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Citation Details


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Running title: Particulate matter and preterm birth

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Abstract

Background: Particulate matter < 2.5 micrometers in aerodynamic diameter (PM$_{2.5}$) has been variably associated with preterm birth (PTB).

Objective: We classified preterm births into four categories (20–27, 28–31, 32–34, and 35–36 weeks completed gestation) and estimated risk differences (RD) for each category in association with a 1-$\mu$g/m$^3$ increase in PM$_{2.5}$ exposure during each week of gestation.

Methods: We assembled a cohort of singleton pregnancies that completed at least 20 weeks of gestation during 2000-2005 using live birth certificate data from three states (Pennsylvania, Ohio, and New Jersey) ($n =$ 1,940,213; 8% PTB). We estimated mean PM$_{2.5}$ exposures for each week of gestation from monitor-corrected Community Multi-Scale Air Quality modeling data. RDs were estimated using modified Poisson linear regression, adjusted for maternal race/ethnicity, marital status, education, age, and ozone.

Results: RD estimates varied by exposure window and outcome period. Average PM$_{2.5}$ exposure during the fourth week of gestation was positively associated with all PTB outcomes, though magnitude varied by PTB category (e.g., for a 1-$\mu$g/m$^3$ increase, RD = 11.8 (95% CI: -6, 29.2); RD = 46 (95% CI: 23.2, 68.9); RD = 61.1 (95% CI: 22.6, 99.7); and RD = 28.5 (95% CI: -39, 95.7) for preterm births during 20-27, 28-31, 32-34, and 35-36 weeks, respectively). Exposures during the week of birth and the two weeks before birth also were positively associated with all PTB categories.

Conclusions: Exposures beginning around the time of implantation and near birth appeared to be more strongly associated with PTB than exposures during other time periods. Because particulate matter exposure is ubiquitous, evidence of effects of PM$_{2.5}$ exposure on PTB, even if small in magnitudes, is cause for concern.
Introduction

Particulate matter under 2.5 micrometers in aerodynamic diameter (PM$_{2.5}$), one of the criteria air pollutants regulated under the Clean Air Act, is a complex mixture of extremely small particles and liquid droplets. PM$_{2.5}$ may be a carrier for hazardous compounds such as PAHs and metals, which particulates absorb. While levels of PM$_{2.5}$ vary across the United States, and are often below EPA standards (24 hour standard: 35 µg/m$^3$ (U.S.EPA 2013; U.S.EPA. 2012)), everyone is exposed to some extent. PM$_{2.5}$ has been associated with adverse health outcomes, including cardiovascular mortality, lung cancer, asthma, and adverse pregnancy and birth outcomes (Backes et al. 2013; Dominici et al. 2003; Dominici et al. 2006; Lewtas 2007; U.S.EPA. 2009). Of the birth outcomes studied in conjunction with PM exposure, PTB is an important marker for fetal underdevelopment, conveying risk for further adverse outcomes, including infant mortality and problems with neurodevelopment and growth (Behrman and Butler 2007; Gilbert et al. 2003; Mathews and MacDorman 2010; Saigal and Doyle 2008). Many studies have reported PTB positively associated with PM$_{2.5}$ over whole pregnancy, first trimester and late pregnancy exposures (Brauer et al. 2008; Chang et al. 2012; Gehring et al. 2011; Huynh et al. 2006; Lee et al. 2012; Warren et al. 2012; Wilhelm et al. 2011; Wu et al. 2009; Wu et al. 2011), though others have reported null or inverse associations of PM$_{2.5}$ on PTB (Darrow et al. 2009; Gehring et al. 2011; Jalaludin et al. 2007; Wilhelm and Ritz 2005). Meta-analyses have found overall increases in associations between PM$_{2.5}$ and PTB (e.g., Sapkota et al. (2012) with PM$_{2.5}$ exposure in the 3$^{rd}$ trimester OR=1.07 (95% CI: 1.00, 1.15)), but noted that variable results across studies may be due to differences in study designs, populations, or exposure metrics and contrasts (Sapkota et al. 2012; Stieb et al. 2012). Most studies have relied upon air monitoring for exposure assignment, limiting inclusion to women residing close to active monitors during
pregnancy. Additionally, reliance on a few central monitors assumes no spatial variation in ambient PM$_{2.5}$ concentrations, which may result in exposure misclassification. Most also examine exposure windows spanning a month or trimester in length, which may mask temporal variability. Finally, previous studies have focused on any births between 20-36 weeks, yet etiology of PTB may vary over this period.

