

Low birth weight and PM_{2.5} in Puerto Rico

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Background: Low birth weight (LBW) has been associated with adverse health outcomes across the lifespan. Among ethnic/racial minority populations, few studies have examined the association between LBW (<2,500 or ≥2,500g) and prenatal exposure to air pollution, a key modifiable environmental risk factor.

Methods: We examined the association between LBW and prenatal exposure to PM_{2.5} in a Hispanic and black population in Puerto Rico between 1999 and 2013, adjusting for individual and municipality-level confounders. We used modified Poisson regression to estimate the association and performed sensitivity analyses treating birth weight as continuous or polychotomous. In secondary analyses, we applied a 2-stage mixed effects model suitable for longitudinally measured exposures and binary outcomes.

Results: Among 332,129 total and 275,814 term births, 12.2% and 6.3% of infants had LBW, respectively. Eighty-eight percent of mothers were Hispanic. Mean (SD) PM_{2.5} concentrations declined from 9.9 (1.7) µg/m³ in 1999 to 6.1 (1.1) µg/m³ in 2013. Mean birth weights dropped to 3,044g in 2010 and rose steadily afterward. Among term births, a SD increase in PM_{2.5} was associated with a 3.2% (95% CI = -1.0%, 6.3%) higher risk of LBW. First (risk ratio, 1.02; 95% CI = 1.00, 1.04) and second (1.02; 95% CI = 1.01, 1.05) trimester exposures were associated with increased LBW risk. In a 2-stage approach that longitudinally modeled monthly prenatal exposure levels, a standard deviation increase in average PM_{2.5} was associated with higher risk of LBW (odds ratio, 1.04; 95% CI = 1.01, 1.08).

Conclusions: In Puerto Rico, LBW is associated with prenatal PM_{2.5} exposure.

Introduction

Low birth weight (LBW) is an established risk factor for numerous adverse health outcomes, including increased risk of neonatal and postneonatal morbidity and mortality and morbidity in adulthood. LBW infants are up to 12× more likely to die in the perinatal period and have up to a 3-fold higher risk for morbidity because of a range of childhood illnesses, with the risk of disease or death decreasing with increasing birth weight.^{1–3} LBW has also been linked to several health problems in adulthood, including systemic arterial hypertension,¹ chronic kidney disease,¹ ischemic heart disease,^{4,5} stroke,⁶ chronic obstructive pulmonary disease,⁷ and metabolic pathologies such as type II diabetes mellitus.⁸ The costs associated with adverse outcomes related to LBW are substantial, with estimates of ≈\$3.4–\$6 billion per year in the United States.^{9,10} Given its prevalence, costs, and health consequences, developing a better understanding of the modifiable etiologic factors for LBW remains essential.

Previous studies have examined the association between exposure to particulate matter <2.5 microns in aerodynamic diameter (PM_{2.5}) and LBW.¹¹ Most of these studies have been conducted over relatively short periods of time and predominantly in mainland United States or Europe, among mostly Caucasian populations, with comparatively little information about the PM_{2.5}-LBW association in Hispanic and other ethnic/racial minority populations. In a recent meta-analysis of 16 studies of PM_{2.5} and birth weight, for example, only 1 included participants from outside continental US, Canada, or Western Europe.¹² In addition, results from the few studies of air pollution and LBW conducted in the US suggested that the prevalence of LBW and air pollution exposures were comparatively higher,^{13,14} and the adverse effects of PM_{2.5} on birth weight were stronger^{15,16} among non-Caucasian whites. These effects may be because of the fact that ethnic/racial minority populations tend to have lower socioeconomic status (SES) and to reside near pollutant emission sources, raising concerns about environmental health and justice.¹⁷ These concerns may be particularly significant in Puerto Rico, which has a predominantly Hispanic or black population with high LBW rates (11.0% versus 8.1% in the conterminous US in 2015) and a high density of Superfund sites.^{18,19}

Understanding whether exposure to PM_{2.5} in certain time-windows during gestation is key for planning interventions and advising pregnant women, but evidence of trimester-specific effects is scant and inconclusive.^{12,15} Because high correlations

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The authors report no conflict of interest.

Data and computing code can be obtained by contacting the corresponding author.

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Environmental Epidemiology (2019) 3:e058

Received: 23 January 2019; Accepted 19 June 2019

Published online 31 July 2019

DOI: 10.1097/EE9.000000000000058

What this study adds

Our study provides new information on the association of PM_{2.5} and LBW in a large Hispanic and black population in Puerto Rico, a little-studied population. We found a substantially larger fraction of low birth weight (LBW) babies born in Puerto Rico (12.2%) as compared with the entire US (8.7%). PM_{2.5} was a significant risk factor for LBW, especially for infants who were female or born to mothers who were unmarried or had fewer prenatal visits. We demonstrated the importance of neighborhood characteristics, such as socioeconomic status, to PM_{2.5} and LBW studies.

among the trimester-specific exposure estimates may make it difficult to identify critical windows of $PM_{2.5}$ exposure, some investigators have used techniques that seek to minimize covariance among variables representing trimester exposures.¹⁵ We examined the association of prenatal $PM_{2.5}$ exposure and birth weights among all births recorded in Puerto Rico from 1999 to 2013. We assessed whether LBW risk was higher among certain women and infants or during different pregnancy exposure windows using a conventional regression technique and a 2-stage method designed for the analysis of longitudinally measured exposures and a single binary outcome.²⁰

Methods

Study design and population

We conducted a population-based cohort study of live births in Puerto Rico from 1999 to 2013, restricting the analysis to 332,129 births to women residing in 37 municipalities with at least 50% of their land area within 10 miles of a US Environmental Protection Agency (EPA) Air Quality System (AQS) regulatory monitor. The median (interquartile range) size of the municipalities studied was 44.6 (27.4–60.3) square miles. Municipality was used as the geographic unit of analysis given the availability of birth, ecological, administrative, and occupational covariates at this level within Puerto Rico (see eFigure 1 for map; <http://links.lww.com/EE/A52>). Birth data, including pregnancy, parental, and infant information based on birth certificates were obtained from the Puerto Rico Department of Health (PRDoH), whose data typically account for more than 99% of all births in Puerto Rico. We restricted the analysis to singleton births with ≥ 20 weeks of gestation and for which the entire pregnancy occurred after 1998 (i.e., the estimated conception date was on or after 1 January 1999) and before 2014 (birth on or before 31 December 2013), consistent with the time span of covariate data availability. Gestational age was assessed via reported date of last menstrual period. The ethics review boards at the University of Puerto Rico, Northeastern University, and Tufts University provided approval.

