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# **Maternal ambient air pollution, preterm birth, and markers of fetal growth in Rhode Island: Results of a hospital-based linkage study**

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# **Abstract**

**Background—**Maternal exposure to ambient air pollution has been associated with higher risk of preterm birth and reduced fetal growth, but heterogeneity among prior studies suggests additional studies are needed in diverse populations and settings. We examined the associations between maternal ambient air pollution levels, risk of preterm birth, and markers of fetal growth in an urban population with relatively low exposure to air pollution.

**Methods—**We linked 61,640 mother-infant pairs who delivered at a single hospital in Providence, Rhode Island from 2002–2012 to birth certificate and hospital discharge data. We used spatial-temporal models and stationary monitors to estimate exposure to fine particulate matter (PM<sub>2.5</sub>) and black carbon (BC) during pregnancy. Using generalized linear models we evaluated the association between pollutant levels, risk of preterm birth, and markers of fetal growth.

Results—In adjusted models, an interquartile range (IQR; 2.5 µg/m<sup>3</sup>) increase in pregnancyaverage PM<sub>2.5</sub> was associated with odds ratios (ORs) of preterm birth of 1.04 (95% CI: 0.94, 1.15) and 0.86 (0.76, 0.98) when considering modeled and monitored  $PM_{2.5}$ , respectively. An IQR increase in modeled and monitored PM<sub>2.5</sub> was associated with a 12.1 g (95% CI:−24.2, -0.1) and

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15.9 g (95% CI: −31.6, −0.3) lower birthweight. Results for BC were highly sensitive to choice of exposure metric.

**Conclusion—**In a population with relatively low exposures to ambient air pollutants, PM<sub>2.5</sub> was associated with reduced birthweight but not with risk of preterm birth.

#### **Keywords**

air pollution; birthweight; preterm; fetal growth

# **Introduction**

Preterm birth (<37 weeks gestation) is the leading cause of infant mortality and has been linked to increased risk of cognitive, behavioral, and medical disabilities in children and increased risk of adult diseases [1–4]. Globally, there are 15 million preterm births each year with the number increasing in many countries [5]. A growing literature suggests that maternal exposure to ambient fine particulate matter air pollution  $(PM_{2.5})$  is associated with adverse birth outcomes [6–13], with the strongest evidence existing for reduced fetal growth [6–9].

Some prior studies have reported that  $PM_{2.5}$  is associated with higher risk of preterm birth [6, 9, 14]. Under the assumption that these associations reflect widely generalizable causal effects, it has been estimated that in 2010 ambient  $PM_{2.5}$  was responsible for 15,808 preterm births in the US (3.3% of all premature births) and a staggering 2.7 million (18% of all premature births) globally [15, 16]. However, a closer examination of the underlying evidence suggests the association between  $PM_{2.5}$  and preterm birth remains incompletely understood. For example, two recent large studies (one in Canada including ∼2.5 million births and one in New York City including ∼258,000 births), as well as a few smaller studies using a novel matched design, and an analysis of detailed individual-level data from the European ESCAPE birth cohorts all failed to find an association between  $PM_{2.5}$  and risk of preterm birth [17–22]. This heterogeneity in results across prior studies suggests the need for additional studies examining the potential impact of  $PM_{2.5}$  on risk of preterm birth in diverse populations and settings.

Accordingly, we examined the associations between  $PM_{2.5}$  and risk of preterm birth in Rhode Island (RI), a small coastal New England state where the majority of children are born at one hospital. We also estimated the association between black carbon (BC, a marker of traffic pollution) on preterm birth, an association that has been less extensively studied. Finally, we estimated the association between  $PM_{2.5}$ , BC, and markers of fetal growth.