**Objectives**

In this study, we examined the association between ambient PM$_{2.5}$ and risk of PTB using a cohort of singleton pregnancies that completed at least 20 weeks of gestation during 2000-2005 across three states (Pennsylvania (PA), Ohio (OH), and New Jersey (NJ)). We employ output from the EPA’s Community Multiscale Air Quality (CMAQ) model (Hogrefe et al. 2009), which offers complete spatial coverage and daily estimated air pollutant concentrations, leading to an extensive study area and population. We classified preterm births into four categories (20–27, 28–31, 32–34, and 35–36 weeks completed gestation) and estimated risk differences (RD) for each category in association with a 1-$\mu$g/m$^3$ increase in PM$_{2.5}$ exposure during each week of gestation.

**Methods**

**Study population**

Live birth records provided by the State Health Departments of PA, NJ, and OH were used to construct a cohort of those at-risk for PTB (i.e., achieving a gestational age of at least 20 weeks) between 1 January 2000 and 31 December 2005. These states have similar source profiles for PM$_{2.5}$ (e.g., electricity generation is the main source of PM$_{2.5}$ for OH and PA), or PM is from regional sources (e.g., air pollutants are transported from Ohio River valley area to PA and NJ)
and therefore PM composition should be similar in these areas (Garcia et al. 2011; U.S.EPA. 2013). From all birth records (n=2,495,350) the study population was restricted to singleton pregnancies with no recorded birth defects at time of birth, with an estimated gestational age available, and having achieved gestational week 20 no earlier than 1 January 2000 and gestational week 44 no later than 31 December 2005 (birth dataset, n=2,142,915/ number excluded = 352,435). Gestational age requirements are necessary so that each pregnancy would have been entirely observable within the study period no matter at which point birth occurred, and to avoid fixed-cohort bias where the beginning of the study misses shorter pregnancies and the end misses longer pregnancies (Barnett 2011; Strand et al. 2011). A point-geocodeable (latitude and longitude assignable) birth address was also required (excluded n=202,702). After restrictions, the final study population included 1,940,213 pregnancies.

**Gestational age, pregnancy start, and preterm birth status**

Gestational age was determined by clinical estimate of gestational age as reported on birth certificates. Estimated date of last menstrual period (LMP) was calculated by subtracting clinical estimate of completed gestational weeks from date of birth. PTB status was defined as having a gestational age between 20-36 completed weeks. PTB was subset into four categories based on definitions from the World Health Organization (WHO 2012): Extremely PTB (ExPTB) gestational age between 20-27 weeks; Very PTB (VPTB) gestational age between 28-31 weeks; Moderate PTB (MPTB) gestational age between 32-34 weeks; and Late PTB (LPTB) gestational age of 35-36 weeks. Term births were between 37 and 44 completed gestational weeks.
**Exposure data**

Maternal address data were taken from birth records and processed with the Zp4 address locator program (Semaphore Corporation, Monterey CA) to assign latitude and longitude values (n=2,042,425). Addresses that were not assigned latitude and longitude values (n=452,925) were geocoded using the ArcGIS online geocoding service in ArcMap10 (ESRI, Redlands CA), which returned 197,125 matched addresses and 8949 addresses that were equally matched to two or more points and were then hand matched to the best candidate. In total, 2,248,499 pregnancies had latitude and longitude values. After restriction to pregnancies meeting all inclusion criteria, the study population was 1,940,213.

Daily estimated concentrations of PM$_{2.5}$ were provided by the EPA’s Atmospheric Exposure Integration Branch for 1999 to 2005 in 12 km grids. These estimates were constructed using output from CMAQ bias-corrected with monitoring network data, as detailed in Hogrefe et al(2009). Briefly, meteorological conditions and criteria pollutant emissions are input into CMAQ, which simulates atmospheric processes and estimates gridded concentrations of ambient air pollutants (Byun and Schere 2006; Hogrefe et al. 2009). Grids were matched to monitoring sites and a filter applied to created baseline concentrations of PM$_{2.5}$. Adjustment factors were then created as the ratio of observed to modeled concentrations, spatially interpolated across the gridded field, and multiplied by CMAQ output to produce the final bias-corrected concentration estimates (Hogrefe et al. 2009). Both spatial and temporal variability in PM$_{2.5}$ concentrations are present in our study.