Exposure assessment

Daily $PM_{2.5}$ concentrations were obtained from EPA AQS monitors located across Puerto Rico, which generally measured $PM_{2.5}$ concentrations every third day. The monitors use the Federal Reference Method (FRM) filtration techniques consistent with the National Ambient Air Quality Standards (NAAQS). $PM_{2.5}$ exposures were estimated for each baby as the measured concentration at the monitor closest to the mother's municipality of residence at the time of birth. If monitors were co-located, $PM_{2.5}$ concentrations from the monitor with the least missing data during the relevant prenatal periods were used.

For each monitor, we assessed missingness in $PM_{2.5}$ data. When a monitor had fewer than 7 $PM_{2.5}$ values in a given month, we imputed missing daily $PM_{2.5}$ concentrations using a random regression imputation technique,²¹ in which we estimated the $PM_{2.5}$ concentration from the most appropriate monitor with non-missing data for that day, with this monitor identified based on the inter-monitor correlation between non-missing PM values, its proximity to the monitor with missing data, and the predominant wind direction. $PM_{2.5}$ values at nearby monitoring sites were strongly correlated (Pearson correlation coefficients, 0.78–0.92). We did not impute exposure values for a monitor if no appropriate monitor from which to impute was identified. Once imputed, we applied a uniform smoother to each monitor's concentration series to calculate the average exposure estimate for each baby's prenatal period, including each month and trimester during gestation, as well as for the entire pregnancy

duration. Exposure estimates were considered valid when at least 75% of the expected exposure data were available.

Outcome assessment

In our main analyses, birth weight was assessed as a binary variable denoting either low or normal birth weight ($< 2,500$ g or $\geq 2,500$ g, respectively) based on birth certificate data from PRDoH. In secondary and sensitivity analyses, birth weight was also modeled as a continuous variable or categorized as very low birth weight ($< 1,500$ g), low birth weight ($\geq 1,500$ to $< 2,500$ g), or normal birth weight ($\geq 2,500$ g).

Covariate data

Data from PRDoH included information on race/ethnicity (Hispanic/non-Hispanic black), infant sex, municipality of residence at the time of infant birth, mother's age (continuous), parity, education level (< 10 , 10–11, 12, 13–15, and ≥ 16 years of school completed), urban or rural dwelling, marital status (married, living together but not married, neither married nor living with a partner), and whether or not the mother was on Medicaid. Pregnancy and delivery data included length of gestation period (days) and number of prenatal visits attended (< 10 or ≥ 10). Because body mass index (BMI) was available for births occurring after 2004, we included BMI as a covariate in sensitivity analyses of births post-2004. While some data on smoking and alcohol use during pregnancy were available, we did not include these variables in our analyses because of extensive missingness. We obtained area-level socioeconomic and health indicators for Puerto Rican municipalities from the American Community Survey (ACS, <https://www.census.gov/programs-surveys/acs>), including population density, income per capita (in 2013 inflation adjusted dollars), proportion of non-white non-Hispanic residents, average unemployment rate over the period 2004 to 2013, proportion of households with at least 1 of 4 severe US Department of Housing and Urban Development-designated problems (overcrowding, high housing cost, lack of kitchen, lack of plumbing), percentage of residents with a less than high school level of education, and the age adjusted prevalence of diabetes mellitus over the period 2004 to 2013.

Statistical analysis

We estimated the association between average prenatal $PM_{2.5}$ exposure and LBW in Puerto Rico using a modified Poisson regression procedure with a sandwich linearized estimator of variance to obtain a direct measure of the risk ratio. We obtained estimates for each trimester and the entire pregnancy period, scaling them to represent effect per standard deviation change in average $PM_{2.5}$ exposure level. We also performed secondary analyses using a 2-stage mixed effects model that accounts for the longitudinal exposure trajectory in the context of a binary outcome.²⁰ In some applications, such models have been shown to be preferable to separate models for average monthly or trimester-specific exposures because separate models may introduce nonrandom missingness and may bias the association between later month exposures and birth outcomes, given collinearity in exposures across months or trimesters and the higher likelihood that preterm babies will not have exposure measures for the eighth and ninth months of pregnancy.²⁰ For this 2-stage modeling approach, we first fit models of prenatal air pollution exposures for each pregnancy longitudinally as a function of time and then used the estimated random intercept and slope coefficients as predictors in a second-stage logistic regression model. Therefore, subject-specific exposure time trends from stage 1 were extracted and used with other covariates in a second stage model. If there is no linear trend in the relationship between the

exposure and the outcome (i.e., exposure during any month is equally associated with adverse pregnancy outcome), the slope coefficient will not be significant in the second stage model, and the intercept coefficient will represent the effect of the mean exposure across each pregnancy month on adverse birth effects. If there is a linear trend in the exposure-response relationship, the slope coefficient will be significant, representing the effect of that trend on birth outcomes. An indicator variable for month was included in the first stage, with the slopes for each of these months corresponding to the month-specific differential effect of the exposure on the outcome. If any of the slope coefficients is significant, it may suggest a potentially critical month of gestation with regard to the effect of $PM_{2.5}$ exposure on the LBW outcome. To facilitate model convergence, exposure and gestation age values were standardized and centered.

