

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

Howard H. Chang

Brian J. Reich

Marie Lynn Miranda

## Abbreviations

AQS	Air Quality System
CMAQ	Models-3/Community Multiscale Air Quality model
FSD	Statistically Fused Air Quality database
IQR	Interquartile range
OR	Odds ratio
PI	Posterior interval
PM <sub>2.5</sub>	Particulate matter < 2.5 μm in aerodynamic diameter
PM <sub>10</sub>	Particulate matter < 10 μm in aerodynamic diameter
PTB	Preterm birth
USEPA	United States Environmental Protection Agency

Correspondence to Howard H. Chang, Nicholas School of the Environment, Room A134

LSRC, Duke University, Durham, NC 27708. Telephone: (919) 613-8723 E-mail:

[howard.chang@duke.edu](mailto:howard.chang@duke.edu)

## **Abstract**

Exposures to air pollution during pregnancy have been suggested as risk factors for preterm birth; however epidemiological evidence remains mixed and limited. This paper examines the association between ambient levels of particulate matter < 2.5  $\mu\text{m}$  in aerodynamic diameter ( $\text{PM}_{2.5}$ ) and the risk of preterm birth in North Carolina between the period 2001 to 2005. The authors estimated the risks of cumulative and lagged average exposures to  $\text{PM}_{2.5}$  during pregnancy via a two-stage discrete-time survival model. The authors also considered exposure metrics derived from (1) ambient concentrations measured by the Air Quality System monitoring network (AQS) and (2) predicted concentrations by statistically fusing AQS with process-based numerical model output (FSD). Using the AQS measurements, an interquartile range ( $1.73 \mu\text{g}/\text{m}^3$ ) increase in cumulative  $\text{PM}_{2.5}$  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 association between trimester 1, trimester 2, and cumulative  $\text{PM}_{2.5}$  exposure and preterm birth. These findings suggest that exposure to ambient  $\text{PM}_{2.5}$  during pregnancy is associated with increased risk of preterm birth even in a region characterized by relatively good air quality.

Key words: air pollution, particulate matter, preterm birth, survival analysis

Word Count for Abstract: 198

Word Count for Text: 3466

Preterm birth (PTB) 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 PTB 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 exposures to environmental pollutants and PTB; however recent reviews concluded that the epidemiologic evidence remains limited and inconsistent (7-8).

This paper examines the association between ambient levels of particulate matter  $< 2.5 \mu\text{m}$  in aerodynamic diameter ( $\text{PM}_{2.5}$ ) and the risk of PTB in North Carolina. The  $\text{PM}_{2.5}$  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  $\text{PM}_{2.5}$  levels have been associated with increased risk of mortality (9-10), hospital admissions (11), and various cardiopulmonary diseases in susceptible population such as children and the elderly (12-13).

We take a discrete-time survival approach for estimating the effects of long-term and short-term exposure to  $\text{PM}_{2.5}$  on PTB. Gestational age is viewed as time-to-event data by defining an at-risk window (e.g. 27<sup>th</sup> - 36<sup>th</sup> gestational week) where PTB can occur. It is motivated by the challenge of defining exposure windows that depend on gestational age. For example, consider the average  $\text{PM}_{2.5}$  levels during the 3<sup>rd</sup> trimester (27<sup>th</sup> gestational week till birth) or the entire pregnancy. Bias in risk estimates can arise because the length of exposure differs between preterm and full-term births. In the survival approach, we align the data such that preterm and full-term births are compared to each other only during the window at-risk of being preterm. Therefore, we can

avoid the above bias by allowing the 3<sup>rd</sup> trimester and total exposure to vary as each pregnancy progresses in time.

The use of time-varying exposures also allows us to examine the effects of 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 that experienced high exposure at week 38. If acute exposure is defined as the week before delivery, this pregnancy will contribute to a protective effect of air pollution even though it is not at-risk of being preterm at week 38. Using only the week prior to birth also discards data from weeks earlier, which are also informative about the acute effect. The time series design overcomes this bias by aggregating preterm births and at-risk ongoing pregnancies on each day (14-15). In the survival approach, we estimate 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<sub>2.5</sub> 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 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<sub>2.5</sub> network typically records concentrations only every 3<sup>rd</sup> day or every 6<sup>th</sup> day. One important innovation in this paper is the use of a recent publically available database of ambient PM<sub>2.5</sub> levels from the U.S. Environmental Protection Agency (USEPA). The Statistically Fused Air Quality database (FSD) includes predicted daily PM<sub>2.5</sub>

concentrations obtained by fusing observed PM<sub>2.5</sub> data from the Air Quality System (AQS) network and outputs from the Models-3/Community Multiscale Air Quality (CMAQ) model (16). While CMAQ provides higher spatial and temporal resolution compared to 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 CMAQ using the observed PM<sub>2.5</sub> concentrations from the AQS network.