We assigned daily values for pollutant exposure to pregnancies by matching geocoded maternal residential location to CMAQ grid. Each day from the calculated start of pregnancy to birth was
matched to date of CMAQ concentration estimation. Exposure was assigned in two ways. First, we assigned average weekly exposures beginning on the estimated LMP date, such that week 1 comprised the estimated LMP date and the following 6 days. Second, we lagged weekly exposures backwards from the date of birth, such that lag 0 represented average PM$_{2.5}$ during the week of birth (including the day of birth and the 6 days before birth), lag 1 represented average PM$_{2.5}$ during the previous week (i.e., 7–13 days before birth), up to lag 8.

**Confounders and effect measure modifiers**

To achieve a least biased estimate of association, potential confounders were identified through directed acyclic graph (DAG) analysis. We constructed the DAG based on review of previous literature and knowledge of factors influencing PTB and air pollution. From the birth certificate, we included: maternal race/ethnicity, education level, marital status, age at delivery, maternal smoking status, prenatal care initiation, and parity; and from the CMAQ model we included daily average ozone. We also considered unmeasured factors, such as infection status of mother during pregnancy, and general/area level environmental quality. We used the DAG Program (Knuppel and Stang 2010) to identify minimally sufficient adjustment sets. Identified covariates included maternal race/ethnicity, education level, marital status, age at delivery, and ozone. Maternal demographic factors are risk factors of PTB and associated with socio-economic status, which can influence where a woman resides and therefore PM$_{2.5}$ exposure. Ozone has been associated with PTB and co-occurs temporally and spatially with PM$_{2.5}$ (Lee et al. 2012; Olsson et al. 2013). We assessed effect measure modification (EMM) to reveal potential differences in the association. We also assessed potential modification by state, region, and population density, as proxy indicators of variation in PM$_{2.5}$ composition.
**Statistical Analysis**

Adjusted RDs were estimated using modified Poisson regression with an identity link; Poisson models produce equally valid estimates as binomial models, and though less efficient are less likely to result in nonconvergence (Spiegelman and Hertzmark 2005; Zou 2004). We estimated absolute effect measures because they, unlike incidence odds ratios and other relative effect measures, are informative for public health impact and decision making, along with outcome severity (e.g., ExPTB, despite its relatively low frequency, is a much more adverse outcome than LPTB). We modeled each category of PTB separately as a dichotomous outcome. We included those at risk of PTB at a given time point in the model as appropriate (e.g., VPTB births were included in ExPTB models as non-events, those who had already experienced ExPTB were not included in VPTB models). PM$_{2.5}$ was treated as a continuous variable. Individual models were produced for exposure during each week of gestation anchored from estimated LMP and each week lagged from birth. Models were adjusted for demographic characteristics (maternal age coded as restricted quadratic spline, others as in Table 1) and co-occurring ozone (continuous).

To evaluate EMM, we ran separate models with an interaction term for each potential modifier and continuous PM$_{2.5}$; interaction terms with p<0.05 (due to the large population) were considered evidence of EMM. Potential modifiers were: maternal race/ethnicity (black non-Hispanic, non-black (includes white non-Hispanic, Hispanic, and other)), smoking status (smoker, non-smoker), parity (primiparous, multiparous), and infant sex. We performed sensitivity analyses to include temperature and season of conception as covariates. Due to concerns about residual confounding, we also examined smoking as a covariate. In addition, for comparability with previous work, we examined exposures averaged by trimester and entire pregnancy period. All analyses were performed using SAS version 9.3 (Cary, NC).
This research was approved by the University of North Carolina at Chapel Hill’s Office of Human Research Ethics, the Pennsylvania Department of Health Bureau of Health Statistics and Research, New Jersey Department of Health and Senior Services Institutional Review Board, and the Ohio Department of Health Human Subjects Institutional Review Board. Informed consent was not required for this study as it was a secondary data analysis of existing data and no participant contact was attempted.

