



Contents lists available at ScienceDirect

Annals of Epidemiology



Original article

Associations between PM_{2.5} and risk of preterm birth among liveborn infants

Breanna L. Alman, MPH^a, Jeanette A. Stingone, PhD^b, Mahsa Yazdy, PhD^c, Lorenzo D. Botto, MD^d, Tania A. Desrosiers, PhD^e, Shannon Pruitt, MPH^{f,g}, Amy H. Herring, ScD^h, Peter H. Langlois, PhDⁱ, Wendy N. Nembhard, PhD^j, Gary M. Shaw, DrPH^k, Andrew F. Olshan, PhD^e, Thomas J. Luben, PhD^{l,*}, and the National Birth Defects Prevention Study

^a Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

^b Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, NY, NY

^c Massachusetts Department of Public Health, Boston, MA

^d Department of Pediatrics, University of Utah, Salt Lake City

^e Department of Epidemiology, Gillings School of Global Public Health, UNC Chapel Hill, NC

^f National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC), Atlanta, GA

^g Oak Ridge Institute for Science and Education, Oak Ridge, TN

^h Global Health Institute, Duke University, Durham, NC

ⁱ Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX

^j Departments of Pediatrics and Epidemiology, University of Arkansas for Medical Sciences, Little Rock, AR

^k Department of Pediatrics, Stanford University, Stanford, CA

^l Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

ARTICLE INFO

Article history:

Received 29 January 2019

Accepted 28 September 2019

Available online 9 October 2019

Keywords:

Preterm birth

PM_{2.5}

Temperature

Air pollution

ABSTRACT

Purpose: Studies suggest exposure to ambient particulate matter less than 2.5 μg/m³ in aerodynamic diameter (PM_{2.5}) may be associated with preterm birth (PTB), but few have evaluated how this is modified by ambient temperature. We investigated the relationship between PM_{2.5} exposure during pregnancy and PTB in infants without birth defects (1999–2006) and enrolled in the National Birth Defects Prevention Study and how it is modified by concurrent temperature.

Methods: PTB was defined as spontaneous or iatrogenic delivery before 37 weeks. Exposure was assigned using inverse distance weighting with up to four monitors within 50 kilometers of maternal residence. To account for state-level variations, a Bayesian two-level hierarchical model was developed.

Results: PTB was associated with PM_{2.5} during the third and fourth months of pregnancy (range: (odds ratio (95% confidence interval) = 1.00 (0.35, 2.15) to 1.49 (0.82, 2.68) and 1.31 (0.56, 2.91) to 1.62 (0.7, 3.32), respectively); no week of exposure conveyed greater risk. Temperature may modify this relationship; higher local average temperatures during pregnancy yielded stronger positive relationships between PM_{2.5} and PTB compared to nonstratified results.

Conclusions: Results add to literature on associations between PM_{2.5} and PTB, underscoring the importance of considering co-exposures when estimating effects of PM_{2.5} exposure during pregnancy.

© 2019 Elsevier Inc. All rights reserved.

The authors have no conflicts of interest to disclose.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Environmental Protection Agency, the Centers for Disease Control and Prevention, or the California Department of Public Health.

Data that CDC collects or holds must be available for data sharing within a year after the data are evaluated for quality and shared with any partners in data collection activity. Because NBDPS data contain PII, NBDPS data are not released publicly.

<https://doi.org/10.1016/j.annepidem.2019.09.008>

1047-2797/© 2019 Elsevier Inc. All rights reserved.

Instead, they are available via a special use agreement. Qualified researchers can be granted access to NBDPS data for analysis through collaboration with one of the Centers for Birth Defects Research and Prevention. The procedure for applying for access to NBDPS data can be found on the NBDPS Public Access Procedures web site: <https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html>.

* Corresponding author. Office of Research and Development, 109 TW Alexander Dr, Durham, NC 27709. Tel.: (919) 541-5762; fax: (919) 541-1818.

E-mail address: luben.tom@epa.gov (T.J. Luben).