In our analysis, we calculate PM<sub>2.5</sub> exposure metrics derived from both the AQS and FSD database. To our knowledge, this is the first large-scale population study that utilizes the FSD database to examine the adverse effects of air pollution and health. Because both 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 length between 27 to 42 weeks conceived 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 live births with birth weight greater than 400g and no congenital anomalies. We further restricted the dataset to those mothers aged 15 to 44 who self-declared as non-Hispanic white, non-Hispanic black, or Hispanic.

Maternal residential addresses at time of delivery were geocoded to the street block level using ArcGIS 9.3. 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% due to invalid, missing, or unmatched addresses.

### **Exposure assessment**

We considered two databases of ambient  $PM_{2.5}$  levels to construct weekly average exposure over the pregnancy. First,  $PM_{2.5}$  data were obtained from the USEPA AQS database. Each geocoded birth was linked to the closest monitor within a buffer of 12km radius. A 36km buffer radius was also considered as a sensitivity analysis. Because AQS monitors exhibit missing data structure that varies across days and across monitors, we handled missing data as follows. We first constructed 1-week average exposure for each gestational week with at least one  $PM_{2.5}$  measurement. We defined a 1-week exposure for gestational week  $t$  by averaging  $PM_{2.5}$  concentrations during the seven 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 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 USEPA's Statistically Fused Air Quality database (FSD) ([http://www.epa.gov/esd/land-sci/lcb/lcb\\_sfads.html](http://www.epa.gov/esd/land-sci/lcb/lcb_sfads.html)). Predictions are based on a Bayesian space-time hierarchical model (18) that fuses monitoring  $PM_{2.5}$  data from AQS and outputs from CMAQ. The FSD database provides predictive mean and standard deviation for

daily PM<sub>2.5</sub> concentration averaged over contiguous 12km by 12km grid cells. To account for uncertainty in predicted PM<sub>2.5</sub> levels, we imputed 10 sets of daily PM<sub>2.5</sub> 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 value.

### **Statistical analysis**

We viewed gestational age as time-to-event data and estimated the risk of PM<sub>2.5</sub> exposure during pregnancy via a two-stage discrete-time survival model. In this design, each pregnancy enters the risk set at the 27<sup>th</sup> week and is followed until either (1) a birth occurs before the 37<sup>th</sup> week (preterm); or (2) it reaches the 37<sup>th</sup> 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.

Due to the large study cohort and geographic region, the analysis was conducted in two 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

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

where  $h_t$  represents the week-specific intercepts and  $\beta$  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, and 40-44 years), maternal education (<9, 9-11, 12, 13-15, >15 years), ethnicity, and indicators for tobacco use during pregnancy, marital status, firstborn, and infant sex. To control

for unmeasured temporal confounders, we included the season of conception (Dec-Feb, Mar-May, Jun-Aug, Sep-Nov) and conception year. 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 PTB model assumes that the risk of  $PM_{2.5}$  was constant across the at-risk window. For the six most populous counties we considered including interaction terms 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 (OR) were combined by assuming the unobserved true risks to be normal distributed with mean  $\mu$  (average risk across counties) and variance  $\sigma^2$  (between-county variability). For the FSD exposures, we combined the results by pooling the posterior samples of  $\mu$  after carrying out independent analysis for each imputed dataset. We also relaxed the assumption that county-specific risk estimates are independent by including additional spatial random effects that follow a conditional autoregressive model (CAR) (22). All statistical analysis was conducted using R version 2.8.0 (23).

