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Original Contribution

Time-to-Event Analysis of Fine Particle Air Pollution and Preterm Birth: Results From North Carolina, 2001–2005

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Exposure to air pollution during pregnancy has been suggested to be a risk factor for preterm birth; however, epidemiologic evidence remains mixed and limited. The authors examined the association between ambient levels of particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and the risk of preterm birth in North Carolina during the period 2001–2005. They estimated the risks of cumulative and lagged average exposures to $PM_{2.5}$ during pregnancy via a 2-stage discrete-time survival model. The authors also considered exposure metrics derived from 1) ambient concentrations measured by the Air Quality System (AQS) monitoring network and 2) concentrations predicted by statistically fusing AQS data with process-based numerical model output (the Statistically Fused Air and Deposition Surfaces (FSD) database). Using the AQS measurements, an interquartile-range (1.73 μg/m^3) increase in cumulative $PM_{2.5}$ exposure was associated with a 6.8% (95% posterior interval: 0.5, 13.6) increase in the risk of preterm birth. Using the FSD-predicted levels and accounting for prediction error, the authors also found significant adverse associations between trimester 1, trimester 2, and cumulative $PM_{2.5}$ exposure and preterm birth. These findings suggest that exposure to ambient $PM_{2.5}$ during pregnancy is associated with increased risk of preterm birth, even in a region characterized by relatively good air quality.

air pollution; particulate matter; premature birth; survival analysis

Abbreviations: AQS, Air Quality System; EPA, Environmental Protection Agency; CMAQ, Models-3/Community Multiscale Air Quality; FSD, Statistically Fused Air and Deposition Surfaces; PI, posterior interval; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter.

Editor's note: *An invited commentary on this article appears on page 108, and these authors' response appears on page 111.*

Preterm birth is associated with significant neonatal morbidity and mortality, as well as long-term health and developmental problems (1–5). In 2006, the short-term costs associated with preterm birth were estimated at over $51,000 per infant and approximately $26 billion for the United States annually (6). There is a growing interest in studying the association between prenatal exposure to environmental pollutants and preterm birth; however, in recent reviews, investigators concluded that the epidemiologic evidence remains limited and inconsistent (7, 8).

In this paper, we examine the association between ambient levels of particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and the risk of preterm birth in North Carolina. The $PM_{2.5}$ mass includes a chemically diverse mixture of carbon compounds, trace metals, and ionic molecules that typically arise from combustion sources such as vehicle emissions, industrial operations, and power generation. High levels of ambient $PM_{2.5}$ have been associated with increased risk of mortality (9, 10), hospital admissions (11), and various cardiopulmonary diseases in susceptible populations such as children and the elderly (12, 13).

Here we take a discrete-time survival approach for estimating the associations of long- and short-term $PM_{2.5}$ exposure with preterm birth. Gestational age is viewed as time-to-event data by defining an at-risk window (e.g., the 27th–36th weeks

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of gestation) in which preterm birth can occur. It is motivated by the challenge of defining exposure windows that depend on gestational age. For example, consider average $PM_{2.5}$ levels during the third trimester (from the 27th week of gestation to birth) or the entire pregnancy. Bias in risk estimates can arise because the duration of exposure differs between preterm births and full-term births. With the survival approach, we align the data such that preterm and full-term births are compared with each other only during the time window in which the fetus is at risk of being born preterm. Therefore, we can avoid the above bias by allowing the third trimester and total exposures to vary as each pregnancy progresses in time.

The use of time-varying exposures also allows us to examine associations with short-term exposure to air pollution. In a logistic regression model that treats prematurity as a binary outcome, defining short-term exposure prior to delivery may lead to bias in the risk estimates. For example, consider a full-term 39-week pregnancy in which the mother experienced high exposure in week 38. If acute exposure is defined as the week before delivery, this pregnancy will contribute to a protective association with air pollution even though the fetus is not at risk of being born preterm at week 38. Using only the week prior to birth also discards data from weeks earlier, which are also informative with regard to the acute effect. The time-series design overcomes this bias by aggregating preterm births and at-risk ongoing pregnancies on each day (14, 15). With the survival approach, we estimate the short-term effect by considering lagged exposure metrics as time-varying covariates. Moreover, we are able to utilize the full spatial and temporal contrast in $PM_{2.5}$ levels while accounting for individual-level covariates.