Introduction

In 2016, the proportion of births delivered preterm (defined as spontaneous or iatrogenic delivery before 37 weeks of completed gestation) in the United States was 9.85% [1]. Preterm birth (PTB) is a public health concern because it is associated with high infant mortality and adverse developmental outcomes later in childhood [2]. Known risk factors for PTB include low socioeconomic factors, age, race, substance abuse, tobacco usage during pregnancy, poor nutritional status, and the presence of a birth defect [3,4]. Recently, some epidemiologic studies have suggested that exposure during pregnancy to ambient particulate matter less than $2.5 \mu\text{g}/\text{m}^3$ in aerodynamic diameter ($\text{PM}_{2.5}$) is associated with an increased risk of PTB; [5–8] however, results have been inconsistent, and the exact biological mechanisms surrounding that relationship and any potential critical exposure windows remain unclear. Ambient outdoor $\text{PM}_{2.5}$ is a ubiquitous pollutant for which personal exposure may vary on a number of factors, including proximity to emission sources (e.g., mobile vehicles) [9].

Whereas studies have generally shown an increase in PTB with an increase in $\text{PM}_{2.5}$ exposure [10], studies on specific, and usually narrower, windows of exposure have been less consistent. Identifying these critical exposure windows may aid in determining the exact biological mechanism(s) behind the relationship. Some studies have provided support for early exposure effects of $\text{PM}_{2.5}$ on PTB (i.e., within the first trimester) [5,8,11,12]. Conversely, others have suggested that exposure during the entire pregnancy and late pregnancy (i.e., during the third trimester), but not during the first trimester, has a stronger association [13], and additional research has reported inverse or null results [14,15]. In addition, there has been a growing body of literature surrounding the relationship between PTB and ambient temperature [16,17], with higher temperatures being positively associated with PTB. For example, study by Schifano et al [18] evaluated PTB's relationship with PM_{10} stratified by season and found that temperature impacted the relationship in the warm season, but not in the cold season. Conversely, in a meta-analysis of the effects of seasonality on the $\text{PM}_{2.5}$ and PTB relationship, authors reported that both summer and winter seasons (compared to the more temperate autumn and spring) may act as modifiers [19]. Although there is limited evidence looking at specific biological mechanisms that may explain this relationship, multiple studies have shown that exposure to $\text{PM}_{2.5}$ can cause placental inflammation during pregnancy [20] potentially resulting in altered placental vascular function [21], which in turn may cause inadequate nutrient exchange or placental perfusion [22,23] leading to PTB. While the ways temperature may act as an effect measure modifier on the $\text{PM}_{2.5}$ and PTB relationship remain unclear, limited toxicological evidence suggests that exposure to concurrent high temperature may intensify the effects of an environmental exposure [24]. Narrowing down when this relationship is the strongest could aid in identifying more specific biological mechanisms behind the relationship and could allow for targeted interventions.

Given the inconsistent relationship between PTB and $\text{PM}_{2.5}$ and the potential for high temperature to have an impact both directly on PTB as well as on the intensity of an effect from an environmental pollutant, our study was designed to investigate the relationship between $\text{PM}_{2.5}$ exposure and PTB during various potential critical windows of exposure and then to further investigate whether the potential relationship is modified by concurrent exposure to high temperatures. Specifically, we hypothesize that exposure to $\text{PM}_{2.5}$ during the first few months of pregnancy could interfere with early placental development (likely by causing placental inflammation during early pregnancy), which in turn could result in PTB. We further hypothesize that this relationship

would be stronger with the added stress of higher ambient temperatures. To evaluate these hypotheses, we conducted a case-control analysis using the controls who participated in the National Birth Defects Prevention Study (NBDPS).