**Results**

Adjusted analyses included 1,781,527 of the 1,940,212 eligible pregnancies (not missing major covariates). Eight percent were preterm. Demographic profiles of women shifted with decreasing gestational age (Table 1) (see Supplemental Material, Table S1 for additional characteristics). Women with preterm pregnancies were less likely to have a bachelor’s degree or be married at time of delivery, and more likely to be non-Hispanic black than women with term pregnancies. The study population was primarily urban, with ~90% falling within metropolitan areas (data not shown).

Women who were excluded because they lacked residence location (and therefore exposure) data were more likely to be white, unmarried, less educated, younger, and to have a PTB (~9% v. 8% in analytic population) than births to included women (data not shown).

Average weekly PM$_{2.5}$ concentrations were similar across categories of PTB for exposure windows anchored at estimated LMP and lagged from birth, with means ~14.5 µg/m$^3$ (SD ~5 µg/m$^3$) and interquartile ranges around 6.2 µg/m$^3$ (Table 2). Weekly PM$_{2.5}$ concentrations were temporally correlated, with correlation coefficients for adjacent weeks of approximately 0.4, but dropping to near 0 for weeks further apart (data not shown).
Results for exposure anchored at estimated LMP are presented in Figure 1, note that scales vary between outcomes due to differing effect estimate and confidence interval magnitudes (numeric data provided in Supplemental Material, Table S2). For Extremely PTB (Figure 1a), elevated RDs were observed with exposure to PM$_{2.5}$ in gestational weeks 2-8 and weeks 11-20, with more consistency in early pregnancy. For Very PTB (Figure 1b), elevations in RDs are highest with exposures at gestational weeks 4-9 and 15-24, though RDs are generally elevated for exposure in most weeks. For Moderate PTB (Figure 1c), RDs were elevated with exposure to PM$_{2.5}$ at gestational week 4 and increased with exposure through gestational week 12. RDs dropped at week 13, though remained positive through the rest of pregnancy. For Late PTB (Figure 1d), associations were negative with the earliest weeks of exposure, with some positive though fluctuating RDs through week 20. However, after week 20 PM$_{2.5}$ associated RDs were positive and remained elevated through week 35. Results with and without adjustment for ozone were similar (Supplement Material, Figure S1, Table S3). Some commonalities are present between birth categories, e.g., a rising of associations in the first few weeks of pregnancy for VPTB and MPTP; however there were also differences in patterns of associations with PM$_{2.5}$ exposure across outcome categories, in particular for the earliest and latest PTBs.

Results for exposures lagged from birth are presented in Figure 2 (numeric data provided in Supplemental Material, Table S4). RDs were consistently elevated for exposures 0 to 2 weeks before birth across PTB categories; but for exposure lagged further from birth, patterns across PTB categories were not consistent. RDs generally dropped to null around lag period 3, then increased again for ExPTB, VPTB and MPTP. LPTB RDs are positive for exposures with lags 0-3 and lags 4-5.
For comparability with previous work, we averaged exposure by trimester and entire pregnancy period. Associations with VTPB and MTPB were generally positive, but varied by trimester (Supplemental Material, Table S5). We observed no evidence of effect measure modification for race/ethnicity, parity, smoking status, infant sex, state or region of birth, or by census tract population density (data not shown). Inclusion of smoking as a covariate did not alter effect estimates (data not shown). Results of sensitivity analyses examining adjusting for temperature and season of conception were similar (Supplemental Material, Table S6).

**Discussion**

We examined associations between exposure to PM$_{2.5}$ at each week of pregnancy and multiple categories of PTB. PM$_{2.5}$ exposure in early and late gestational weeks and near-birth was associated with multiple categories of PTB, supporting the potential for multiple or overlapping pathways of action for PM$_{2.5}$, based both on timing of exposure and severity of outcome.