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

In order to estimate the baseline hazard for each gestational week, counties with fewer than 500 births were excluded (less than 1% of total births). For counties with small population, the

pregnancies entered the at-risk window later than the 27<sup>th</sup> week because there were insufficient data to estimate the county-specific baseline hazard 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 four independent analyses for three different subsets of the study population as follows. First we considered all available births and used PM<sub>2.5</sub> exposure derived from the FSD database (*FSD full*). We then considered only the births linked to an AQS monitors within a 12 km radius (*AQS buffer*) 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 two PM<sub>2.5</sub> 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 (*FSD county*). Note that these cohorts are not mutually 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<sub>2.5</sub> 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 maternal residence and the closest AQS monitor was 5.87 km. Table 1 compares the characteristics of the three study populations. Births around AQS monitors had higher proportions of mothers who

were younger, not married, Hispanic or non-Hispanic black, and fewer years of education compared to the other two study cohorts.

The hazard of PTB tends to increase by gestational age and Web Figure 1 (on the *Journal's* Web site) shows the baseline weekly hazards ( $h_t$ ) for the six most populous counties. Across the *FSD full* cohort, higher risks of PTB were observed for older, unmarried, non-Hispanic black mothers and among those who had less education or reported tobacco use. Firstborn babies were also more likely to be preterm. The OR estimates and 95% confidence intervals are given in Web Table 1. Except for infant sex, the above characteristics were also associated with levels of  $PM_{2.5}$  exposures (Web Table 2).

Table 2 gives the median and interquartile range (IQR) 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 week 1 to 6 and week 27 to describe, respectively, the distribution of 6-week lag and 1-week lag exposure. Within-county variation in exposure measured by IQR was highest for weekly exposure and lowest for total exposure due to different exposure window lengths.

Table 3 summarizes county-specific correlations between exposures derived from the AQS and the FSD databases. 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 at a longer time-scale. The decrease in correlation for exposure over the entire pregnancy compared to

trimester exposure can be attributed to the strong negative correlation between trimester 1 and trimester 3 introduced by the seasonality of PM<sub>2.5</sub> ambient concentrations.

Figure 2 shows the state-wide average log odds ratio estimates and 95% posterior interval for the risk of PTB per IQR increase in each of the PM<sub>2.5</sub> exposure metrics. We used the IQR for the *AQS buffer* cohort given in Table 3. Across births within a 12km buffer of an AQS monitor, an IQR (1.73 µg/m<sup>3</sup>) increase in cumulative average PM<sub>2.5</sub> exposure was associated with a 6.8% (95% posterior interval (PI): 0.5%, 13.6%) increase in risk of PTB. 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 using a buffer of 36km radius (Web Table 3).

We found the state-wide 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 per IQR increase in trimester 1, trimester 2, and cumulative were associated with 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%) increases in PTB, respectively. The posterior intervals associated with FSD exposures are narrower because of the considerable increase in sample [size](#). Including additional spatial random effects produced similar estimates. For the six most populous counties, we did not find evidence that the risks varied between gestational week 27 to 36. The estimates were also robust against 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 criterion for all seven exposure metrics.

## **DISCUSSION**

We conducted a state-wide analysis to estimate the association between ambient PM<sub>2.5</sub> levels and the risk of PTB in North Carolina. We found statistically significant adverse associations for PM<sub>2.5</sub> levels during the first trimester, the second trimester, and the cumulative average. The risk estimates were robust between observed and predicted PM<sub>2.5</sub> levels. Considerable effort is required for geocoding birth records in studies of birth outcomes and environmental pollutants. Most studies of PTB 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 attainment for the PM<sub>2.5</sub> National Ambient Air Quality Standard as of October 2009.

The reported risk estimates between PTB and long-term PM<sub>2.5</sub> exposures are consistent with previous findings. A study in Vancouver, Canada, (29) found an OR of 1.06 (95% CI: 1.01, 1.11) per 1 µg/m<sup>3</sup> increase in the overall pregnancy. For first trimester exposure, Ritz et al. (28) found an OR of 1.10 (95% CI: 1.01, 1.20) between pregnancies exposed to greater than 21.36 µg/m<sup>3</sup> versus those exposed to less than 18.63 µg/m<sup>3</sup> in Southern California. In a similar study using a matched-case control design, Huynh et al. (27) report an OR of 1.21 (95% CI: 1.12, 1.30).