Methods

Study population

The study population consisted of singleton liveborn infants without a major birth defect that participated in the NBDPS with estimated due dates from January 1, 1999 through December 31, 2006. The methods of the NBDPS are described in detail elsewhere [25,26]. Briefly, the NBDPS is a multisite population-based case-control study where liveborn infants without a major birth defect served as controls and were randomly selected from the same geographic region and time period as case infants using birth certificate files or hospital records from seven of the NBDPS states (Arkansas, California, North Carolina, Georgia, Texas, New York, and Utah). New Jersey, an additional NBDPS state, was not included in our study population because they did not provide geocoded residential data. Similarly, data from Iowa and Massachusetts were not used as we were unable to link all the exposures of interest to geocoded addresses throughout the entire pregnancy. Mothers were invited to participate in the NBDPS computer-assisted telephone interview, which collected information on sociodemographic factors, behavioral factors (e.g., cigarette smoking, alcohol), illness history, medication use, and residential history during pregnancy. The use of the NBDPS control group, which is generally representative of the base population, provides a unique opportunity to examine the prevalence for prenatal exposures to a variety of risk factors on birth outcomes such as PTB [27]. The participation rate for study subjects was 65.8% and ranged from 62.1 to 76.9% based on center [27].

Outcome assessment

PTB (yes/no) was defined as a birth with a gestational age before 37 completed weeks. The clinical estimate for gestational age was obtained from the NBDPS clinical database; if the clinical estimate of gestational age was missing, gestational age was computed using the mother's report of the due date provided by her clinician during the pregnancy and the baby's date of birth, as in the study by Stingone et al [28]. We did not have information about spontaneous compared to indicated PTB for this analysis, nor were we able to analyze subtypes of PTB (e.g., very PTB).

Exposure assessment

Individual-level exposure during each week of pregnancy (data from January 1, 1999 through December 31, 2006) was assigned using the US EPA's Air Quality Systems (AQS) data with inverse distance weighting from the woman's geocoded address and the nearest AQS monitors. To maximize the population captured, daily weighted averages of concentrations measured from up to four air monitors within 50 km of the maternal residence were constructed, with weights being calculated as the squared-inverse of the distance to the monitor. If at least one monitor was within 5 km of the maternal residence, then only monitors within 5 km were used to construct the daily weighted averages. Only mothers with at least one measurement per gestational week are included, as in the study by Stingone et al [28]. First, we calculated weekly averages taken from daily averages if a mother had more than one measurement per week, and then from those we calculated monthly averages, so each week had the same weight within a month

regardless of the number of days of data. If a woman had more than one address during the pregnancy, each address was used during the relevant time period. Effect estimates are reported as both continuous measures of exposure and at each quartile of PM_{2.5} (i.e., <25th percentile (the referent group), 25th to 50th percentile, 50th to 75th percentile, and >75th percentile) to capture potential departures from linearity. Distribution quartiles were calculated from the entire study population (i.e., cases and controls). Out of all eligible study participants ($n = 5694$), 2472 were missing PM_{2.5} exposure data (i.e., they were not located within 50 km of any monitor) and thus were excluded from analyses. An additional 629 participants were excluded due to missing covariate data. Meteorological data were obtained from the National Center for Atmospheric Research (NCAR) weather monitoring stations and linked to geocoded residence, then averaged over weeks and months as the model required.

Statistical analysis

We used a Bayesian two-level hierarchical logistic regression model based on a Markov chain Monte Carlo simulation, clustered by state of residence and using fixed effects for all other covariates, to examine the relationship between PM_{2.5} and PTB in a way that assesses month of exposure and simultaneously accounts for state-level variations, should they exist. This approach considers potential differences in state-varying PM components that may impact the relationship between exposure and outcome, as well as other state-level considerations that may not be accounted for explicitly in the model. Analyses were completed using SAS (Cary, NC). Owing to somewhat inconsistent information regarding the relationship between PTB and PM_{2.5}, the hyperprior and priors were that variables were normally distributed with a mean of 0 and a variance of 100, and convergence was determined based on a visual analysis of the resulting trace plots (i.e., we determined that the models converged if the plots did not show substantial fluctuation).