Our results for PM$_{2.5}$ exposures in early pregnancy were consistent with six studies across geographic areas that reported positive odds ratios (OR) (Chang et al. 2012; Hansen et al. 2006; Huynh et al. 2006; Jalaludin et al. 2007; Lee et al. 2012; Ritz et al. 2007). Studies have also reported positive associations for exposures late in pregnancy or near birth (Chang et al. 2012; Gehring et al. 2011; Hansen et al. 2006; Wilhelm and Ritz 2005). Chang et al. (2012) also observed positive associations for exposure to PM$_{2.5}$ in the second trimester.

Inverse or null ORs with early pregnancy PM$_{2.5}$ exposure have also been reported. Jalaludin et al. (2007) reported inverse ORs for exposures occurring in the 1$^{st}$ trimester during summer months only. Gehring et al. (2011) found inverse associations with PM$_{2.5}$ exposures in the first trimester and last month before birth that attenuated or reversed after adjustment for region. Wilhelm et al.
reported inverse ORs with single pollutant models of PM$_{2.5}$ for exposures during early pregnancy (Wilhelm and Ritz 2005; Wilhelm et al. 2011); however, in the later study of a population from a similar area, analysis using multi-pollutant models (including criteria air pollutants and traffic related air toxics) produced positive ORs (Wilhelm et al. 2011). Shifts in associations with regional or multi-pollutant adjustment suggest the importance of considering composition of pollutants co-occurring with PM$_{2.5}$. It is possible that residual confounding due to co-pollutants is also a factor in our study; however, our estimates were robust to adjustment for co-occurring ozone.

Like our study, Warren et al. (2012) evaluated weekly windows of exposure, reporting elevated RDs with PM$_{2.5}$ exposure in weeks 4-22 of gestation. While these results do not perfectly align with ours, possibly because of differences in PM$_{2.5}$ composition in Texas compared to the northeast, they do corroborate our findings of positive associations with exposures in earlier weeks of gestation. Identification of increased associations in very specific vulnerable periods in development may aid in the elucidation of potential mechanisms.

Most studies assessed exposure using monitors or monitoring based methods (e.g., kriging, land-use regression). While kriging and land use regression impute concentrations with complete spatial and temporal coverage, they are best suited for areas with reasonably dense spatial and temporal monitoring. Chang et al. (2012) examined PM$_{2.5}$ exposure in North Carolina using both monitor data and monitor-corrected CMAQ data, reporting similar associations between PM$_{2.5}$ and PTB for women with exposure information from both sources; but not all women had monitoring data. For our study, the use of monitor-corrected CMAQ data offered more complete spatial and temporal coverage, including regions for which monitor data was not available. This
expands generalizability of our results over monitor-based studies restricted to urban centers. Our large population also allowed examination of EMM by several factors and detection of very small associations across multiple time windows of exposure.

In this work, we examined more specific definitions of PTB than <37 weeks of gestation. The two other studies that used a more specific definition of PTB (27-36 weeks for Chang et al. (2012); 29-36 weeks for Darrow et al. (2009)) found opposing results to one another for the first trimester/month of pregnancy. But, they used different analytic methods: Chang et al. (2012) used time-to-event analysis and Darrow et al. (2009) a time-series approach. Using a cohort study design, our study found mostly positive RDs for these gestational ages and exposure windows, with the exception of LPTBs. The etiology of PTB may differ greatly at different gestational weeks, as fetal development and periods of vulnerabilities shift rapidly. Using the four categories may have helped reveal differences in associations that would otherwise have been masked by collapsing all categories of PTB into a single outcome.

It is challenging to directly compare and interpret differences across studies because of different research methodologies (study designs, outcome definitions, and exposure assessments, metrics, and contrasts) (Stieb et al. 2012). In addition to the methodological differences noted above, differences in results across studies may also be explained by actual differences in PM$_{2.5}$ composition over time and geographical area due to pollutant sources and meteorological conditions (Bell et al. 2007).