Model covariates were selected based on their documented importance to either exposure or outcome in previous studies. Base models adjusted for individual-level covariates including mother's age, number of other children (alive or deceased), infant's sex, gestational age, education level, urban/rural residence, marital status, number of prenatal visits attended, and season of birth. Fully adjusted models further controlled for area/municipality-level covariates including population density, income per capita, proportion of non-white non-Hispanic residents, average unemployment rate, proportion of households with at least one of four severe US Department of Housing and Urban Development-designated problems, percentage of residents with a less than high school level of education, and the age adjusted prevalence of diabetes mellitus. In addition, in all models, we adjusted for year of birth to account for long-term trends in birth outcomes and levels of pollution and allowed for potential clustering by municipality.

To assess the robustness of our results to alternative model specifications, we conducted several sensitivity analyses. First, we treated the outcome as either a continuous variable or a 3-category variable (very LBW, LBW, and normal birth weight) and performed linear regression or cumulative logistic single-stage analyses, respectively. We also modeled gestation age and $PM_{2.5}$ with quadratic terms, given literature suggesting that fetal growth is more rapid mid-term and slower later (i.e., after about 36 weeks) and that the effect of $PM_{2.5}$ may plateau at higher concentrations.²² Finally, we ran models that excluded gestational age as a covariate because some authors have highlighted its potential to introduce collider bias.²³ All analyses were performed using Stata 15.1 (StataCorp, TX) and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Our analytical dataset contained 332,129 Puerto Rican births that occurred between 1999 and 2013, constituting 74% of births recorded by PRDoH over that period in the 37 municipalities included in our analysis. The characteristics of the 26% of births not included in our analysis were similar to those in the analytic sample (eTable 1; <http://links.lww.com/EE/A52>). Of the total, 275,814 were term births (gestational age ≥ 37 weeks). Mothers were predominantly Hispanic (88.2%) with a mean age (standard deviation) of 25.4 (5.9) years, at least 10 years of schooling (89.7%), and most had attended 10 or more prenatal care visits (76.6%) (Table 1). Two-thirds of mothers lived in urban areas and about 43% reported being married when the birth occurred. Approximately 12.3% and 5.4% of all and term infants, respectively, were born with low (below 2,500g) birth weights (Table 1 and eTable 2; <http://links.lww.com/EE/A52>). About 52% of all infants were male and 17% were born preterm (eTable 2; <http://links.lww.com/EE/A52>). These statistics were similar to those observed in the entire sample of births with gestational age ≥ 20 weeks (Supplementary Materials, eTables 7–13; <http://links.lww.com/EE/A52>).

Although mean $PM_{2.5}$ concentrations in Puerto Rico have declined gradually – from 9.9 (standard deviation 1.7) $\mu\text{g}/\text{m}^3$ in 1999 to 6.1 (1.1) $\mu\text{g}/\text{m}^3$ in 2013—mean annual rates of LBW have remained high. Mean birth weights dropped from 1999 to 2010, when the mean birth weight equaled 3,044 grams, and rose steadily afterward (Figure 1). The range of $PM_{2.5}$ concentrations over the observation period was 2.9–12.5 $\mu\text{g}/\text{m}^3$, and the distribution of exposure levels across the prenatal period was similar for LBW and non-LBW infants. Mean monthly exposure levels ranged between 6.9 and 7.2 $\mu\text{g}/\text{m}^3$ for LBW infants and 7.0–7.2 $\mu\text{g}/\text{m}^3$ for their non-LBW counterparts, with standard deviations of ≈ 2 $\mu\text{g}/\text{m}^3$.

LBW risk decreased monotonically with increasing levels of mother's education and was also significantly lower for mothers who attended more prenatal care visits [risk ratio (RR), 0.75; 95% CI = 0.72, 0.78; Table 2]. Black mothers (RR, 1.06; 95% CI = 1.00, 1.12) and female infants (RR, 1.44; 95% CI = 1.39, 1.49) were positively associated with the risk of low birth weight. Type of medical insurance and rural or urban residence were not associated with low birth weight in our population of term infants (Table 2).

Our data are consistent with an increased risk of LBW with higher prenatal $PM_{2.5}$ concentrations, significant at the 10% alpha level, based on fully adjusted, single-stage modified Poisson models (RR, 1.03; 95% CI = 0.99, 1.06 for a standard deviation increase in $PM_{2.5}$; Table 3). When we modeled birth weight as a 3-category variable using an ordinal logistic model, $PM_{2.5}$ was significantly associated with having a low (above 1,500g but below 2,500g) or very low (<1,500g) birth weight, compared with having a normal birth weight (cumulative odds ratio, 1.04; 95% CI = 1.00, 1.07 for a standard deviation increase in $PM_{2.5}$). Consistent with this finding, we found a standard deviation increase in prenatal $PM_{2.5}$ exposures to be associated with a significantly higher risk of very low birth weight (<1,500g; RR, 1.06; 95% CI = 1.01, 1.17). When treating birth weight as a continuous variable (measured in grams), we observed that on average, a standard deviation increase in prenatal $PM_{2.5}$ concentration was associated with a 4.8 (95% CI = -7.3, 1.1) gram decrease in birth weight; however, this decrease was not statistically significant (Table 3).