We did not find a significant association between short-term exposure to PM<sub>2.5</sub> and PTB in North Carolina. Several studies have reported significant association between short-term exposure and preterm births (14-15, 30). However, no association was found for weekly or daily PM<sub>10</sub> levels in a time series analysis in London, UK (31) and in Shanghai, China (25). The low PM<sub>2.5</sub> 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 exposures to PM, the mechanisms by which PM affects pregnancy length and fetal growth are not well documented and may vary by timing of exposure (32). Biologically plausible pathways by which PM may affect pregnancy outcomes include the inflammatory response, systemic oxidative stress, and placental dysfunction. Maternal exposure to PM 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 PM 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 PTB (33). PM 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 exposures to PM air pollution. PM may also directly impair placental function by binding receptors of key placental growth factors (32).

Our analysis has 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<sub>2.5</sub>. As indicated by Bosetti et al. (7), previous studies often do 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<sub>2.5</sub> levels from the USEPA FSD database to overcome spatial and temporal misalignment. Third, we employed a time-to-event approach that allows us to efficiently exam long-term 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, and the seasonality in conception. Finally, the North Carolina birth records contain detailed maternal information, specifically 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 of  $PM_{2.5}$  changes across the at-risk window (early versus late PTB). 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 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 two-stage approach with the ability to borrow information across spatial units in estimating model coefficients may be beneficial, especially for counties with small sample size.

This study has 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 geographical area: a 12km radial buffer around each monitor, or a 12km by 12km grid cell. We also assumed 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 level is well recognized (36). Examples of known risk factors that are not available from birth certificate include the parents' socio-economic status, 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 remains due to the reliability of birth certificates (37). Confounding by secular trends and seasonality in PTB 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 PTB 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.

## ACKNOWLEDGEMENTS

Author affiliations: Department of Statistical Science, Duke University, North Carolina, USA (Howard H. Chang); Department of Statistics, North Carolina State University, North Carolina, USA (Brian J. Reich); Nicholas School of The Environment and Department of Pediatrics, Duke University, Durham, USA (Marie Lynn Miranda)

The research is supported by grant DMS-0635449 from the National Science Foundation and grant RD-83329301-4 from the United States Environmental Protection Agency. The authors also thank the editor and three anonymous reviewers for their useful suggestions for improvements.

## REFERENCES

1. Crump C, Winkleby MA, Sundquist K, et al. Preterm birth and psychiatric medication prescription in young adulthood: a Swedish national cohort study. *Int J Epidemiol.* 2010;39(6):1522-1530.
2. Hille ET, Dorrepaal C, Perenboom R, et al. Social lifestyle, risk-taking behavior, and psychopathology in young adults born very preterm or with a very low birthweight. *J Pediatr.* 2008;152(6):793-800.
3. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. *Lancet.* 2008;371:75-94.
4. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet.* 2008;371(9608):261-269.
5. Spittle AJ, Treyvaud K, Doyle LW, et al. Early emergence of behavior and social-emotional problems in very preterm infants. *J Am Acad Child Adolesc Psychiatry.* 2009;48(9):909-918.
6. Institute of Medicine. Preterm Birth: Causes, Consequences, and Prevention. National Academies Press, Washington DC, 2006.
7. Bosetti C, Nieuwenhuijsen MJ, Gallus S, et al. Ambient particulate matter and preterm birth or birth weight: a review of the literature. *Arch Toxicol.* 2010;84(6):447-460.
8. Šrám RJ, Binkova B, Dejmek J, Bobak M. Ambient air pollution and pregnancy outcomes: A review of the literature. *Environ Health Perspect.* 2005;113(4):375-382.
9. Samoli E, Peng RD, Ramsay T, et al. Acute effects of ambient particulate matter on mortality in Europe and North America; Results from the APHENA study. *Environ Health Perspect.* 2008;116(11):1480-1486.