Potential confounders were identified through a directed acyclic graph analysis (Fig. A1) [29,30] based on previous literature on factors that influence air pollution exposure [31,32] and PTB [33–35] and included ambient temperature derived from the closest NCAR monitoring station to the maternal residence (continuous, averaged over the week and month), parity (continuous), maternal age at delivery (<18, between 18 and 35, older than 35), household income (<\$10,000, \$10,000–50,000, >\$50,000), maternal education (less than high school graduate, high school graduate, any postsecondary education), maternal nativity (yes/no born in the United States), and maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, Native American/Alaskan Native, Other). Women were not included in the analyses for months occurring after their delivery (i.e., if a woman delivered in month 6, she was not included in analyses from month 7 onward). Though we had data on smoking status (cigarette smoking during pregnancy [yes/no]), we did not control for it to avoid collider stratification bias. Three distinct models were developed: a crude model looking at PM_{2.5}, a model that controlled for temperature, and a full model that contained all aforementioned potential confounders.

In addition, although we assessed temperature as a potential confounder, we also assessed it as a potential effect measure modifier by stratifying by the 75th percentile of state-specific average temperature over the course of pregnancy. To elucidate more precise critical windows of exposure, we conducted analyses on data from weeks that occurred during the months that showed a relationship between PTB and PM_{2.5}. We looked at each week individually and, due to small case counts, did not control for other weeks of exposure in the model. In these models, we controlled for

location-specific average monthly temperature, to account for short-term fluctuations in local temperature. Previous research into the PM_{2.5} and PTB relationship has demonstrated techniques to aid in stabilizing coefficient estimation by borrowing information across exposure and outcome windows in a distributed exposure analysis (i.e., by assigning a prior structure to the vectors of the parameters of the exposure of interest) [36]. One of our aims was to identify discrete periods (i.e., weeks, months) of gestation during which exposure to PM_{2.5} may elevate risk of PTB. Thus, we looked at exposure periods of interest individually, assuming temporal independence from adjacent exposure periods (i.e., that one month of exposure is not highly associated with the preceding and preceding months).

Results

Overall, 2839 births were included in these analyses, 246 PTBs as cases and 2593 term births as controls, though the number of births in each model varied slightly. In general, the study population was composed primarily of non-Hispanic white women with some postsecondary education, household income between \$10,000 to \$50,000 annually, born in the United States, and non-smokers (Table 1). The average interquartile range for PM_{2.5} concentrations across states was 4.7 $\mu\text{g}/\text{m}^3$, and temperature distributions varied between states (Table 2). There was no appreciable or consistent difference between the PM_{2.5} concentrations that were stratified and not stratified by high average temperature, suggesting that in stratifying high temperature days, we were not inadvertently also stratifying by high PM_{2.5} days. In addition, quartiles of temperature did not vary substantially between cases and controls (Table A3). Most preterm births were less than 37 weeks of gestation and greater than or equal to 32 weeks ($n = 222$), with few births occurring less than 32 weeks ($n = 24$). The average distance between the first reported maternal residence and the closest monitor for the first eight weeks of pregnancy was 13.3 km, with a median distance of 9.2 km (SD: 11.4 km).

When the PM_{2.5} and PTB relationship was modeled using categories of PM_{2.5} exposure, we observed a positive relationship between PTB and PM_{2.5} for the third and fourth months of pregnancy (Table 3). We used the full models for all subsequent analyses (i.e., temperature stratified and weekly PM_{2.5} exposure). We did not observe the relationship that we saw in the categorical models in months 3 and 4 in any of the continuous models; however, that could be due to potential departure from linearity not captured in the continuous model rather than a true lack of association, though we note that we did not test for departures from linearity, rather we opted to reported categorical exposure results.

In addition, we conducted analyses for months 2 through 4 of pregnancy in which PM_{2.5} concentrations and temperature were averaged over each week instead of each month, to see if there were specific weeks where the associations were stronger (Fig. 1 and Table A1). We observed that weeks 9 through 12 all had point estimates that were elevated, corresponding to months 3 and 4, respectively; however, there was no single week that stood out as demonstrating a stronger association between PM_{2.5} exposure and PTB.