In fully adjusted 2-stage models, a standard deviation increase in the predicted intercept was associated with a 4% higher odds of LBW (Table 4), suggesting that the mean $PM_{2.5}$ exposure level across the entire pregnancy is associated with LBW (as indicated by the subject-specific predicted intercepts). At the same time, we found a positive but nonstatistically significant slope coefficient, suggesting that each month of gestation was equally critical to the observed $PM_{2.5}$ -LBW association and that there is not a linear association between monthly $PM_{2.5}$ exposure levels throughout the pregnancy and odds of LBW. Given the nonsignificant slope coefficient, we fit a 2-stage model in which only the intercepts were estimated and extracted from the first stage and obtained similar results for the associations between average $PM_{2.5}$ exposure level across the entire pregnancy and LBW (OR, 1.04; 95% CI = 1.01, 1.08; Table 4). For both the Poisson and 2-stage models, exposure-outcome associations were not significant in base models that adjusted only for individual covariates.

In trimester-specific modified Poisson models, higher levels of exposure in the first (RR, 1.02; 95% CI = 1.00, 1.04) and second (RR, 1.02; 95% CI = 1.01, 1.05) trimesters were significantly associated with the risk of LBW, although third trimester exposure levels were not (eTable 3; <http://links.lww.com/EE/A52>). We did not find evidence to suggest that the association between prenatal exposure to $PM_{2.5}$ and risk of LBW varied by mother's age, infant sex, prenatal care utilization, urban/rural residence, or parity (eTable 4; <http://links.lww.com/EE/A52>). The risk of LBW was significantly higher among unmarried mothers ($P = 0.021$), those living in more densely populated

Table 1
Characteristics associated with term births in 37 municipalities in Puerto Rico, 1999–2013^a

Characteristic	All-term births (<i>N</i> = 275,814)	LBW (<i>n</i> = 14,739)	Not LBW (<i>n</i> = 261,075)
Individual-level characteristics			
Sex			
Male	140,669 (51.0)	6,224 (42.2)	134,445 (51.5)
Female	135,145 (49.0)	8,515 (57.8)	126,630 (48.5)
Estimated gestation length, mean (SD), weeks			
37–42 (normal)	38.6 (1.3)	38.1 (1.3)	38.6 (1.3)
>42	273,243 (99.1)	14,598 (99.0)	258,645 (99.1)
	2,571 (0.9)	141 (1.0)	2,430 (0.9)
Residential zone			
Urban	181,362 (65.8)	9,292 (63.1)	172,070 (65.9)
Rural	94,386 (34.2)	5,444 (36.9)	88,942 (34.1)
Birth weight, mean (SD), grams			
<1,000 (extremely LBW)	3,185.0 (436.5)	2,308.2 (225.2)	3,234.6 (390.5)
<1,500 (very LBW)	55 (0.02)		
1,500–2,499 (LBW)	224 (0.08)		
2,500–4,200 (normal)	14,739 (5.34)		
>4,200	257,205 (93.25)		
	3,870 (1.40)		
Health insurance: medicaid or charity	15,484 (6.6)	867 (7.0)	14,617 (6.6)
Number of other children (alive or deceased)			
0	116,051 (42.1)	7,041 (47.8)	109,010 (41.8)
1	85,910 (31.2)	4,036 (27.4)	81,874 (31.4)
2	44,061 (16.0)	2,057 (14.0)	42,004 (16.1)
3	17,444 (6.3)	893 (6.1)	16,551 (6.3)
≥4	12,346 (4.5)	712 (4.8)	11,634 (4.5)
Mother's level of education, years			
0–9	28,354 (10.3)	1,965 (13.4)	26,389 (10.1)
10–11	28,097 (10.2)	1,884 (12.8)	26,213 (10.1)
12	86,189 (31.3)	4,814 (32.7)	81,375 (31.2)
13–15	64,010 (23.3)	3,229 (22.0)	60,781 (23.3)
≥16	68,633 (24.9)	2,816 (19.2)	65,817 (25.3)
Mother's age, mean (SD), years			
	25.4 (5.9)	24.5 (6.0)	25.4 (5.9)
Mother's race/ethnicity			
Hispanic	242,931 (88.2)	12,896 (87.5)	230,035 (88.2)
Black	32,660 (11.8)	1,835 (12.5)	30,825 (11.8)
Marital status			
Legally married	117,096 (42.5)	5,322 (36.1)	111,774 (42.8)
Not married, living together	102,087 (37.0)	5,953 (40.4)	96,134 (36.8)
Not living together	56,591 (20.5)	3,461 (23.5)	53,130 (20.4)
Number of prenatal visits			
<10	64,434 (23.4)	4,524 (30.8)	59,910 (23.0)
≥10	211,157 (76.6)	10,187 (69.2)	200,970 (77.0)
Season of birth			
January–March	66,641 (23.4)	3,502 (23.8)	61,139 (23.4)
April–June	60,469 (21.9)	3,161 (21.4)	57,308 (22.0)
July–September	70,013 (25.4)	3,704 (25.1)	66,309 (25.4)
October–December	80,691 (29.3)	4,372 (29.7)	76,319 (29.2)
Maternal BMI, ^b mean (SD), kg/m ²			
Prepregnancy	25.5 (5.9)	24.4 (5.9)	25.5 (5.9)
At time of delivery	30.2 (5.8)	28.6 (5.8)	30.3 (5.8)
Maternal prepregnancy BMI ^b			
Underweight (<18.5)	9,674 (6.9)	976 (12.0)	8,698 (6.6)
Normal (18.5–24.9)	67,861 (48.1)	4,097 (50.4)	63,764 (47.9)
Overweight (25–29.9)	36,083 (25.6)	1,750 (21.6)	34,333 (25.9)
Obese (>30)	27,297 (19.4)	1,296 (16.0)	26,001 (19.6)
Municipal-level characteristics ^c			
Median household income in 2013 inflation-adjusted US dollars, mean (SD)	21,751 (5,573)	21,425 (5,564)	21,770 (5,573)
Population density per square mile, mean (SD)	3,194 (2,591)	3,024 (2,528)	3,204 (2,595)
% Adults (>25 year) with <high school education, %, mean (SD)	26.5 (5.3)	26.9 (5.4)	26.5 (5.3)
% Occupied units with 1 or more severe housing problems, mean (SD) ^d	33.4 (7.6)	33.5 (7.7)	33.4 (7.6)
% Population that is non-white non-Hispanic, mean (SD)	33.4 (11.3)	33.0 (11.8)	33.4 (11.3)
Unemployment rate 2004–2013, %, mean (SD)	12.5 (3.8)	12.9 (3.8)	12.6 (3.8)
Mean age-adjusted diabetes prevalence 2004–2013, %, mean (SD)	12.5 (1.3)	12.6 (1.3)	12.5 (1.3)