# **Methods**

#### **Study Population**

The study population consists of mother-infant pairs of women delivering at Women and Infants Hospital of Rhode Island (WIHRI) between 2001 and 2012. Located in Providence, RI, WIHRI is the 9th largest stand-alone obstetrical service in the United States with ∼8,500 deliveries annually [23]. Approximately 75% of pregnant women living in RI give birth at

WIHRI, and therefore this study sample is representative of the population living in this area. WIHRI provides hospital records, including individual-level demographic, clinical, and financial data on all deliveries to the National Perinatal Information Center (NPIC). We obtained these records from the NPIC Perinatal Center Data Base and merged them with birth certificate data from the RI Department of Health (RIDOH). The study protocol was approved by the Institutional Review Boards of Brown University, WIHRI, and RIDOH.

Initially we matched 76,590 (79.8%) of the 95,948 hospital discharge records from WIHRI to state birth certificates, but upon closer examination few births were matched to birth certificate data in 2001 or between July 2004 and December 2005 as RIDOH transitioned to a new birth records system. Thus, we restricted our analyses to 74,165 deliveries occurring during time periods with high match rates (>88.6%, January 2002-June 2004 and January 2006-December 2012) and successfully matched to birth certificate data. We used ArcMap (ESRI, Redlands, CA) to geocode maternal residential addresses listed on birth certificates and linked 2010 census and geographic data to each address point. We excluded women aged  $\langle 18 \rangle$  years at delivery (1,575) or missing maternal age (2,198); those who had multiple births (3,176); and those with addresses outside of RI (7,418) or missing (14). We also excluded women missing data for birthweight (6) or those with an implausible birthweight of <500 g or >5000 g (194). Our final sample included 61,640 mother-infant pairs.

#### **Exposure Assessment**

We estimated daily  $PM_{2.5}$  levels at each maternal residential address using a hybrid of landuse regression and satellite remote sensing, as previously described [24]. Briefly, the model  $(R^2=0.88)$  uses a land-use regression model that includes spatial and temporal factors and satellite measurements of aerosol optical depth (AOD) on a 1 km grid and fits a daily calibration regression using ground-level  $PM_{2.5}$  measurements. Differences between grid cell AOD and measured  $PM<sub>2.5</sub>$  are regressed against local land use features to generate estimates of local source (mostly automobile traffic) exposure on a finer scale (200 m  $\times$  200 m).

We also examined BC as a marker of traffic-related air pollution. We estimated daily BC levels at each address using an extended version of a validated spatial-temporal land-use regression model [25]. Briefly, this model incorporates daily average BC measurements from five RI monitors, meteorological data from nearly 2 dozen local weather stations, land use data, latitude and longitude, daily meteorological factors, and interaction terms between land use and daily meteorological factors. The model performed well in cold (November – April) and warm (May – October) seasons (10 fold cross-validated  $R^2$  of 0.73 and 0.75, respectively).

To facilitate comparison with previous studies, we also obtained daily  $PM_{2.5}$  and BC measurements from stationary monitors operated by the RI Department of Environmental Management. We obtained  $PM<sub>2.5</sub>$  data from six monitors in Providence County and BC data from two monitors in Providence and East Providence, RI and calculated daily averages of each pollutant.

Thus, modeled and monitored  $PM_{2.5}$  estimates were available for deliveries taking place anytime during the study period (2002–2012), modeled BC estimates were available for 2004–2011, and monitored BC was available for 2005–2012. For both monitored and modeled pollutant levels, we averaged the daily exposure estimates to determine the average levels for the entire pregnancy as well as for the first trimester (weeks 1–12), second trimester (weeks 13–26), and third trimester (weeks 27 to birth), as in previous studies [26]. While our primary analyses were based on pregnancy-average pollutant levels, we additionally investigated trimester-specific exposures as vulnerability to air pollution may change over the course of pregnancy [9, 14, 27].

#### **Outcome Assessment**

We defined preterm birth as births before 37 completed weeks of gestation. Term birthweight, small for gestational age (SGA), and low birthweight (LBW) were used as markers of fetal growth among term births. Birthweight was obtained from birth certificates and was measured in grams. SGA was defined as the lowest  $10<sup>th</sup>$  percentile for gestational age and sex based on 1999 and 2000 U.S. births [28–31]. We defined LBW as term births having a birthweight <2500 g.

