	<0.001	1.6 (1.3,2.1)	<0.001
Obesity	No	174	86 (49.4)	1.8 (1.4,2.2)	<0.001	1.6 (1.3,2.1)	<0.001
Obesity	Yes	181	108 (59.7)	2.1 (1.7,2.7)	<0.001	2.0 (1.6,2.5)	<0.001
Interaction $PM_{2.5}$[a] Overweight				0.8 (0.5,1.1)	0.179	0.8 (0.5,1.2)	0.281
Interaction $PM_{2.5}$[a] Obesity				0.9 (0.6,1.3)	0.460	0.9 (0.6,1.4)	0.698
Interaction $PM_{2.5}$[a] Overweight + Obesity[a]				1.0 (0.7,1.4)	0.885	1.0 (0.7,1.5)	0.854
$RERI_{overweight}$ (95% CI) = –0.08 (–0.62, 0.09)							
$RERI_{obesity}$ (95% CI) = 0.04 (–0.46, 0.25)							
The first 2 y of life	≥10.46						
Normal weight	No	342	90 (26.3)	1.0 (1.0,1.0)	Reference	1.0 (1.0,1.0)	Reference
Normal weight	Yes	315	128 (40.6)	1.5 (1.2,1.9)	<0.001	1.5 (1.2,1.9)	<0.001
Overweight	No	207	97 (46.9)	1.8 (1.4,2.2)	<0.001	1.7 (1.3,2.1)	<0.001
Overweight	Yes	227	105 (46.3)	1.8 (1.4,2.2)	<0.001	1.7 (1.4,2.1)	<0.001
Obesity	No	174	84 (48.3)	1.8 (1.5,2.3)	<0.001	1.7 (1.3,2.1)	<0.001
Obesity	Yes	181	110 (60.8)	2.3 (1.9,2.9)	<0.001	2.2 (1.8,2.8)	<0.001
Interaction $PM_{2.5}$[a] Overweight				0.6 (0.4,0.9)	0.023	0.7 (0.5,1.0)	0.039
Interaction $PM_{2.5}$[a] Obesity				0.8 (0.6,1.2)	0.307	0.9 (0.6,1.3)	0.469

(Continued)

Table 3. Continued

Maternal BMI	$PM_{2.5}$ $\mu g/m^3$ [ξ]	*n*	COWO Number (%)	Crude RR (95% CI)	Crude *p*-value	Adjusted RR (95% CI)	Adjusted *p*-value
Interaction $PM_{2.5}$[a] Overweight+Obesity[a]				1.0 (0.7,1.4)	0.988	1.0 (0.7,1.5)	0.797
$RERI_{overweight}$ (95% CI) = –0.21 (–0.92, 0.01)							
$RERI_{obesity}$ (95% CI) = 0.04 (–0.48, 0.31)							

Notes: Normal weight, overweight, and obesity are defined as maternal prepregnancy BMI: 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m^2, respectively. Adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marriage status, household income per year, season of delivery, preterm birth, birth weight, and breastfeeding. Mothers with prepregnancy BMI <18.5 kg/m^2 were excluded. BMI, body mass index; CI, confidence interval; COWO, childhood overweight or obesity; F2YL, first 2 y of life; IQR, interquartile range; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm; RERI, relative excess risk of childhood overweight/obesity due to interaction using method of variance estimates recovery (MOVER) method; RR, relative risk.

[a]A Wald test was performed on the first two interaction terms to evaluate the interaction between $PM_{2.5}$ and Overweight + Obesity.

factor for COWO (Reilly et al. 2005). That said, the observation of an effect of $PM_{2.5}$ on COWO at relatively low exposures (near or below the current U.S. EPA daily $PM_{2.5}$ standard of 12 $\mu g/m^3$) raises a possibility that populations at similar or higher exposures may also be at risk. $PM_{2.5}$ concentrations in Boston are highest in summer, reflecting the large contribution of regional air pollution to $PM_{2.5}$ concentrations in the area. A study of $PM_{2.5}$ composition in Boston conducted between 2002 and 2010 found that regional air pollution sources account for nearly half of the $PM_{2.5}$ pollution in Boston (48%), followed by motor vehicles (21%) and wood burning (19%) as the next highest–contributing sources, underscoring the public health importance of decreases in both regional and traffic-related pollution (Masri et al. 2015).