The following is the number (%) of observations with missing data for various variables: Urban/rural residence—66 (0.0%), medical insurance—40,127 (14.6%), total children—2 (0.0%), mother's education—531 (0.2%), mother's age—53 (0.0%), mother's race—223 (0.1%), marital status—40 (0.0%), number of prenatal visits—223 (0.1%). None of the other variables had any missing values.

^aN (%) unless otherwise specified. Although available, data on smoking, alcohol use, and some risk factors were inadequately collected. For instance, only 1616 women are indicated as reporting smoking (ever or during pregnancy); 662 as drinking alcohol during pregnancy; 8,538 had diabetes before pregnancy; 4,081 with self-reported hypertension; 6,892 reported preeclampsia or eclampsia; and 3,425 reported previous experience of poor pregnancy outcomes. Given this deficiency, we did not use these variables in the analysis.

^bAvailable only for births occurring in 2005 onward (*N* = 173,964), not included in the main analysis but used in some sensitivity analysis.

^cThese data are publicly available at <https://www.census.gov/programs-surveys/acs/data.html> and <https://www.huduser.gov/portal/datasets/cp.html>.

^dThese are designated by the US Department of Housing and Urban Development as overcrowding, lack of kitchen, lack of plumbing, and high housing cost.

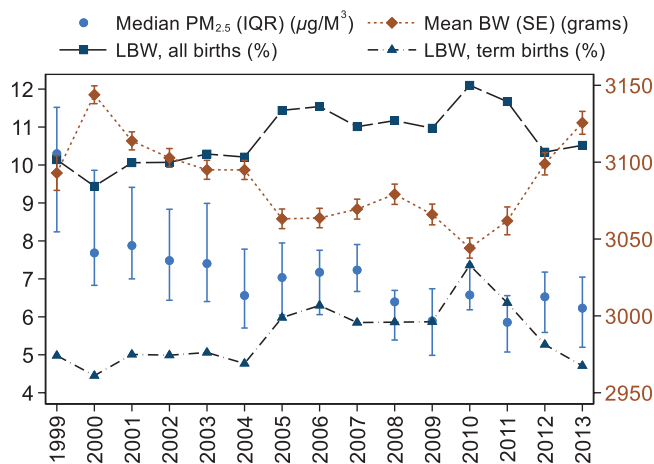


Figure 1. Median PM_{2.5} concentrations and rates of low birth weight among all births and among only term births in 37 municipalities in Puerto Rico, 1999–2013, shown on the left Y-axis, and mean birth weight on the right Y-axis. IQR indicates interquartile range.

municipalities ($P = 0.058$), those living in municipalities with higher rates of Type 2 diabetes ($P = 0.056$), and for births occurring in May to October, months generally associated with an influx of African dusts in Puerto Rico ($P = 0.016$).^{24,25} There was a tendency toward higher risk of LBW among black mothers (though not statistically different from their Hispanic counterparts) and increased LBW risk for characteristics associated with lower SES, as assessed using lower individual ($P = 0.067$) and municipal-level ($P = 0.108$) educational attainment and residence in a municipality with higher unemployment rates ($P = 0.046$; eTable 4; <http://links.lww.com/EE/A52>). In sensitivity analyses, models that included quadratic forms of PM_{2.5} and gestational age, and those which omitted gestational age did not materially alter results relative to the primary modified Poisson model (eTable 3; <http://links.lww.com/EE/A52>). Findings were also similar when analysis was restricted to mothers' first births (eTables 5 and 6; <http://links.lww.com/EE/A52>). In addition, findings from the primary analysis using term births were similar to those using all births, albeit with slightly stronger associations among term births, and somewhat wider CIs owing to the comparatively lower sample size (eTables 7–13; <http://links.lww.com/EE/A52>). In the subset of births for which for maternal prepregnancy BMI information was available, there was a non-statistically significant tendency for higher LBW risk among overweight and obese mothers relative to those with BMI below 25 (eTables 4 and 5; <http://links.lww.com/EE/A52>).

Discussion

Few studies have examined the association between prenatal exposure to PM_{2.5} and birth weight in racial minority populations. In this study of more than 330,000 births to Hispanic and black mothers over a 14-year period in Puerto Rico, we found that higher average prenatal exposure was associated with higher risk of both low and very low birth weight. This association was evident irrespective of modeling approach and was robust to a number of sensitivity analyses. We also found that the PM_{2.5}-associated risk of LBW was higher among female infants and infants born to mothers who had poorer utilization of prenatal care, lower education levels, were unmarried, or were of lower SES. In addition, although the association between prenatal PM_{2.5} exposure and LBW in models adjusting for both individual- and municipal-level covariates was statistically significant, the association in models that adjusted only for individual-level covariates was not, suggesting the importance of controlling for ecological indicators of SES, demographics,

Table 2
Risk ratios (95% CIs) for associations between low birth weight and covariates among term infants in fully adjusted modified Poisson model.^a