The ability to link publicly available birth record data and air quality measurements from monitoring networks has encouraged investigators to conduct many population-based studies. However, they often encounter difficulties in exposure assessment when the monitoring networks do not provide sufficient spatial-temporal resolution to define exposures over specific pregnancy windows. For example, the relatively sparse $PM_{2.5}$ network typically records concentrations only every third day or every sixth day. One important innovation in this paper is the use of a recently created, publicly available database of ambient $PM_{2.5}$ levels from the Environmental Protection Agency (EPA). The EPA's Statistically Fused Air and Deposition Surfaces (FSD) database (http://www.epa.gov/esd/land-sci/lcb/lcb_sfads.html) includes predicted daily $PM_{2.5}$ concentrations obtained by fusing observed $PM_{2.5}$ data from the Air Quality System (AQS) network and outputs from the Models-3/Community Multiscale Air Quality (CMAQ) model (16). While the CMAQ model provides higher spatial and temporal resolution than the AQS network, its outputs are known to exhibit bias, particularly for capturing short-term variation between days (17). The FSD database attempts to adjust the bias in the CMAQ model using the observed $PM_{2.5}$ concentrations from the AQS network.

In our analysis, we calculate $PM_{2.5}$ exposure metrics derived from both the AQS and the FSD database. To our knowledge, this is the first large-scale population study that has utilized the FSD database to examine the adverse association of air pollution with health. Because the databases have different limitations, our goal is not to determine which database is more appropriate in studies of birth outcomes and air pollution but to examine the robustness of risk estimates across air quality databases.

MATERIALS AND METHODS

Study population

Birth data were obtained from the North Carolina Detailed Birth Record database. We considered pregnancies with gestational lengths of 27–42 weeks in which conception had occurred between 2001 and 2005. We used the clinical estimate of gestation in completed weeks to back-calculate the date of conception. We restricted the analysis to singleton livebirths with birth weights greater than 400 g and no congenital anomalies. We further restricted the data set to mothers aged 15–44 years who declared themselves non-Hispanic white, non-Hispanic black, or Hispanic.

Maternal residential addresses at the time of delivery were geocoded to the street block level using ArcGIS 9.3 (ESRI, Redlands, California). We used the 2006 Topologically Integrated Geographic Encoding and Referencing (TIGER) street data from the US Census Bureau as the spatial reference file. The geocoding success rate was 83% because of invalid, missing, or unmatched addresses.

Exposure assessment

We considered 2 databases of ambient $PM_{2.5}$ levels to construct weekly average exposure over the course of pregnancy. First, $PM_{2.5}$ data were obtained from the EPA's AQS database. Each geocoded birth was linked to the closest monitor within a buffer area with a 12-km radius. A 36-km buffer radius was also considered in a sensitivity analysis. Because AQS monitors exhibit a missing data structure that varies across days and across monitors, we handled missing data as follows. We first constructed the 1-week average exposure for each gestational week with at least 1 $PM_{2.5}$ measurement. We defined a 1-week exposure for gestational week t by averaging $PM_{2.5}$ concentrations during the 7 days leading up to the date that week t was completed. For weeks without any $PM_{2.5}$ measurements, the average of the weeks before and after that week was used as a proxy for the exposure concentration during that week. Births with 2 or more consecutive missing weeks were excluded.