Another limitation of this study is that our exposure assessment may not fully account for spatial variability in ambient $PM_{2.5}$ concentrations within the area around each stationary monitor, resulting in some exposure misclassification, which might lead us to underestimate the risk of exposure on COWO. However, >85% of our population lived within 10 km of a monitor, a distance within which $PM_{2.5}$ concentrations are relatively homogeneous (Kloog et al. 2012). Furthermore, our results were robust in subgroup analysis of subjects within 10 km and within 5 km of a monitor, supporting the characterization of exposure in our study by stationary $PM_{2.5}$ monitors.

Conclusion

To the best of our knowledge, this is the first longitudinal birth cohort study to examine the joint effect of MPBMI and early-life exposure to ambient $PM_{2.5}$ on the risk of COWO. We report a positive monotonic relationship between exposure to ambient $PM_{2.5}$ *in utero* and from birth through F2YL and the risk of COWO. Furthermore, children of mothers who were obese at conception and who were exposed to $PM_{2.5}$ at or above concentrations of 10.5–10.9 $\mu g/m^3$ were at least twice the risk of COWO compared with children of mothers with MPBMI in the normal range and low $PM_{2.5}$ exposure. These findings have implications for air pollution policies given the significant effect among participants exposed at near or below the annual federal standard for $PM_{2.5}$ of 12 $\mu g/m^3$ (U.S. EPA 2013).