Covariate	RR (95% CI)	P-value
Individual-level covariates		
Infant sex		
Male	1.00 (Ref)	
Female	1.44 (1.39–1.49)	<0.001
Mother's age (years)		
Number of prenatal visits	1.00 (Ref)	
<10	0.75 (0.72–0.78)	<0.001
≥10		
Mother's education, years of school completed		
0–9	1.00 (Ref)	
10–11	0.91 (0.85–0.98)	0.009
12	0.82 (0.76–0.88)	<0.001
13–15	0.75 (0.68–0.82)	<0.001
≥16	0.65 (0.60–0.71)	<0.001
Mother's race		
Hispanic	1.00 (Ref)	
Black	1.06 (1.00–1.12)	0.063
Marital status		
Married, living with partner	1.00 (Ref)	
Not married, co-habiting with partner	1.12 (1.08–1.15)	<0.001
Not married, not living with any partner	1.11 (1.06–1.06)	<0.001
Medical insurance		
Other private or public	1.00 (Ref)	
Medicaid or charity	1.00 (0.94–1.06)	0.975
Number of other children (living or deceased)		
0	1.00 (Ref)	
1	0.70 (0.67–0.73)	<0.001
2	0.66 (0.63–0.70)	<0.001
3	0.69 (0.63–0.75)	<0.001
≥4	0.76 (0.69–0.85)	<0.001
Residence		
Urban	1.00 (Ref)	
Rural	0.99 (0.95–1.03)	0.555
Gestational age (1-week difference)		
	0.70 (0.68, 0.72)	<0.001
Season of birth		
January–March	1.00 (Ref)	
April–June	0.96 (0.91–1.02)	0.213
July–September	0.95 (0.90–1.00)	0.037
October–December	0.98 (0.93–1.02)	0.293
Maternal prepregnancy BMI ^b		
<25	1.00 (Ref)	
≥25	0.73 (0.68–0.78)	<0.001
Municipal-level covariates		
Household income, 2013 inflation-adjusted US dollars		
Below median for PR (USD 22,754)	1.00 (Ref)	
Above median	0.95 (0.91–1.02)	0.128
Population density		
≤median for PR (2,760/square mile)	1.00 (ref)	
>median	0.99 (0.93–1.06)	0.767
% adults (>25 year) with <high school education		
≤median for PR (23.9%)	1.00 (Ref)	
>median	0.97 (0.88–1.06)	0.511
% occupied units with 1 or more severe housing problems ^c		
≤median for PR (34.8%)	1.00 (Ref)	
>above median	0.98 (0.92–1.04)	0.547
% non-white, non-Hispanic population		
≤median for PR (35.7%)	1.00 (Ref)	
>median	0.98 (0.92–1.04)	0.444
Average unemployment rate, 2004–2013		
≤median for PR (10.3%)	1.00 (Ref)	
>median	1.05 (0.95–1.16)	0.323
Age-adjusted diabetes prevalence, 2004–2013		
≤median for PR (12.4%)	1.00 (Ref)	
>median	1.03 (0.92–1.14)	0.627

^aAll models are adjusted for individual-level covariates [mother's age, number of other children (alive or deceased), infant's sex, gestational age, season of birth, education level, urban/rural residence, marital status, number of prenatal visits attended, and year of birth] and area/municipality-level covariates (including population density, income per capita, proportion of non-white non-Hispanic residents, average unemployment rate, proportion of occupied housing units with at least 1 of 4 severe US Department of Housing and Urban Development-designated defects, percentage of residents with a less than high school level of education, and the age adjusted prevalence of diabetes mellitus).

^bAvailable only for births occurring in 2005 onward ($N = 173,964$), not included in the main analysis but used in sensitivity analysis.

^cThese are designated by the US Department of Housing and Urban Development as overcrowding, lack of kitchen, lack of plumbing, and high housing cost.

Table 3
Association between low birth weight and prenatal PM_{2.5} exposure in Puerto Rico (1999–2013), based on single-stage models.

Model	N	Modified Poisson model Risk ratio for LBW per SD increase in PM _{2.5} exposure RR (95% CI)	Linear model	Ordinal logistic model	Modified Poisson model Risk ratio for VLBW per SD increase in PM _{2.5} exposure RR (95% CI)
			Average change in birth weight per SD increase in PM _{2.5} exposure β (95% CI)	Odds ratio for VLBW versus LBW or normal birth weight per SD increase in PM _{2.5} exposure OR (95% CI)	
Model 1	All: 275,814 LBW: 14,739	0.92 (0.90 to 0.95)	23.5 (17.7 to 29.4)	0.92 (0.90 to 0.95)	1.07 (0.96 to 1.19)
Model 2	All: 275,814 LBW: 14,739	0.98 (0.96 to 1.01)	-1.2 (-6.2 to 4.9)	0.98 (0.95 to 1.01)	0.91 (0.75 to 1.11)
Model 3	All: 275,814 LBW: 14,739	1.03 (0.99 to 1.06)	-4.8 (-7.3 to 1.1)	1.04 (1.00 to 1.07)	1.06 (1.01 to 1.17)

Model 1: Unadjusted associations.

Model 2: Adjusted for individual-level covariates, including mother’s age, number of other children (alive or deceased), infant’s sex, gestational age, season of birth, education level, urban/rural residence, marital status, number of prenatal visits attended, and year of birth.

Model 3: Model 2 plus adjustment for area/municipality-level covariates, including population density, household income per capita, proportion of non-white non-Hispanic residents, average unemployment rate, proportion of occupied housing units with at least one of four severe US Department of Housing and Urban Development-designated defects, percentage of residents with a less than high school level of education, and the age-adjusted prevalence of diabetes mellitus.

LBW indicates low birth weight; VLBW, very low birth weight.

Table 4
Association between low birth weight and prenatal PM_{2.5} exposure in Puerto Rico (1999–2013), based on a 2-stage model.