Second, predicted $PM_{2.5}$ levels were obtained from the EPA's FSD database. Predictions are based on a Bayesian space-time hierarchical model (18) that fuses monitoring $PM_{2.5}$ data from AQS and outputs from the CMAQ model. The FSD database provides predictive mean values and standard deviations for daily $PM_{2.5}$ concentration averaged over contiguous 12-km by 12-km grid cells. To account for uncertainty in predicted $PM_{2.5}$ levels, we imputed 10 sets of daily $PM_{2.5}$ levels by treating the posterior predictive distributions as independent normals across days and grid cells. Finally, we linked each birth to the associated FSD grid cell and calculated 1-week average exposure without missing values.

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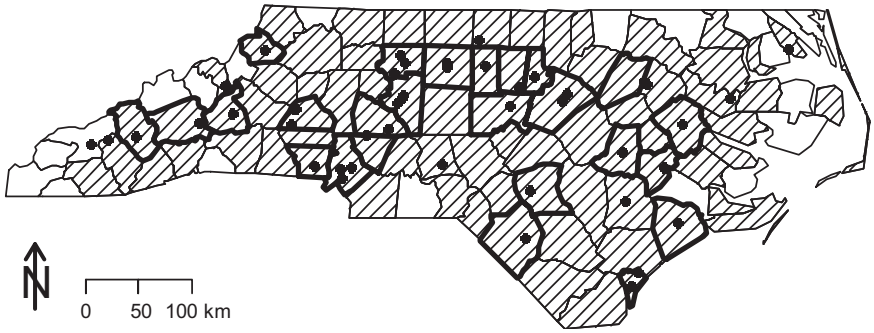

Figure 1. Counties included in a study of levels of particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and preterm birth risk and locations of nearby Air Quality System (AQS) $PM_{2.5}$ monitors (•), North Carolina, 2001–2005. Counties that contained at least 500 births linked to an AQS monitor within a 12-km radius are indicated by thick borders. Counties that contained at least 500 births linked to a grid cell of the Statistically Fused Air and Deposition Surfaces database are shaded.

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Statistical analysis

We viewed gestational age as time-to-event data and estimated the risk of $PM_{2.5}$ exposure during pregnancy via a 2-stage discrete-time survival model. In this design, each pregnancy enters the risk set at the 27th week of gestation and is followed until either 1) a birth occurs before the 37th week (preterm) or 2) it reaches the 37th week and a full-term birth is expected. Full-term births are censored at week 36, and no censoring occurs within the at-risk window.

Because of the large study cohort and geographic region, the analysis was conducted in 2 stages (19). First, we fitted a discrete-time survival model with a logistic link and time-varying covariates (20, 21). Specifically, let Y_{it} denote the indicator of whether a birth occurs during gestational week t for pregnancy i. We modeled

$$\text{logit}\, P\,(Y_{it} = 1 | \text{no birth before week } t) = h_t + \beta Z_{it},$$

where h_t represents the week-specific intercepts and β represents the coefficients for covariate vector Z_{it}. We controlled for the following variables: maternal age (15–19, 20–24, 25–29, 30–34, 35–39, or 40–44 years), maternal education (<9, 9–11, 12, 13–15, or >15 years), ethnicity, and indicators for tobacco use during pregnancy, marital status, firstborn birth order, and infant sex. To control for unmeasured temporal confounders, we included season of conception (winter (December–February), spring (March–May), summer (June–August), or fall (September–November)) and year of conception. We also considered a smooth function of conception date modeled using natural cubic splines with degrees of freedom ranging from 2 to 6 per year. The preterm birth model assumed that the risk of $PM_{2.5}$ was constant across the at-risk window. For the 6 most populous counties in North Carolina, we considered including terms for interaction between the exposure and each gestational week simultaneously. We then performed a joint hypothesis test with all week-specific risks being identical as the null hypothesis.

At the second stage, county-specific log odds ratios were combined by assuming the unobserved true risks to be normally distributed with mean μ (average risk across counties) and variance σ^2 (between-county variability). For the FSD exposures, we combined the results by pooling the posterior samples of μ after carrying out independent analysis for each imputed data set. We also relaxed the assumption that county-specific risk estimates are independent by including additional spatial random effects that follow a conditional autoregressive model (22). All statistical analysis was conducted using R, version 2.8.0 (23).