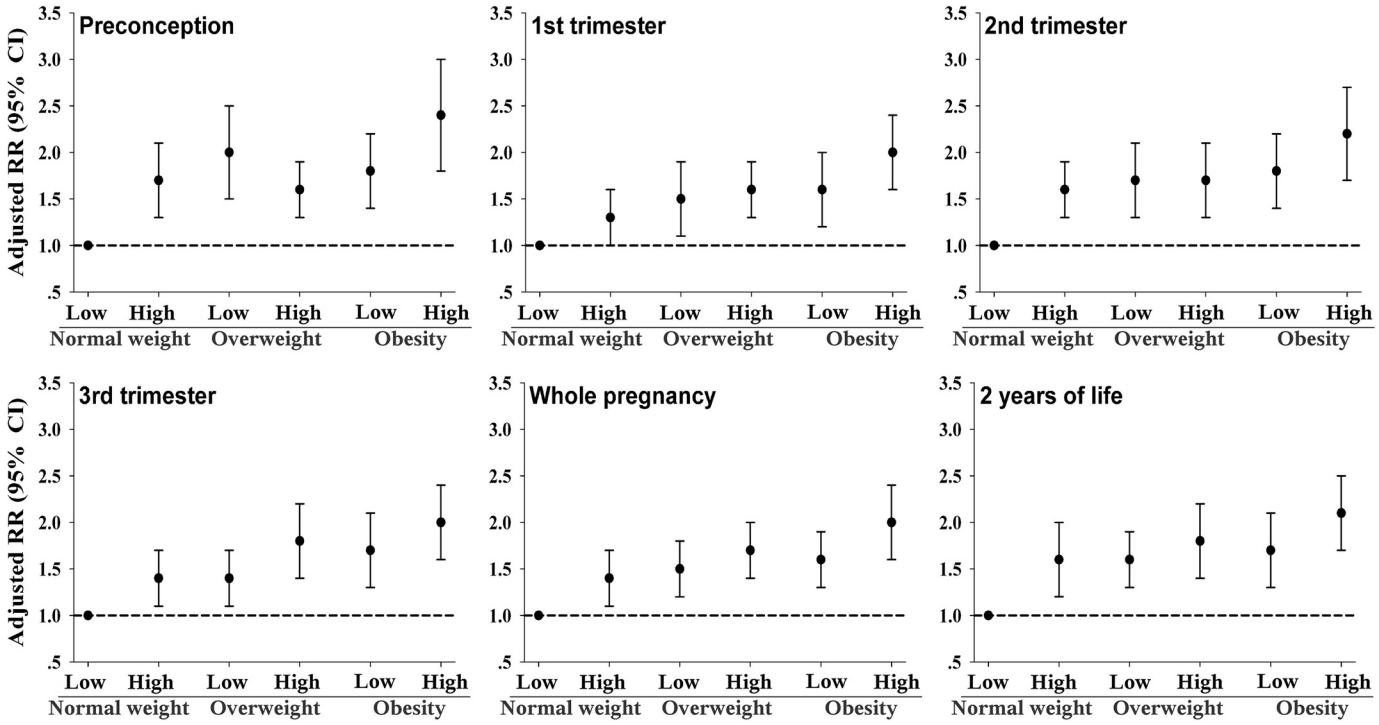

Figure 2. Adjusted combined effects of mother's prepregnancy BMI and exposure to $PM_{2.5}$ on the risk of childhood overweight or obesity by time point (sorted by $PM_{2.5}$ level). All estimates are adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marriage status, household income per year, season of delivery, preterm birth, breastfeeding and birth weight. Normal, overweight, and obese categories indicating mother's prepregnancy BMI are 18.5–24.9, 25.0–29.9 and ≥30 kg/m^2, respectively; Low indicates ambient $PM_{2.5}$ <12 $\mu g/m^3$; High indicates ambient $PM_{2.5}$ ≥12 $\mu g/m^3$. BMI, body mass index; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.

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References

CDC (Centers for Disease Control and Prevention). 2011. Growth chart training. http://www.Cdc.Gov/nccdphp/dnpao/growthcharts/resources/sas.Htm. [accessed 5 February 2014].

de Melo JO, Soto SF, Katayama IA, Wenceslau CF, Pires AG, Veras MM, et al. 2015. Inhalation of fine particulate matter during pregnancy increased IL-4 cytokine levels in the fetal portion of the placenta. Toxicol Lett 232:475–480, PMID: 25481569, https://doi.org/10.1016/j.toxlet.2014.12.001.

Dong GH, Qian Z, Liu M-M, Wang D, Ren W-H, Flick LH, et al. 2014. Ambient air pollution and the prevalence of obesity in Chinese children: The seven northeastern cities study. Obesity 22:795–800, https://doi.org/10.1002/oby.20198.

Durrleman S, Simon R. 1989. Flexible regression models with cubic splines. Stat Med 8:551–561, PMID: 2657958, https://doi.org/10.1002/sim.4780080504.

Fleisch AF, Luttmann-Gibson H, Perng W, Rifas-Shiman SL, Coull BA , Kloog I, et al. 2017. Prenatal and early life exposure to traffic pollution and cardiometabolic health in childhood. Pediatr Obes 12:48–57, https://doi.org/10.1111/ijpo.12106.

Fleisch AF, Rifas-Shiman SL, Koutrakis P, Schwartz JD, Kloog I, Melly S, et al. 2015. Prenatal exposure to traffic pollution: Associations with reduced fetal growth and rapid infant weight gain. Epidemiology 26:43–50, PMID: 25437317, https://doi.org/10.1097/EDE.0000000000000203.

Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. 2010. Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med 362:485–493, PMID: 20147714, https://doi.org/10.1056/NEJMoa0904130.

Gesta S, Tseng YH, Kahn CR. 2007. Developmental origin of fat: Tracking obesity to its source. Cell 131:242–256, PMID: 17956727, https://doi.org/10.1016/j.cell.2007.10.004.

Gillman MW. 2005. Developmental origins of health and disease. N Engl J Med 353:1848–1850, PMID: 16251542, https://doi.org/10.1056/NEJMe058187.

Goran MI, Ball GD, Cruz ML. 2003. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. J Clin Endocrinol Metab 88:1417–1427, PMID: 12679416, https://doi.org/10.1210/jc.2002-021442.

Janesick A, Blumberg B. 2012. Obesogens, stem cells and the developmental programming of obesity. Int J Androl 35:437–448, PMID: 22372658, https://doi.org/10.1111/j.1365-2605.2012.01247.x.