10. Zanobetti A, Schwartz J. The effect of fine and coarse particulate air pollution on mortality: a national analysis. *Environ Health Perspect.* 2009;117(6):898-903.
11. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA.* 2006;295(10):1127-1134.
12. Pope CA,3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc.* 2006;56(6):709-742.
13. Ostro B, Roth L, Malig B, et al. The effects of fine particle components on respiratory hospital admissions in children. *Environ Health Perspect.* 2009;117(3):475-480.
14. Darrow LA, Klein M, Flanders WD, et al. Ambient air pollution and preterm birth: a time-series analysis. *Epidemiology.* 2009;20(5):689-698.
15. Sagiv SK, Mendola P, Loomis D, et al. A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997-2001. *Environ Health Perspect.* 2005;113(5):602-606.
16. Byun DJ, Schere KL. Review of the governing equations, computational algorithms, and other components of the Models-3 Community Multiscale Air Quality (CMAQ) modeling system. *Appl Mech Rev.* 2006;59(2):51-77.
17. Mebust MR, Eder BK, Binkowski FS, et al. Models-3 Community Multiscale Air Quality (CMAQ) model aerosol component 2. Model evaluation. *J Geophys Res.* 2003;108(D6):4184-4202.
18. McMillan NJ, Holland DM, Morara M, et al. Combining numerical model output and particulate data using Bayesian space-time modeling. *Environmentrics.* 2009;21(1):48-65.

19. Dominici F. Invited commentary: air pollution and health-what can we learn from a hierarchical approach? *Am J Epidemiol.* 2002;155(1):11-15.
20. Richardson DB. Discrete time hazards models for occupational and environmental cohort analysis. *Occup Environ Med.* 2010;67(1):67-71.
21. Collett D. *Modelling Survival Data in Medical Research.* 2nd ed. Boca Raton, Florida: CRC Press; 1998.
22. Lawson AB. *Statistical Methods in Spatial Epidemiology.* 2nd ed. Chichester: Wiley; 2006.
23. R Development Core Team. *R: A Language and Environment for Statistical Computing.* : R Foundation for Statistical Computing, 2009.
24. Xu X, Ding H, Wang X. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study. *Arch Environ Health.* 1995;50(6):407-415.
25. Jiang LL, Zhang YH, Song GX, et al. A time series analysis of outdoor air pollution and preterm birth in Shanghai, China. *Biomed Environ Sci.* 2007;20(5):426-431.
26. Ritz B, Yu F, Chapa G, et al. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. *Epidemiology.* 2000;11(5):502-511.
27. Huynh M, Woodruff TJ, Parker JD, et al. Relationships between air pollution and preterm birth in California. *Paediatr Perinat Epidemiol.* 2006;20(6):454-461.

28. Ritz B, Wilhelm M, Hoggatt KJ, et al. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. *Am J Epidemiol.* 2007;166(9):1045-1052.
29. Brauer M, Lencar C, Tamburic L, et al. A cohort study of traffic-related air pollution impacts on birth outcomes. *Environ Health Perspect.* 2008;116(5):680-686.
30. Wilhelm M, Ritz B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. *Environ Health Perspect.* 2005;113(9):1212-1221.
31. Lee SJ, Hajat S, Steer PJ, et al. A time-series analysis of any short-term effects of meteorological and air pollution factors on preterm births in London, UK. *Environ Res.* 2008;106(2):185-194.
32. Leem JH, Kaplan BM, Shim YK, et al. Exposures to air pollutants during pregnancy and preterm delivery. *Environ Health Perspect.* 2006;114(6):905-910.
33. Kannan S, Misra DP, Dvonch JT, et al. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. *Environ Health Perspect.* 2006;114(11):1636-1642.
34. Ghosh R, Rankin J, Pless-Mullooli T, et al. Does the effect of air pollution on pregnancy outcomes differ by gender? A systematic review. *Environ Res.* 2007;105(3):400-408.

35. Perera FP, Jedrychowski W, Rauh V, et al. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. *Environ Health Perspect.* 1999;107(Suppl 3):451-460.
36. Strickland MJ, Klein M, Darrow LA, et al. The issue of confounding in epidemiological studies of ambient air pollution and pregnancy outcomes. *J Epidemiol Commun H.* 2009; 63(6):500-504.
37. Northam S, Knapp TR. The reliability and validity of birth certificates. *J Obstet Gynecol Neonatal Nurs.* 2006;35(1):3-12.
38. Jane H, Dominici F, Zeger SL. On quantifying the magnitude of confounding. *Biostatistics.* 2010;11(3):572-582.
39. Peng RD, Dominici F, Louis TA. Model choice in time series studies of air pollution and mortality. *J Roy Stat Soc A Sta.* 2006;169(2):179-203.