We investigated average $PM_{2.5}$ exposure defined over 7 pregnancy windows. We considered 3 exposure windows with fixed lengths: 1) trimester 1 (weeks 1–13); 2) trimester 2 (weeks 14–27); and 3) 6 weeks since conception. Given that a pregnancy completed gestational week t, we also considered 4 time-varying exposures: 1) trimester 3 (week 27 to t); 2) cumulative (week 1 to t); 3) a 6-week lag (week $t - 5$ to t); and 4) a 1-week lag (week t).

In order to estimate the baseline hazard for each gestational week, counties with fewer than 500 births were excluded (<1% of total births). For counties with a small population, the pregnancies entered the at-risk window later than the 27th week because there were insufficient data to estimate the county-specific baseline hazards for the earlier weeks.

All geocoded births were linked to an FSD grid cell, but only a subset of births was linked to an AQS monitor. Since AQS monitors are preferentially placed in urban locations where nonattainment of federal standards is likely to occur, we conducted 4 independent analyses for 3 different subsets of the study population, as follows. First, we considered all available births and used $PM_{2.5}$ exposure derived from the FSD database (the FSD full cohort). We then considered only the births linked to an AQS monitor within a 12-km radius (the AQS buffer cohort) and used exposure measures derived from either the AQS or the FSD database. This restricted study population also allowed us to assess the correlation between exposures calculated from the 2 $PM_{2.5}$ databases. Because not all births in a county were linked to an AQS monitor, we also considered a fourth analysis using the FSD exposures for counties with birth records linked to an AQS monitor (the FSD county cohort). Note that these cohorts are not mutually

Table 1. Characteristics[a] of Participants in a Study of $PM_{2.5}$ Levels and Risk of Preterm Birth, by Study Cohort, North Carolina, 2001–2005

	Study Cohort					
	AQS Buffer[b]		FSD County[c]		FSD Full[d]	
	No.	%	No.	%	No.	%
Total no. of counties	25		25		80	
Total no. of births	161,078		306,606		453,562	
Preterm birth		8.8		8.6		8.6
Male sex		51.3		51.1		51.1
Firstborn birth order		42.4		42.0		41.4
Ethnicity						
Non-Hispanic white		52.1		58.1		61.6
Non-Hispanic black		29.5		25.5		23.4
Hispanic		18.4		16.2		15.0
Maternal education, years						
<9		7.3		6.6		6.6
9–11		15.6		14.2		15.2
12		27.2		26.1		28.4
13–15		20.8		21.3		22.1
>15		29.1		31.8		27.7
Maternal age, years						
15–19		11.2		10.1		11.0
20–24		27.5		25.2		26.5
25–29		26.4		26.9		27.0
30–34		22.6		24.5		23.1
35–39		10.4		11.2		10.3
40–44		1.9		2.1		1.9
Tobacco use during pregnancy		9.8		10.3		11.9
Not married		39.0		35.5		35.6
Season of conception						
Winter (December–February)		25.5		25.1		25.1
Spring (March–May)		24.9		24.4		24.5
Summer (June–August)		24.3		24.9		24.8
Fall (September–November)		25.3		25.6		25.6

Abbreviations: AQS, Air Quality System; FSD, Statistically Fused Air and Deposition Surfaces; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter.

[a] Based on the availability of $PM_{2.5}$ measurements from the AQS or the FSD database.

[b] Births linked to an AQS monitor within a 12-km radius.

[c] Births occurring in counties with AQS monitors and linked to an FSD grid cell.

[d] Births linked to an FSD grid cell.

exclusive: "AQS buffer" is a subset of "FSD county," and "FSD county" is a subset of "FSD full." Figure 1 shows the locations of the AQS $PM_{2.5}$ monitors and the counties within each cohort.