Like most studies of air pollution and PTB, we relied on imperfect exposure classification and the results may reflect residual or unmeasured confounding. Exposure misclassification may be due to the use of a model for exposure assessment (even with bias correction), the use of ambient
rather than personal data, the use of a single residential point rather than a profile of where a woman’s time is spent, and the assumption that residence at birth was unchanged throughout pregnancy. These factors would likely be nondifferential by outcome, though not necessarily by confounding factors. Consequences of exposure misclassification on the observed associations are complicated to predict. True exposure may be higher or lower than assigned based on residence, depending on the pollution levels where a woman works, the amount of time she commutes, or the amount of time spent indoors, potentially biasing associations in either direction (Allen et al. 2012; Hodas et al. 2012). Results for exposures during individual weeks may also be confounded by exposures during temporally correlated weeks. Some bias may also be introduced through the women who were not able to be geo-located. There are demographic differences between these women and the included population, some of which may indicate a higher likelihood of exposure to worse air quality (Miranda et al. 2011). In addition, bias due to residual or unmeasured confounding may have arisen from the use of proxy variables for socio-economic status or lack of data on important factors, such as maternal obesity. Socio-economic status, while approximated in a manner similar to other studies, was not well defined and may not have fully captured the influence of socioeconomic status on the PM$_{2.5}$/PTB association. Area-level SES has been linked to PTB, and PM exposure may vary by neighborhood characteristics linked to SES; thus there may be some unmeasured confounding by area-level characteristics in our study. Unmeasured factors such as maternal obesity and diet may modify the association between PM$_{2.5}$ and PTB, potentially masking associations in some sub-groups. Again such relationships are complex and many patterns are possible, potentially resulting in biases both toward and away from the null.
RDs as absolute measure of risk are easily interpretable and can be simply transformed into a number need to harm (NNH = 1/RD), providing information about how changes to exposure would be expected to affect public health. For example, with exposure during week 15 of gestation, NNHs for PM$_{2.5}$ and LPTB correspond to 5,587, meaning for every 1 $\mu$g/m$^3$ increase in ambient PM$_{2.5}$ concentrations for 5,587 pregnant women 1 LPTB occurs (assuming associations are causal). For ExPTB the NNH is much higher, at 39,526; this is due to the rarity of ExPTB. It is important to note that while magnitude of association for ExPTB may be small, this outcome also carries the most severe consequences and costs. Given the ubiquitous nature of exposure to PM$_{2.5}$, even the small changes we observed may impact public health.

In general, the positive associations observed here and throughout the literature call for consideration of potentially complex and subtle mechanisms by which PM$_{2.5}$ may play a role in PTB. Several pathways are possible. PM$_{2.5}$ exposure has been associated with markers of systemic inflammation in humans that have been associated with preterm delivery, such as high sensitivity C-reactive protein (CRP) and fibrinogen, and gestational hypertension (Lee et al. 2012; Lee et al. 2013). Maternal inflammation may alter placental vascular function (Backes et al. 2013). In a study of mice, Veras et al. (2008) found PM exposure altered placental morphology, decreasing maternal blood space volume and maternal-fetal surface ratio, and increasing fetal capillary proliferation with inhaled exposure to non-filtered ambient air (mean PM$_{2.5}$ = 27.5 $\mu$g/m$^3$) versus filtered ambient air (mean PM$_{2.5}$ = 6.5 $\mu$g/m$^3$). Based on the experimental findings in rodents and hypothesized mechanisms of preterm labor it is plausible that these changes may lead to PTB through inadequate placental perfusion or impaired nutrient exchange (Bobak 2000; Kannan et al. 2006; Veras et al. 2012).
A variety of means have been proposed for the possible mechanisms of PM$_{2.5}$ to act on PTB, including susceptibility to infection, disruption of placentation, and nutrient deprivation. PM$_{2.5}$ has been shown to increase susceptibility to respiratory infections in toxicological studies, including influenza and respiratory syncytial virus in mice, potentially acting through impaired clearance of PM or pathogens (U.S.EPA. 2009). Respiratory infections may either act as a primer for secondary infection (wherein immunological response to/clearance of secondary infection is reduced) or be an indicator of systemic inflammation. (Behrman and Butler 2007; U.S.EPA. 2009; Wilhelm and Ritz 2005). Interruption of placental implantation, development, or function is another plausible mechanism, though at present only investigated non-human studies (Backes et al. 2013; Veras et al. 2008; Veras et al. 2012). Particulates may interfere in placental processes by the transfer of sorbed toxic compounds to the fetus or placenta, inflammatory processes including oxidative stress pathways, or by increasing susceptibility to infectious agents which in turn act on fetal development (Lee et al. 2012; U.S.EPA. 2009). Near-birth exposures may increase PTB risk by nutritional deprivation, for example PM$_{2.5}$ exposure may lead to inflammation leading to inadequate placental perfusion or a constricted umbilical cord, wherein the stressed fetus may produce pro-inflammatory cytokines which can trigger the cascade of events leading to labor and birth (Kannan et al. 2006). Some of these potential mechanisms would be exposure-timing restricted (e.g., disruption of placentation) while others may act throughout gestation (e.g., inflammation).