#### **Covariates**

We considered the following potential confounders: maternal age, parity  $(0, 1, \text{or } 2)$ , maternal race (Black, White, Other), maternal education (less than high school, high school, attended college but did not graduate, graduated from college, attended graduate school), marital status (married, single, other: divorced, separated, widowed, unknown), health insurance (private, public, other: Medicare, Champus, self-coverage, other coverage, coverage unknown), and tobacco use during pregnancy (yes, no). Public insurance (Medicaid or Medicaid/HMO) during this time was only provided to low income women. Gestational age was measured in weeks.

We assessed the following six census tract characteristics to address potential confounding by neighborhood SES: median household income; percent of households with interests, dividends, or rent income; percent of residents with high school diploma; percent with college degree; percent with professional occupation; and median value of owner-occupied housing units. We calculated a z-score for each variable and summed the scores to create a zsum score [32].

#### **Statistical Analyses**

We used linear regression to quantify the association and 95% confidence intervals (CI) between pollutants and birthweight and used logistic regression models to obtain odds ratios and 95% CIs of the association between pollutants and odds of preterm birth, SGA, and LBW. Analyses examining birthweight, SGA, and LBW were restricted to term births only. We used causal diagrams to identify potential confounders requiring adjustment in each model [33]. All models were adjusted for maternal age (modeled as a natural spline with 3 degrees of freedom), tobacco use during pregnancy, parity, education, race, insurance, marital status, neighborhood SES z-sum score, and year of last menstrual period modeled as

a factor to account for secular trends in pollutant levels (Supplemental Figure 1). Models for birthweight and LBW were additionally adjusted for gestational age.

Our primary definition of preterm birth based on gestational age at delivery does not distinguish between spontaneous and induced preterm deliveries. We hypothesize that air pollution would be more strongly associated with spontaneous than medically-induced preterm birth. Thus, we conducted exploratory analyses to examine the association between each exposure and preterm birth identified by ICD9 code 644.21, which defines preterm birth as the onset of spontaneous delivery before 37 completed weeks of gestation [34].

We conducted all analyses using R  $(v3.2.0)$  and imputed missing covariate data using the Multivariate Imputation by Chained Equations (MICE) package [35]. Missing covariate data included: tobacco (13.7% missing), parity (2.4%), maternal education (3.7%), maternal race (8.4%), maternal insurance (0.6%), and marital status (1.0%). We also conducted a complete-case analysis examining the associations between pregnancy-average air pollution levels and birthweight, SGA, and LBW adjusted for the same covariates as the primary analyses.

# **Results**

Most of the women in this study were white (64.7%), married (62.6%), and did not use tobacco during pregnancy (93.4%) (Table 1). The mean maternal age was 29 (standard deviation,  $SD = 5.9$ ) years. The mean gestational age at delivery was 39 ( $SD = 2.0$ ) weeks with about 8% of births delivered preterm. Among term births, we found that gestational age, parity, maternal race, maternal education, marital status, health insurance, and tobacco use during pregnancy were associated with birthweight (Supplemental Table 1). Modeled pregnancy-average PM<sub>2.5</sub> levels had a mean of 9.5  $\mu$ g/m<sup>3</sup> (SD=1.5), which is below the current National Ambient Air Quality Standard for annual  $PM_{2.5}$  of 12  $\mu$ g/m<sup>3</sup> [36]. Levels of modeled PM<sub>2.5</sub> and BC were similar to monitored levels (Supplemental Table 2).

In fully adjusted models, modeled pregnancy-average  $PM_{2.5}$  was not associated with risk of preterm birth (Table 2). In secondary analyses considering trimester-specific  $PM_{2.5}$ , only first-trimester  $PM_{2.5}$  was associated with a lower risk of preterm birth (OR=0.93; 95% CI: 0.88, 0.98). Results were qualitatively similar, when instead considering measured  $PM_{2.5}$ from stationary monitors and when considering risk of spontaneous preterm birth identified from discharge diagnosis codes rather than gestational age (Supplemental Table 3).