RESULTS

The analysis included a total of 80 counties linked to an FSD grid cell. Among these, 25 counties had at least 500 birth records linked to an AQS monitor. The average distance between the maternal residence and the closest AQS monitor was 5.87 km. Table 1 shows the characteristics of the 3 study populations. Births to women living near AQS monitors had higher proportions of mothers who were younger, unmarried, and Hispanic or non-Hispanic black and higher proportions of mothers with fewer years of education compared with the other 2 study cohorts.

The hazard of preterm birth tended to increase by gestational age. Web Figure 1 (presented on the *Journal's* Web site (http://aje.oxfordjournals.org/)) shows the baseline weekly hazards (h_t) for the 6 most populous counties. Across the FSD full cohort, higher risks of preterm birth were observed

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Table 2. Median Values (μg/m^3) for Exposure Metrics in a Study of $PM_{2.5}$ Levels and Risk of Preterm Birth, North Carolina, 2001–2005

	Study Cohort		
	AQS Buffer	FSD County	FSD Full
Total	13.88 (1.73)[a]	15.25 (2.25)	15.12 (2.51)
Trimester 1	13.18 (3.85)	14.81 (4.14)	14.68 (4.22)
Trimester 2	13.16 (3.83)	14.63 (4.16)	14.51 (4.22)
Trimester 3	13.19 (3.88)	14.67 (4.26)	14.56 (4.32)
Weeks 1–6	13.13 (4.06)	14.94 (4.61)	14.80 (4.71)
Week 27	12.97 (6.05)	14.16 (6.40)	14.03 (6.43)

Abbreviations: AQS, Air Quality System; FSD, Statistically Fused Air and Deposition Surfaces; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter.

[a] Numbers in parentheses, interquartile range.

for older, unmarried, non-Hispanic black mothers and among mothers who had less education or reported tobacco use. First-born babies were also more likely to be preterm. The odds ratio estimates and 95% confidence intervals are given in Web Table 1. Except for infant sex, the above characteristics were also associated with levels of $PM_{2.5}$ exposure (Web Tables 2 and 3).

Table 2 gives the median values and interquartile ranges for the exposure metrics. Here we used the predicted levels from FSD. To describe time-varying cumulative exposure, we used the average exposure over the entire pregnancy. Similarly, we used the average exposure over weeks 1–6 and week 27 to describe the distribution of 6-week lag and 1-week lag exposures, respectively. Within-county variation in exposure measured by interquartile range was highest for weekly exposure and lowest for total exposure because of different exposure window lengths.

Table 3 summarizes county-specific correlations between exposures derived from the AQS and the FSD database. We found minor heterogeneity across the counties. More than half of the counties had correlations for trimester exposures above 0.80. We also observed that the correlation between AQS and FSD exposures increased from weekly exposure to trimester exposures, suggesting that both databases were capturing similar trends in $PM_{2.5}$ level on a longer time scale. The decrease in correlation for exposure over the entire pregnancy as compared with trimester exposure can be attributed to the strong negative correlation between trimester 1 and trimester 3 introduced by the seasonality of $PM_{2.5}$ ambient concentrations.

Figure 2 shows the statewide average log odds ratio estimates (and 95% posterior intervals) for the risk of preterm birth per interquartile-range increase in each of the $PM_{2.5}$ exposure metrics. We used the interquartile range for the AQS buffer cohort, given in Table 3. Among births to women living within a 12-km buffer of an AQS monitor, an interquartile-range (1.73 μg/m^3) increase in cumulative average $PM_{2.5}$ exposure was associated with a 6.8% (95% posterior interval (PI): 0.5, 13.6) increase in the risk of preterm birth. Using metrics derived from the FSD database, the corresponding increase in risk was 4.1% (95% PI: 0.9, 7.3) for the same study cohort. The estimates were similar to those obtained using a buffer with a 36-km radius (Web Table 4).