Model	Odds ratio for LBW per SD increase in mean exposure level across the entire pregnancy (coefficient of intercept from 2-stage model)		Odds ratio for LBW per SD increase in trend across the entire pregnancy (coefficient of slope from 2-stage model)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Model 1A	0.98 (0.96–1.02)	0.379	1.00 (0.95–1.04)	0.628
Model 1B	1.03 (1.01–1.05)	0.039	1.02 (0.99–1.05)	0.202
Model 2A	0.99 (0.96–1.02)	0.408	-	-
Model 2B	1.04 (1.01–1.08)	0.021	-	-

Model 1A: a 2-stage model accounting for the effect of the linear trend in exposure on the outcome by including random intercepts and random slopes in stage 1. Stage 2 of the model incorporates individual-level covariates, including mother’s age, number of other children (alive or deceased), infant’s sex, gestational age, season of birth, education level, urban/rural residence, marital status, number of prenatal visits attended, and year of birth. The interpretation of coefficients is described in the main text.

Model 1B: a 2-stage model accounting for the effect of the linear trend in exposure on the outcome by including random intercepts and random slopes in Stage 1. Stage 2 of the model additionally controls for individual and municipal-level covariates, i.e., Model 1A plus adjustment for area/municipality-level covariates, including population density, income per capita, proportion of non-white non-Hispanic residents, average unemployment rate, proportion of occupied housing units with at least 1 of 4 severe US Department of Housing and Urban Development-designated defects, percentage of residents with a less than high school level of education, and the age adjusted prevalence of diabetes mellitus. The interpretation of coefficients is described in the main text.

Models 2A and 2B are analogous to 1A and 1B, respectively, except that Stage 1 models only include intercepts, as the Stage 1 slopes were not statistically significant in Model 1.

LBW indicates low birth weight; VLBW, very low birth weight; IQR, interquartile range.

population density, health status, and other factors at the area level.

Our primary findings add to the literature on the effect of prenatal exposure to PM_{2.5} on LBW, whose results remain inconsistent. In a recent meta-analysis that included 18 studies of term LBW and PM_{2.5} in predominantly North American and European populations, an interquartile range increase in exposure throughout pregnancy was associated with a 3% higher (95% CI = 2%, 3%) risk of LBW—very similar to, though more precise than, our primary finding in our Puerto Rican population. A pooled analysis drawing from 14 recent cohorts in 12 European countries found a significantly increased odds of LBW with higher exposure to prenatal PM_{2.5} averaged across the entire pregnancy among women with term births (OR, 1.18; 95% CI = 1.06, 1.33 per 5 µg/m³ increase in PM_{2.5}), and similar, albeit attenuated results for trimester-specific exposures.²⁶ These ORs are higher than those in our study and in the more recent meta-analysis, perhaps because of differences in study settings (e.g., Europe vs. Puerto Rico), design, and cohort characteristics. In contrast, 2 previous meta-analyses of multiple older (1990 to 2000s) studies reported increased odds of LBW with increased PM_{2.5} exposure across the whole pregnancy, but their results were not statistically significant at the 5% alpha level [pooled OR: Stieb et al¹¹: 1.05 (95% CI = 0.99, 1.12); Sapkota et al²⁷:

1.09 (95% CI = 0.90, 1.32) per 10 µg/m³ increase in PM_{2.5}]. Their nonsignificant findings reflect the wide range of effect estimates observed in the primary studies, which again may be attributed to considerable heterogeneity in study designs, differences in cohort characteristics, and variations in exposure averaging times. Their null findings, however, were supported by a subsequent large nationwide Canadian study of nearly 3 million singleton births between 1999 and 2008, which found consistently null associations between PM_{2.5} and LBW, regardless of whether exposures were averaged by month of gestation, trimester, or entire pregnancy period.²⁸

Findings from previous studies were more robust when continuous birth weights were examined as the outcome. For instance, a 5 µg/m³ increase in PM_{2.5} was associated with a 7 g decrease (95% CI = 17, 2) in birthweight in Pedersen et al,²⁶ a 10 µg/m³ increase in PM_{2.5} was associated with a 23-g decrease (95% CI = -46, -1) in Stieb et al,¹¹ and a 10 µg/m³ increase in PM_{2.5} was associated with a 21 g decrease (95% CI = -25, -16) in a more recent study by Stieb et al.²⁸ We, however, did not find a significant change in birthweight for a standard deviation (less than 2 µg/m³ in our sample) change in average exposure to prenatal PM_{2.5}. Our null findings may result from characteristics of our cohort, which was Puerto Rican and largely of lower socioeconomic status (SES) relative to the study populations of the

Pedersen and Stieb studies, which consisted of mostly Caucasian participants in higher SES settings.

Our findings suggest higher rates and $PM_{2.5}$ -associated risks of LBW for female as compared with male infants. Higher rates of LBW among female infants may be because of the respective distributions of birth weights for female and male infants in Puerto Rico, with the entire distribution of birth weights for female infants shifted toward lower birth weights as compared with male infants. Mean weights (SD) for term female infants were lower than those of their male counterparts [3,128 (423) and 3,240 (442) g, respectively], consistent with prior studies.^{13,15,16} Findings of greater $PM_{2.5}$ -associated risks of LBW for female infants in Puerto Rico were also consistent with results from some previous studies,^{29,30} although in some cohorts based in Northeastern United States,^{31,32} female infants were reported to have lower $PM_{2.5}$ -associated risks. Differences in findings between our study and the Northeastern US studies may be because of differences in the cohorts, as environmental risk factors for pregnancies in Puerto Rico may differ.

Little is known, however, as to whether some women are more vulnerable than others to the negative effects of prenatal $PM_{2.5}$ exposure on LBW. In our study setting, the association between $PM_{2.5}$ on LBW was significantly stronger among unmarried women, who may generally be younger, and those of lower SES. Westergaard et al³³, while noting the paucity of data, concluded from an examination of 6 prior studies that women who smoked, were underweight, overweight or obese, or of low SES may be more likely than their counterparts to experience the adverse impacts of $PM_{2.5}$ on LBW. Pedersen et al²⁶ observed stronger, though insignificant, $PM_{2.5}$ -LBW associations among mothers who smoked and those with comparatively lower educational attainment. In our study population, which is likely to be of lower average SES as compared with the women in the above previous studies, we found significantly stronger $PM_{2.5}$ -LBW associations among women with less education. We also found that the $PM_{2.5}$ -LBW association among overweight and obese women was marginally stronger than among counterparts with normal BMI.