Jerrett M, McConnell R, Chang CC, Wolch J, Reynolds K, Lurmann F, et al. 2010. Automobile traffic around the home and attained body mass index: A longitudinal cohort study of children aged 10–18 years. Prev Med 50:S50–S58, https://doi.org/10.1016/j.ypmed.2009.09.026.

Jerrett M, McConnell R, Wolch J, Chang R, Lam C, Dunton G, et al. 2014. Traffic-related air pollution and obesity formation in children: A longitudinal, multilevel analysis. Environ Health 13:49, PMID: 24913018, https://doi.org/10.1186/1476-069X-13-49.

Kim SY, Dietz PM, England L, Morrow B, Callaghan WM. 2007. Trends in prepregnancy obesity in nine states, 1993–2003. Obesity (Silver Spring) 15:986–993, PMID: 17426334, https://doi.org/10.1038/oby.2007.621.

Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. 2012. Using new satellite based exposure methods to study the association between pregnancy $pm_{2.5}$ exposure, premature birth and birth weight in Massachusetts. Environ Health 11:40, https://doi.org/10.1186/1476-069X-11-40.

Kumar R, Yu Y, Story RE, Pongracic JA, Gupta R, Pearson C, et al. 2008. Prematurity, chorioamnionitis, and the development of recurrent wheezing: A prospective birth cohort study. J Allergy Clin Immunol 121:878–884, e876, https://doi.org/10.1016/j.jaci.2008.01.030.

Lawlor DA, Leon DA. 2005. Association of body mass index and obesity measured in early childhood with risk of coronary heart disease and stroke in middle age: Findings from the Aberdeen Children of the 1950s prospective cohort study. Circulation 111:1891–1896, PMID: 15837941, https://doi.org/10.1161/01.CIR.0000161798.45728.4D.

Lawlor DA. 2013. The Society for Social Medicine John Pemberton Lecture 2011. Developmental overnutrition–an old hypothesis with new importance? Int J Epidemiol 42:7–29, https://doi.org/10.1093/ije/dys209.

Lobstein T, Baur L, Uauy R, IASO International Obesity TaskForce. 2004. Obesity in children and young people: A crisis in public health. Obes Rev 5:4–104, PMID: 15096099, https://doi.org/10.1111/j.1467-789X.2004.00133.x.

Masri S, Kang CM, Koutrakis P. 2015. Composition and sources of fine and coarse particles collected during 2002–2010 in Boston, MA. J Air Waste Manag Assoc 65:287–297, PMID: 25947125, https://doi.org/10.1080/10962247.2014.982307.

McConnell R, Shen E, Gilliland FD, Jerrett M, Wolch J, Chang CC, et al. 2015. A longitudinal cohort study of body mass index and childhood exposure to secondhand tobacco smoke and air pollution: The Southern California Children's Health Study. Environ Health Perspect 123:360–366, PMID: 25389275, https://doi.org/10.1289/ehp.1307031.

Nachman RM, Mao G, Zhang X, Hong X, Chen Z, Soria CS, et al. 2016. Intrauterine inflammation and maternal exposure to ambient $PM_{2.5}$ during preconception and specific periods of pregnancy: The Boston Birth Cohort. Environ Health Perspect 124:1608–1615, PMID: 27120296, https://doi.org/10.1289/EHP243.

Ogden CL, Carroll MD, Kit BK, Flegal KM. 2014. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA 311:806–814, PMID: 24570244, https://doi.org/10.1001/jama.2014.732.

Oken E, Levitan EB, Gillman MW. 2008. Maternal smoking during pregnancy and child overweight: Systematic review and meta-analysis. Int J Obes (Lond) 32:201–210, PMID: 18278059, https://doi.org/10.1038/sj.ijo.0803760.

Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. 2005. Early life risk factors for obesity in childhood: Cohort study. BMJ 330:1357, PMID: 15908441, https://doi.org/10.1136/bmj.38470.670903.E0.

Rifas-Shiman SL, Gillman MW, Oken E, Kleinman K, Taveras EM. 2012. Similarity of the CDC and WHO weight-for-length growth charts in predicting risk of obesity at age 5 years. Obesity (Silver Spring) 20:1261–1265, PMID: 22158005, https://doi.org/10.1038/oby.2011.350.