We found the statewide estimates to be robust against the choice of AQS or FSD exposures and between different study cohorts. Using the FSD exposure metrics, across 80 counties, we estimated that each interquartile-range increase in trimester 1, trimester 2, and cumulative average $PM_{2.5}$ exposure was associated with a 2.8% (95% PI: 0.9, 4.7), 3.9% (95% PI: 1.0, 6.8), and 3.5% (95% PI: 0.8, 6.3) increase in the risk of preterm birth, respectively. The posterior intervals associated with FSD exposures were narrower because of the considerable increase in sample size. Including additional spatial random effects produced similar estimates. For the 6 most populous counties, we did not find evidence that the risks varied between gestational weeks 27 and 36. The estimates were also found to be robust after controlling for temporal trends using natural cubic splines (Web Figure 2). Moreover, the model with indicators for conception season and conception year consistently had the smallest Akaike and Bayesian information criteria for all 7 exposure metrics.

DISCUSSION

We conducted a statewide analysis to estimate the association between ambient $PM_{2.5}$ levels and the risk of preterm birth in North Carolina. We found statistically significant

Table 3. County-Specific Correlations Between $PM_{2.5}$ Exposure Metrics Derived From the AQS and the FSD database, North Carolina, 2001–2005[a]

	Minimum	Quartile 1 (25th Percentile)	Median	Quartile 3 (75th Percentile)	Maximum
Total	0.25	0.61	0.67	0.77	0.86
Trimester 1	0.42	0.72	0.83	0.85	0.89
Trimester 2	0.44	0.72	0.82	0.86	0.89
Trimester 3	0.37	0.73	0.83	0.86	0.90
Weeks 1–6	0.28	0.61	0.77	0.78	0.85
Week 27	0.20	0.58	0.63	0.69	0.79

Abbreviations: AQS, Air Quality System; FSD, Statistically Fused Air and Deposition Surfaces; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter.

[a] Statistical summaries were calculated across 30 counties in the AQS buffer cohort.

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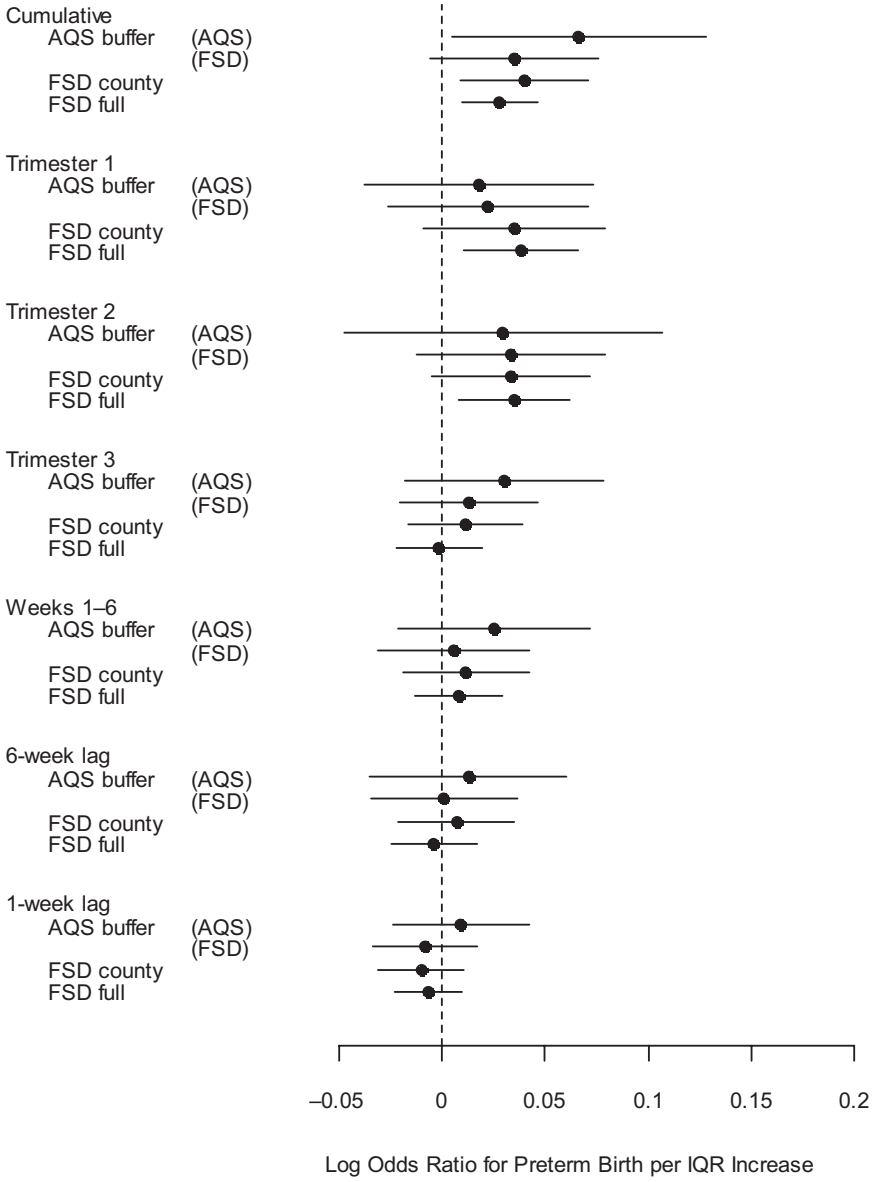