Figure 1. Locations of the North Carolina counties and Air Quality System (AQS) PM<sub>2.5</sub> monitors (●). Counties contained at least 500 births linked to an AQS monitor within a 12km radius are indicated by thick borders. Counties contained at least 500 births linked to a grid cell of the Statistically Fused Air Quality Database are shaded.

Figure 2. State-wide average estimate and 95% posterior interval for odds ratio of preterm birth per interquartile increase in different PM<sub>2.5</sub> exposure metrics. Estimates from different study cohorts are presented side-by-side: (1) *AQS buffer*, births within a 12 km radius of an Air Quality System (AQS) monitor; (2) *FSD county*, births in counties with AQS monitors and linked to a Statistically Fused Air Quality Database (FSD) grid cell; and (3) *FSD full*, all births linked to an FSD grid cell. For the *FSD county* and *FSD full* cohorts, exposure were derived from the FSD database. For the *AQS buffer* cohort, exposures were derived from AQS or FSD database indicated in parentheses.

Table 1. Characteristics of the Study Populations Based on the Availability of PM<sub>2.5</sub> Measurements from the Air Quality System (AQS) or the Statistically Fused Air Quality Database (FSD).

	AQS buffer <sup>†</sup>	FSD county <sup>††</sup>	FSD full <sup>†††</sup>
Total Counties	25	25	80
Total births	161,078	306,606	453,562
% Preterm	8.8	8.6	8.6
% Male	51.3	51.1	51.1
% Firstborn	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	9.8	10.3	11.9
% Not married	39.0	35.5	35.6
% Conception season			
Winter (Dec – Feb)	25.5	25.1	25.1
Spring (Mar – May)	24.9	24.4	24.5
Summer (Jun – Aug)	24.3	24.9	24.8
Fall (Sept – Nov)	25.3	25.6	25.6

<sup>†</sup> births linked to an AQS monitor within a 12 km radius

<sup>††</sup> births in counties with AQS monitors and linked to an FSD grid cell

<sup>†††</sup> births linked to an FSD grid cell

Table 2. Median ( $\mu\text{g}/\text{m}^3$ ) and interquartile range (IQR,  $\mu\text{g}/\text{m}^3$ ) values for  $\text{PM}_{2.5}$  Exposure Metrics for the Three Study Cohorts.

	AQS buffer	FSD county	FSD full
	Median (IQR)	Median (IQR)	Median (IQR)
Total	13.88 (1.73)	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)
Week 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)

Table 3. County-specific Correlation between PM<sub>2.5</sub> Exposure Metrics Derived from the AQS and the FSD Database. Values are across 30 Counties in the AQS Buffer Cohort.

	Min	Q1	Med	Q3	Max
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
Week 1 - 6	0.28	0.61	0.77	0.78	0.85
Week 27	0.20	0.58	0.63	0.69	0.79

Abbreviation: Min, minimum; Q1, 25<sup>th</sup> percentile; Med, median; Q3, 75<sup>th</sup> percentile; Max, maximum

Figure 1

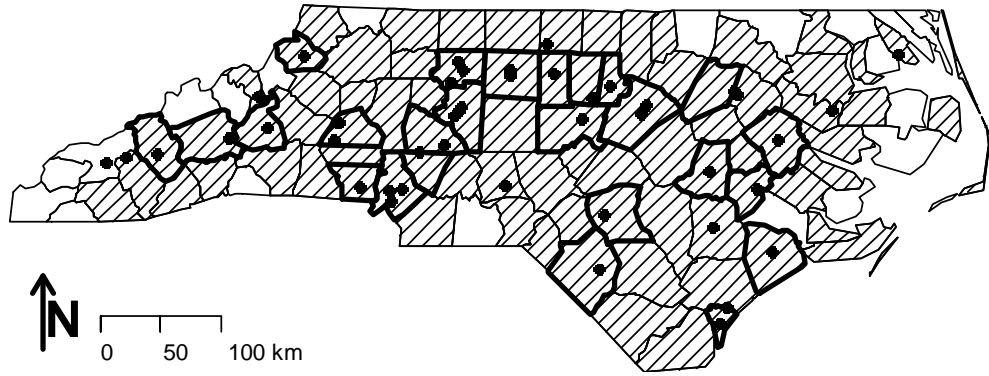


Figure 2

Log Odds Ratio for Prete