Romano ME, Savitz DA, Braun JM. 2014. Challenges and future directions to evaluating the association between prenatal exposure to endocrine disrupting chemicals and childhood obesity. Curr Epidemiol Rep 1:57–66, https://doi.org/10.1007/s40471-014-0007-3.

Rundle A, Hoepner L, Hassoun A, Oberfield S, Freyer G, Holmes D, et al. 2012. Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. Am J Epidemiol 175:1163–1172, PMID: 22505764, https://doi.org/10.1093/aje/kwr455.

Shah PS, Balkhair T, Knowledge Synthesis Group on Determinants of Preterm/LBW births. 2011. Air pollution and birth outcomes: A systematic review. Environ Int 37:498–516, PMID: 21112090, https://doi.org/10.1016/j.envint.2010.10.009.

Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, et al. 2009. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 119:538–546, https://doi.org/10.1161/CIRCULATIONAHA.108.799015.

The NS, Suchindran C, North KE, Popkin BM, Gordon-Larsen P. 2010. Association of adolescent obesity with risk of severe obesity in adulthood. JAMA 304:2042–2047, PMID: 21063014, https://doi.org/10.1001/jama.2010.1635.

U.S. EPA (U.S. Environmental Protection Agency). 2013. U.S. Environmental protection agency, national ambient air quality standards for particulate matter; final rule. Fed Reg 78:3086–3287.

Vahratian A. 2009. Prevalence of overweight and obesity among women of childbearing age: Results from the 2002 national survey of family growth. Matern Child Health J 13:268–273, PMID: 18415671, https://doi.org/10.1007/s10995-008-0340-6.

Wang G, Hu FB, Mistry KB, Zhang C, Ren F, Huo Y, et al. 2016. Association between maternal prepregnancy body mass index and plasma folate concentrations with child metabolic health. JAMA Pediatr 170:e160845, PMID: 27295011, https://doi.org/10.1001/jamapediatrics.2016.0845.

Wang X, Ding H, Ryan L, Xu X. 1997. Association between air pollution and low birth weight: A community-based study. Environ Health Perspect 105:514–520, PMID: 9222137, https://doi.org/10.1289/ehp.97105514.

Wang X, Zuckerman B, Pearson C, Kaufman G, Chen C, Wang G, et al. 2002. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. JAMA 287:195–202, PMID: 11779261, https://doi.org/10.1001/jama.287.2.195.

Wei Y, Zhang JJ, Li Z, Gow A, Chung KF, Hu M et al. 2016. Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: Findings from a natural experiment in Beijing. FASEB J 30:2115–2122, PMID: 26891735, https://doi.org/10.1096/fj.201500142.

Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. 2004. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 350:2362–2374, PMID: 15175438, https://doi.org/10.1056/NEJMoa031049.

WHO (World Health Organization). 2013. Country profiles on nutrition, physical activity and obesity in the 53 WHO European Region Member States. Methodology and summary (2013). http://www.euro.who.int/en/publications/abstracts/country-profiles-on-nutrition,-physical-activity-and-obesity-in-the-53-who-european-region-member-states.-methodology-and-summary-2013 [accessed 6 January 2016].

Xu X, Ding H, Wang X. 1995. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: A community-based cohort study. Arch Environ Health 50:407–415, PMID: 8572718, https://doi.org/10.1080/00039896.1995.9935976.

Xu X, Yavar Z, Verdin M, Ying Z, Mihai G, Kampfrath T, et al. 2010. Effect of early particulate air pollution exposure on obesity in mice: Role of p47phox. Arterioscler Thromb Vasc Biol 30:2518–2527, https://doi.org/10.1161/ATVBAHA.110.215350.

Zou GY. 2004. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 159:702–706, PMID: 15033648, https://doi.org/10.1093/aje/kwh090.

Zou GY. 2008. On the estimation of additive interaction by use of the four-by-two table and beyond. Am J Epidemiol 168:212–224, PMID: 18511428, https://doi.org/10.1093/aje/kwn104.