Figure 2. Statewide average odds ratio estimates (and 95% posterior intervals) for preterm birth per interquartile-range (IQR) increase in different metrics of exposure to particulate matter <2.5 μm in aerodynamic diameter, North Carolina, 2001–2005. Estimates from 3 different study cohorts are presented side-by-side: 1) AQS buffer, births to women living within a 12-km radius of an Air Quality System (AQS) monitor; 2) FSD county, births occurring in counties with AQS monitors and linked to a Statistically Fused Air and Deposition Surfaces (FSD) grid cell; and 3) FSD full, all births linked to an FSD grid cell. For the FSD county and FSD full cohorts, exposures were derived from the FSD database. For the AQS buffer cohort, exposures were derived from the AQS or FSD database indicated in parentheses. Horizontal bars, 95% posterior interval.

adverse associations for $PM_{2.5}$ levels during the first trimester, during the second trimester, and for the cumulative average. The risk estimates were robust between observed and predicted $PM_{2.5}$ levels. Considerable effort is required for geocoding birth records in studies of birth outcomes and environmental pollutants. Most studies of preterm birth and air pollution have been limited to urban communities with high population density and high levels of air pollution (14, 24–28). All of the counties in our study are currently in compliance with the $PM_{2.5}$ National Ambient Air Quality Standard (http://www.epa.gov/air/criteria.html) as of October 2009.

The reported risk estimates for the relation between preterm birth and long-term $PM_{2.5}$ exposure are consistent with previous findings. In a study in Vancouver, Canada, Brauer et al. (29) found an odds ratio of 1.06 (95% confidence interval: 1.01, 1.11) per 1-μg/m^3 increase in $PM_{2.5}$ exposure for the overall pregnancy. For first-trimester exposure, Ritz et al. (28) found an odds ratio of 1.10 (95% confidence interval: 1.01,

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1.20) for pregnancies exposed to $PM_{2.5}$ concentrations greater than 21.36 μg/m^3 versus those exposed to less than 18.63 μg/m^3 in Southern California. In a similar study using a matched-case control design, Huynh et al. (27) report an odds ratio of 1.21 (95% confidence interval: 1.12, 1.30).

We did not find a significant association between short-term exposure to $PM_{2.5}$ and preterm birth in North Carolina. Several studies have found a significant association between short-term $PM_{2.5}$ exposure and preterm birth (14–15, 30). However, in time-series analyses carried out in London, United Kingdom (31) and Shanghai, China (25), no association was found for weekly or daily levels of particulate matter less than 10 μm in aerodynamic diameter. The low $PM_{2.5}$ levels in North Carolina may not be high enough to induce an acute effect.