Pregnancy-average PM<sub>2.5</sub> was associated with a 12.1 g lower (95% CI:  $-24.2$ ,  $-0.1$  g) birthweight per interquartile range (IQR; 2.5  $\mu$ g/m<sup>3</sup>) increase in model-estimated PM<sub>2.5</sub> (Table 3). Results were qualitatively similar when considering instead  $PM_{2.5}$  measured at stationary monitors. Pregnancy-average  $PM_{2.5}$  was associated with higher risk of being born SGA, but this only reached statistical significance for monitor-estimated  $PM_{2.5}$  (Table 4; OR=1.15; 95% CI: 1.00, 1.31). PM<sub>2.5</sub> was not associated with risk of being born LBW. The complete-case analysis results were similar to the main results with imputation, but have wider 95% CIs (Supplemental Table 4).

We also considered the association between BC and birth outcomes. Modeled BC was not associated with risk of preterm birth (Table 2). Monitored BC levels were positively associated with preterm birth when averaged over the entire pregnancy but negatively associated in the third trimester. Model-estimated BC was not associated with birthweight and results were more extreme with wider CIs when considering monitored BC (Table 3). BC was not associated with risk of SGA and LBW, except for monitored second trimester BC (OR=0.88; 95% CI: 0.79, 0.98). Complete-case analysis results were similar to the main analysis with multiple imputation, but have wider 95% CIs (Supplemental Table 4).

# **Discussion**

Among more than 60,000 deliveries, we found no evidence to suggest that  $PM_{2.5}$  is associated with higher risk of preterm birth in the current study population in RI. Indeed, the only statistically significant associations between  $PM<sub>2.5</sub>$  and risk of preterm birth were negative rather than positive. Results were qualitatively similar when considering  $PM_{2.5}$ levels estimated by a spatial-temporal model versus measured values from stationary monitors. On the other hand, we did observe the expected association between  $PM_{2.5}$  and lower birthweight.

The lack of association between  $PM<sub>2.5</sub>$  and preterm birth stands in contrast to a number of prior studies. Pooled estimates of the relative risk for preterm birth from four recent metaanalyses ranged from 1.05 (95% CI: 0.98, 1.13) to 1.15 (95% CI: 1.14, 1.16) per 10  $\mu$ g/m<sup>3</sup> change in  $PM_{2.5}$  [6, 9, 14, 37]. Comparatively, our results for pregnancy-average  $PM_{2.5}$ rescaled to a 10  $\mu$ g/m<sup>3</sup> increase would yield an estimate of 1.17 (95% CI: 0.89, 1.75), which is within the CIs of three of these estimates. Thus, our results could be interpreted as consistent with the prior evidence, but lacking statistical significance due to our smaller sample size. However, our results are closer to those from several studies that have either failed to find an association between  $PM<sub>2.5</sub>$  and preterm birth or have reported a negative association [17–22]. These findings suggest that there is little evidence of an increased risk of preterm birth associated with PM2.5 levels in this and at least some other populations.

Our results for  $PM<sub>2.5</sub>$  and birthweight are similar in direction and magnitude to prior studies. For example, in New York City Savitz, et al. [26] found that a 10  $\mu$ g/m<sup>3</sup> increase in PM<sub>2.5</sub> was associated with a 48.4 g (95% CI: −62.3, −34.5) lower birthweight. For comparison, extrapolating our results to a 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> yields a 48.5 g (95% CI: -96.6, −0.44) difference in birthweight. In neighboring Massachusetts, Kloog, et al. [38] applied the same spatial-temporal model as our study to estimate  $PM_{2.5}$  and found a more modest 13.8 g (95% CI: −21.10, −6.05) lower birthweight per 10  $\mu$ g/m<sup>3</sup> increase in PM<sub>2.5</sub>. More broadly, in comparison to estimates reported in recent meta-analyses [7, 8, 37] our estimates of the association between  $PM_{2.5}$  and birthweight are comparable to some and larger than others. However, our estimates have wider CIs that include the null hypothesis of no association when considering trimester-specific exposures.