Characterizing exposure in two ways, anchored from LMP and lagged from birth, allowed us to examine different relationships between PM and PTB, hypothesizing two different potential mechanisms by which PM$_{2.5}$ might act on PTB. Exposures anchored at gestational age allowed us to examine associations of PM$_{2.5}$ exposure that may signal disruption in specific stages of
pregnancy; while associations identified with exposures anchored at birth may signal effects “triggering” early labor and birth. Examining these different hypotheses required different approaches. Our results indicate heterogeneity by both period of exposure and by stage of PTB should be considered in future analyses.

PM$_{2.5}$ exposures in early and late gestation were associated with increased RD for PTB, though the specific windows of exposure associated with elevated RDs varied by PTB category. Our findings suggest that exposures beginning around the time of implantation and near birth may be of particular importance. Refined exposure windows and outcome definitions may have improved our ability to detect subtle associations. The ubiquitous nature of particulate matter means exposure increases the potential for harm, even when effect estimate magnitudes are small. Many properties of PM$_{2.5}$ could be responsible for the observed associations, and further studies examining specific PM$_{2.5}$ components or properties could add valuable information about the properties of particulate matter for which regulation or intervention should be targeted to reduce adverse outcomes.
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Table 1. Maternal and fetal characteristics according to preterm birth category for included pregnancies among women living in OH, PA, or NJ (2000-2005) [n(%)].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ExPTB</th>
<th>VPTB</th>
<th>MPTB</th>
<th>LPTB</th>
<th>Term births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations (n)</td>
<td>8,664</td>
<td>12,004</td>
<td>31,446</td>
<td>90,037</td>
<td>1,639,376</td>
</tr>
</tbody>
</table>

Maternal education

| Grad school | 550 (6) | 933 (8) | 2,865 (9) | 9,245 (10) | 202,783 (12) |
| Bachelor's degree | 1,021 (12) | 1,651 (14) | 4,688 (15) | 14,964 (17) | 325,596 (20) |
| Some college | 1,905 (22) | 2,604 (22) | 6,982 (22) | 20,429 (23) | 372,682 (23) |
| High school diploma | 3,221 (37) | 4,227 (35) | 10,789 (34) | 29,566 (33) | 491,888 (30) |
| Some high school | 1,664 (19) | 2,199 (18) | 5,048 (16) | 12,918 (14) | 185,703 (11) |
| <8th grade | 303 (3) | 390 (3) | 1,074 (3) | 2,918 (3) | 60,724 (4) |

Maternal race/ethnicity

| Non-Hispanic White | 4,120 (48) | 6,549 (55) | 18,848 (60) | 58,868 (65) | 1,152,731 (70) |
| Non-Hispanic Black | 3,279 (38) | 3,671 (31) | 7,781 (25) | 17,034 (19) | 225,430 (14) |
| Hispanic | 1,009 (12) | 1,337 (11) | 3,435 (11) | 10,004 (11) | 177,708 (11) |
| Other | 256 (3) | 447 (4) | 1,382 (4) | 4,131 (5) | 83,507 (5) |

Maternal age

| <15 | 126 (1) | 141 (1) | 290 (1) | 637 (1) | 8,033 (<1) |
| 15-19 | 1,228 (14) | 1,408 (12) | 3,259 (10) | 8,496 (9) | 131,159 (8) |
| 20-24 | 2,114 (24) | 2,798 (23) | 7,166 (23) | 20,201 (22) | 352,319 (21) |
| 25-29 | 2,031 (23) | 2,768 (23) | 7,582 (24) | 23,058 (26) | 438,679 (27) |
| 30-34 | 1,844 (21) | 2,821 (24) | 7,584 (24) | 22,587 (25) | 446,350 (27) |
| 35-39 | 1,044 (12) | 1,620 (13) | 4,387 (14) | 12,070 (13) | 218,275 (13) |
| 40-44 | 259 (3) | 423 (4) | 1,108 (4) | 2,816 (3) | 42,739 (3) |
| 45+ | 18 (<1) | 25 (<1) | 70 (<1) | 172 (<1) | 1,822 (<1) |