While multiple studies have shown an association between birth outcomes and maternal exposure to particulate matter, the mechanisms by which particulate matter affects pregnancy length and fetal growth are not well documented and may vary by timing of exposure (32). Biologically plausible pathways by which particulate matter may affect pregnancy outcomes include the inflammatory response, systemic oxidative stress, and placental dysfunction. Maternal exposure to particulate matter air pollution triggers inflammation that could increase maternal susceptibility to infections, which have been linked to uterine contractions and the initiation of preterm labor (33, 34). The component chemicals of particulate matter can lead to oxidative stress, resulting in DNA damage that has been linked to restricted fetal growth and lower birth weights (33–35). Inflammation and oxidative stress may also affect birth outcomes by causing vasoconstriction, elevating blood pressure and exacerbating maternal hypertension, a risk factor for preterm birth (33). Particulate matter may also restrict fetal growth by causing placental dysfunction. Reduced placental perfusion may result from the inflammation (32, 33) and increased blood viscosity (34) associated with maternal exposure to particulate matter air pollution. Particulate matter may also directly impair placental function by binding receptors of key placental growth factors (32).

Our analysis had several strengths. First, using the same regression model and confounding controls, we were able to estimate the association of both long-term and short-term exposures to ambient $PM_{2.5}$. As Bosetti et al. (7) indicated, investigators in previous studies often did not report results for all exposure metrics, resulting in the possibility of selective reporting and difficulty in synthesizing findings. Second, we considered an alternative source of ambient $PM_{2.5}$ levels from the EPA FSD database to overcome spatial and temporal misalignment. Third, we employed a time-to-event approach that allowed us to efficiently examine long- and short-term exposures. The potential bias associated with treating time-varying exposures as fixed windows in a logistic regression setting is likely to depend on the length of exposure, the seasonality in ambient air pollution levels, and the seasonality in conception. Finally, the North Carolina birth records contain detailed maternal information, specifically data on maternal smoking, which is an important risk factor for adverse birth outcomes.

Extensions of the time-to-event model offer several opportunities for future studies. First, by considering interactions between exposure and gestational age, one can examine how the risk associated with $PM_{2.5}$ changes across the at-risk window (early preterm birth vs. late preterm birth). Second, multiple exposures of different time scales (e.g., cumulative and 4-week lag) can be included simultaneously to examine the relative toxicity of long-term exposures versus shorter exposures. Another way is to exploit the exposure structure with time-varying covariates that capture the relative proportions of exposure during different pregnancy windows. Finally, a 2-stage approach with the ability to borrow information across spatial units in estimating model coefficients may be beneficial, especially for counties with small sample sizes.

This study had several limitations. The first challenge arises from assigning exposure measures to each individual pregnancy and the associated measurement error. We assumed that ambient $PM_{2.5}$ concentrations were spatially homogeneous within a small geographic area: a 12-km radial buffer around each monitor, or a 12-km by 12-km grid cell. We also assumed that the mothers did not move during pregnancy. Finally, ambient levels were used as a surrogate measure for actual personal $PM_{2.5}$ exposure.

When comparing birth outcomes across space and time, the possibility of confounding at both the individual and neighborhood levels is well recognized (36). Examples of known risk factors for which data are not available from birth certificates include parental socioeconomic status, the residential built environment, and amount of physical activity during pregnancy. In our study, maternal characteristics were also associated with levels of $PM_{2.5}$ exposure, and potential residual confounding remained because of the unreliability of birth certificates (37). Confounding by secular trends and seasonality in preterm birth presents another challenge, particularly because the exposures of interest are averaged across long pregnancy windows. While there has been considerable work in air pollution epidemiology to address unmeasured confounders (38, 39), new methods are needed for studies of preterm birth and air pollution.

Overall, our findings suggest that exposure to ambient $PM_{2.5}$ during pregnancy is associated with increased risk of preterm birth, even in regions characterized by relatively good air quality. However, the critical window of exposure warrants further investigation.

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