Consistent with our findings for birthweight, pregnancy-average  $PM<sub>2</sub>$  was associated with higher risk of SGA, although these results only reached statistical significance when considering monitored PM2.5 levels. These associations were in the same direction, but

larger in magnitude compared to estimates from recent meta-analyses. In particular, our finding of relative risks of SGA of 1.41 (95% CI: 0.92, 2.16) per 10  $\mu$ g/m<sup>3</sup> modeled PM<sub>2.5</sub> are somewhat larger than the pooled estimate of 1.15 (95% CI: 1.10, 1.20) reported previously for SGA [7–9, 14, 27, 37]. However, our CIs are wide and include the null, suggesting that our study may have been underpowered to detect associations of this magnitude.

Our findings for BC are difficult to interpret since we unexpectedly found discrepant results depending on whether we used BC estimated from a land-use regression model or from stationary monitors, and the time period being considered. For example, we observed that monitored pregnancy-average BC was associated with a pronounced higher risk of preterm birth while third trimester BC was associated with a significantly lower risk of preterm birth. Similarly contradictory results were observed between monitored BC and birthweight, suggesting that estimates of associations with monitored BC are unstable and should be interpreted with caution. On the other hand, modeled BC was not associated with either risk of preterm birth or birthweight. Interestingly, our results for BC are consistent with findings by Brauer, et al. [39] who estimated residential BC from a land-use regression model and found no association between BC and preterm birth (defined as birth <30 weeks of gestation; OR=0.99, 95% CI: 0.87, 1.13) in Vancouver, Canada. Similarly, in the Dutch PIAMA study, Gehring, et al. [40] did not find a statistically significant association between soot (a component of BC, estimated with a land-use regression model) and preterm birth (OR=1.08, 95% CI: 0.88, 1.34). Thus, the effects of BC and other markers of traffic pollution on risk of preterm birth require further study.

Our study has important limitations. First, as is common to studies based on large-scale administrative data, we expect exposure misclassification due to lack of information on residential history throughout pregnancy, amount of time spent at home, and housing characteristics such as air conditioning and air ventilation. However, we used sophisticated spatial-temporal models to estimate  $PM_{2.5}$  and BC levels at the residence representing an improvement over some prior studies and resulting in lower exposure misclassification compared to using stationary monitors alone. Second, our results may not be generalizable to pregnant women living in metropolitan regions outside of the study area. Third, there may be residual confounding due to misclassification of tobacco use during pregnancy and unmeasured data for diet, exposure to environmental tobacco smoke, substance abuse, and alcohol consumption during pregnancy. Also, information on tobacco use during pregnancy was missing in 13.4% of women, which potentially may not be missing at random, even when multiply imputed conditional on other available covariates. However, results of a complete-case analysis were similar to the main analyses with multiple imputation. Fourth, average pollutant levels in the study area were relatively low with limited variation over space or time, limiting our statistical power to detect associations of the expected magnitude. The contradictory and sometimes unexpected results related to monitored BC in particular suggest that we may have had limited statistical power for some of these analyses. On the other hand, strengths of this study include use of spatial-temporal models to estimate  $PM<sub>2.5</sub>$ and BC exposure at each address, adjustment for several potentially important confounders, multiple imputation to reduce the risk of selection bias from missing data, and investigation

within the context of births from a single hospital that delivers the great majority of babies in this state.

In conclusion, we did not find evidence of a positive association between  $PM_{2,5}$  and risk of preterm birth, but did find the expected association between PM<sub>2.5</sub> and lower birthweight. These findings suggest that the etiologic relationship between  $PM_{2.5}$  and risk of preterm birth remains incompletely understood and that further research is needed before attributing a large proportion of global preterm births to  $PM<sub>2</sub>$ , Our results also add further support to the mounting evidence that  $PM_{2.5}$  is associated with reduced fetal growth and extend previous findings to a new location.