ExPTB = extremely preterm births (20-27 weeks completed gestation); VPTB= very preterm births (28-31 weeks); MPTB=moderate preterm births (32-34 weeks); LPTB=late preterm births (35-36 weeks); Term=term births (37-44 weeks).
Table 2. Descriptive statistics for PM$_{2.5}$ (µg/m$^3$) exposure concentrations, averaged over all weeks of exposure.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>ExPTB</th>
<th>VPTB</th>
<th>MPTB</th>
<th>LPTB</th>
<th>Term births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>3.73</td>
<td>3.55</td>
<td>3.15</td>
<td>2.84</td>
<td>2.45</td>
</tr>
<tr>
<td>25th</td>
<td>11</td>
<td>10.93</td>
<td>10.87</td>
<td>10.76</td>
<td>10.74</td>
</tr>
<tr>
<td>50th</td>
<td>13.8</td>
<td>13.72</td>
<td>13.65</td>
<td>13.54</td>
<td>13.51</td>
</tr>
<tr>
<td>75th</td>
<td>17.33</td>
<td>17.24</td>
<td>17.17</td>
<td>17.04</td>
<td>16.98</td>
</tr>
<tr>
<td>Max</td>
<td>50.82</td>
<td>50.87</td>
<td>53.33</td>
<td>55.19</td>
<td>58.25</td>
</tr>
<tr>
<td>SD</td>
<td>5.07</td>
<td>5.04</td>
<td>5.03</td>
<td>5.01</td>
<td>4.98</td>
</tr>
<tr>
<td>IQR</td>
<td>6.33</td>
<td>6.31</td>
<td>6.3</td>
<td>6.28</td>
<td>6.24</td>
</tr>
</tbody>
</table>

ExPTB = extremely preterm births (20-27 weeks completed gestation); VPTB= very preterm births (28-31 weeks); MPTB=moderate preterm births (32-34 weeks); LPTB=late preterm births (35-36 weeks); Term=term births (37-44 weeks); LMP = last menstrual period.
Figure legends

**Figure 1.** Results for PM$_{2.5}$, exposures anchored at estimated LMP. Risk differences (with 95% confidence intervals) for preterm birth with 1µg/m$^3$ increases in particulate matter under 2.5 micrometers in aerodynamic diameter (PM$_{2.5}$) per 1,000,000 pregnancies with exposures anchored at estimated LMP. For women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race/ethnicity, education level, marital status, age at delivery, and co-occurring ozone. (a) risk of birth at 20-27 weeks of gestation (ExPTB), (b) risk of birth at 28-31 weeks of gestation (VPTB), (c) risk of birth at 32-34 weeks of gestation (MPTB), and (d) risk of birth at 35-36 weeks of gestation (LPTB). Numeric estimates are provided in Supplemental Material, Table S2.

**Figure 2.** Results for PM$_{2.5}$, lagged exposures. Risk differences with 95% confidence interval for preterm birth with 1 µg/m$^3$ increases in particulate matter under 2.5 micrometers in aerodynamic diameter (PM$_{2.5}$) per 1,000,000 pregnancies with exposures lagged from birth. For women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race/ethnicity, education level, marital status, age at delivery, and co-occurring ozone. a) risk of birth at 20-27 weeks of gestation (ExPTB), (b) risk of birth at 28-31 weeks of gestation (VPTB), (c) risk of birth at 32-34 weeks of gestation (MPTB), and (d) risk of birth at 35-36 weeks of gestation (LPTB). Numeric estimates are provided in Supplemental Material, Table S4.
Figure 1
Figure 2

Risk differences for 1 μg/m³ increase in PM$_{2.5}$ per 1,000,000 pregnancies

Week from birth in which exposure occurred