Our analyses illustrate the utility of a 2-stage modeling approach, which accounts for the trajectory of exposure values over the observation period, especially when exposure contrasts are limited because of low average pollution levels and assignment of exposures from central monitoring locations. The 2-stage model allowed us to assess potential trends in exposures across monthly time intervals throughout the pregnancy, as compared with the often used trimester- or pregnancy-long exposure windows. These 9 monthly intervals, as opposed to 3 trimester intervals, provided adequate data to model exposure trajectories. As a result, we had sufficient power to estimate the effect of $PM_{2.5}$ on LBW in the 2-stage model. Our findings are consistent with a recent analysis demonstrating the importance of methods in studies of $PM_{2.5}$ and LBW that (1) better account for cohort or site differences and (2) enhance exposure contrasts, both of which contribute to increased statistical power to detect associations over conventional methods.³⁴ In our application, the 2-stage approach enabled us to examine whether average pollutant exposure levels and trends in exposure across pregnancy are associated with LBW. The 2-stage model allows for the analysis of longitudinally assessed exposures combined with a single binary outcome. Further, a nonstatistically significant slope coefficient from stage 1, which suggests that the average pregnancy exposure adequately captures the longitudinal trend, indicates that any benefits provided by inclusion of trimester specific effects may not overcome the biases or inflated standard errors that could result from these collinear covariates. In addition, our analyses suggested that in the Puerto Rican setting, accounting for area-level socioeconomic and demographic factors was important, perhaps reflecting spatial clustering of air pollutant sources, healthcare resources, and social support,

which may play key roles in determining levels of exposure and effect. Support for this theory is provided by previous studies that demonstrated the importance of ecological-level measures of socioeconomic status to associations of air pollution and health.³⁵

Considerable uncertainty remains regarding which times during gestation represent periods of the highest susceptibility to assault from environmental pollutants, with respect to LBW outcomes. In our trimester-specific analysis, we found that first and second trimester $PM_{2.5}$ exposures were associated with higher risk of LBW, while third trimester exposures were not. Previous studies have reported significant adverse impact on LBW of particulate matter exposure during the second trimester but not the first or third,³⁶ the second and third but not the first,¹⁵ and only the first.¹⁶ Yet, other investigations suggest that both second and third trimester $PM_{2.5}$ ^{26,37,38} and third trimester EC³⁹ exposures are related to increased LBW risk, and a recent meta-analysis found no clear evidence of a particularly sensitive gestational time-window, reporting nonstatistically significant odds ratios for all trimesters, although third trimester effects tended to be larger.¹² In addition, the specific mechanisms by which $PM_{2.5}$ exposure contribute to birth weights below the common threshold of 2,500 g are not well known, but oxidative stress is thought to play an important role.⁴⁰ Human mitochondrial DNA are particularly susceptible to systemic oxidative stress, and a recent study showed that heightened mitochondrial DNA sensitivity to increased $PM_{2.5}$ exposure was most evident in the third trimester, from 35 weeks of gestation, identifying this as a potential window of high susceptibility.³⁸ Taken together, many studies observed larger associations of $PM_{2.5}$ exposure in the second and third trimesters, possibly indicating that the impact of $PM_{2.5}$ on LBW increases with gestational age, and suggesting higher likelihood of adverse consequences beginning from when fetal growth is most rapid until late gestation.

Our study has several limitations. First, our exposure assessment is derived from area-wide averages of measurements at EPA monitors and does not account for any residential moves of the mother during pregnancy. While both factors will contribute to exposure error, this error will likely bias effect estimates towards the null⁴¹ lending support to our observed significant associations, particularly because $PM_{2.5}$ concentrations in Puerto Rico likely do not have large spatial variations within our averaging radii. Second, variability in $PM_{2.5}$ exposures was relatively low during the study period, with concentrations ranging between ≈ 3 and $13 \mu\text{g}/\text{m}^3$. However, our use of a 2-stage mixed effects model that captures trends at shorter intervals allows us to account for temporal variation in exposure across the prenatal period and complement estimates from the single-stage models that are based on trimester- or pregnancy-long exposure averages.²⁰ Third, although we allowed for potential clustering by municipality, our unit of analysis was individual births, with no information on repeated births to the same mother. Fourth, we did not have data for some confounders such as smoking, alcohol consumption, and multiple markers of individual socioeconomic status, raising the possibility of unmeasured confounding. We also relied on maternal municipality at the time of birth, in the absence of data on residential mobility, implying the possibility of exposure misclassification for women who may have moved to another municipality during pregnancy. In addition, some pregnant women continue to work during pregnancy, but we had no information relevant to maternal occupation or related work practices. Despite this, we controlled for numerous other individual mother-infant covariates and a suite of municipal-level socioeconomic information that informed our analysis.

Outweighing these limitations are our study's substantial strengths, which include its focus on an understudied population of Puerto Rican infants, its large sample size, including all births in Puerto Rico for nearly 15 years, its well-characterized birth data, and numerous municipal level socioeconomic

variables. The 2-stage model showed that any potential linear exposure trends during pregnancy do not significantly impact the risk of a low weight at birth. These factors provided us with sufficient statistical power to find a positive association between prenatal PM_{2.5} exposure and risk of birth weight below 2,500 grams.

Conflicts of interest statement

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

Research supported by Award Number P50ES026049 from the National Institute of Environmental Health Sciences and Assistance Agreement Number 83615501 from the US Environmental Protection Agency for each author.

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