# **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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# **Summary Box**

#### **What is already known on this subject?**

- **•** Maternal exposure to ambient air pollution during fetal development has been associated with reduced fetal growth, with some studies also suggesting an increased risk of preterm birth.
- **•** Heterogeneity among prior studies suggests the need to evaluate these relationships in diverse populations and settings.

# **What this study adds?**

- We used spatial-temporal models to estimate PM<sub>2.5</sub> and black carbon (a marker of traffic-related pollution) levels at each residential address to capture both spatial and temporal variation in exposure.
- **•** In this population with relatively low exposures to ambient air pollutants, PM<sub>2.5</sub> was not associated with risk of preterm birth, but was associated with lower birthweight.
- **•** Further research is needed before attributing a large proportion of global preterm births to  $PM_{2.5}$

# Characteristics of study population<sup>a</sup>





a<br>Frequencies may not sum to full sample size due to missing data

b<br>Includes American Indian, Filipino, Hispanic, Other Asian, and Other (not specified)

 $c$ Includes divorced, separated, widowed, and unknown

d Private: Blue Cross/Blue Shield, Commercial insurance, and HMO coverage; Public: Medicaid or Medicaid/HMO; Other: Medicare, Champus, self-coverage, other coverage, and coverage unknown

Odds ratio (95% confidence intervals) for preterm birth per interquartile range  $(IQR)^a$  increase in  $PM_{2.5}$  and black carbon, overall and by trimester among 61,640 deliveries



All models are adjusted for maternal age, tobacco, parity, education, race, health insurance, marital status, last menstrual period, and neighborhood socioeconomic status. We used multiple imputation to account for covariates with missing data: tobacco (13.7% missing), parity (2.4% missing), maternal education (3.7% missing), maternal race (8.4% missing), maternal insurance (0.6% missing), and marital status (1.0%).

 ${}^{a}$ IQR is 2.5 µg/m<sup>3</sup> for PM<sub>2.5</sub> and 0.11 µg/m<sup>3</sup> for black carbon.

\* p<0.05

Gram change in birthweight (95% CI) per interquartile range  $(IQR)^a$  increase in  $PM_{2.5}$  and black carbon among 56,633 term births, overall and by trimester of pregnancy



All models adjusted for maternal age, gestational age, tobacco, parity, maternal education, maternal race, maternal insurance, marital status, last menstrual period, and neighborhood socioeconomic status. We used multiple imputation to account for covariates with missing data: tobacco (13.7% missing), parity (2.4% missing), maternal education (3.7% missing), maternal race (8.4% missing), maternal insurance (0.6% missing), and marital status (1.0%).

 ${}^{a}$ IQR is 2.5 µg/m<sup>3</sup> for PM<sub>2.5</sub> and 0.11 µg/m<sup>3</sup> for black carbon.

\* p<0.05

Odds ratios and 95% CIs for small for gestational age (SGA) and low birthweight (LBW) per interquartile range (IQR)  $^a$  increase in PM<sub>2.5</sub> and black carbon among 56,633 term births, overall and by trimester of pregnancy



All models adjusted for maternal age, gestational age, tobacco, parity, maternal education, maternal race, maternal insurance, marital status, last menstrual period, and neighborhood socioeconomic status. Models of LBW are additionally adjusted for gestational age.We used multiple imputation to account for covariates with missing data: tobacco (13.7% missing), parity (2.4% missing), maternal education (3.7% missing), maternal race (8.4% missing), maternal insurance (0.6% missing), and marital status (1.0%).

 ${}^{a}$ IQR is 2.5 µg/m<sup>3</sup> for PM<sub>2.5</sub> and 0.11 µg/m<sup>3</sup> for black carbon.

\* p<0.05