In the models where we assessed effect measure modification by average temperature during pregnancy, we found that in almost every instance, the low temperature group, representing the state-specific lower 75th percentile of temperature during pregnancy, showed no relationship between PTB and PM_{2.5}. These models were adjusted for local temperature and all other covariates in the nonstratified full models. In addition, the low temperature group displayed consistently lower point estimates than the upper 25th percentile group for the months and surrounding months where

Table 1
Characteristics of mothers of preterm ($N = 246$) (PTB) and term ($N = 2593$) infants

Variable	PTB	Term	Total
State of residence at the child's birth, n (%)			
Arkansas	32 (13.96)	228 (86.04)	260
California	51 (8.37)	546 (91.63)	597
New York	28 (6.34)	375 (93.66)	403
Texas	28 (11.56)	201 (88.44)	229
Georgia	46 (7.56)	508 (92.44)	554
North Carolina	32 (7.4)	373 (92.6)	405
Utah	29 (6.57)	362 (93.43)	391
Total	246 (8.57)	2593 (91.43)	2839
Maternal smoking status, n (%)			
Smoker	40 (9.3)	383 (90.7)	423
Nonsmoker	206 (8.44)	2210 (91.56)	2416
Total	246 (8.57)	2593 (91.43)	2839
Maternal race/ethnicity, n (%)			
Non-Hispanic white	112 (7.06)	1395 (92.94)	1507
Non-Hispanic black	48 (11.93)	354 (88.07)	402
Hispanic	61 (9.06)	644 (90.94)	705
Asian/Pacific Islander	4 (5.06)	70 (94.94)	74
Native American/Alaskan Native	5 (22.72)	14 (77.27)	19
Other	16 (12.68)	116 (87.32)	132
Total	246 (8.57)	2593 (91.43)	2839
Whether the mother was born in the United States, n (%)			
Yes	207 (9.01)	2046 (90.99)	2253
No	39 (6.94)	547 (93.06)	586
Total	246 (8.57)	2593 (91.43)	2839
Maternal household income, n (%)			
<\$10,000	52 (11.03)	498 (88.97)	550
>\$50,000	85 (7.84)	914 (92.16)	999
\$10,000–\$50,000	109 (7.96)	1181 (92.04)	1290
Total	246 (8.57)	2593 (91.43)	2839
Maternal education, n (%)			
<High school graduate	44 (10.41)	498 (89.59)	542
12 Y, completed high school or equivalent	57 (9.88)	914 (90.12)	971
Postsecondary	145 (7.51)	1181 (92.49)	1326
Total	246 (8.57)	2593 (91.43)	2839
Maternal age, n (%)			
≤17 y	12 (11.32)	94 (88.68)	106
18 to 35 y	211 (8.51)	2267 (91.49)	2478
≥35 y	23 (9.01)	232 (91.98)	255
Total	246 (8.57)	2593 (91.43)	2839
Number of previous livebirths, n (%)			
0	83 (8.53)	955 (91.47)	1038
1	81 (7.86)	864 (92.14)	945
2	47 (8.57)	462 (91.43)	509
>2	35 (10.59)	312 (89.41)	347
Total	246 (8.57)	2593 (91.43)	2839

we saw a relationship in the nonstratified results (Fig. 2 and Table A2), though we note that credible intervals overlap. Although we observed a positive relationship between $PM_{2.5}$ concentrations and PTB in months 3 and 4 in the nonstratified analyses, in the analysis stratifying by temperature, the effect of $PM_{2.5}$ in months 2 through 5 was elevated for the high temperature group. Although we cannot directly compare the two strata, we can compare each to the crude estimates and note that there is a trend of the upper 25th percentile being higher than the crude estimate, while the lower 75th percentile is generally below it; however, results were imprecise and credible intervals overlapped (Fig. 2). In addition, the length of pregnancy for the cases in the high temperature group was 2.4 days shorter than the length of pregnancy in the cases in the low temperature group.

Discussion

The elevated odds ratios (ORs) that we observed for exposure in months 3 and 4 are consistent with recent studies that reported elevated risk associated with exposure averaged over the first [37,38] or second trimester [37,39]. In our study, the months we found to have elevated effect estimates would generally be split

into two different exposure periods in analyses that average exposure over trimesters (i.e., exposures during month 3 would be assigned to trimester 1 and exposures during month 4 would be assigned to trimester 2). If $PM_{2.5}$ exposures during months 3 and 4 are etiologically relevant to PTB, evaluation of exposure averaged over trimesters could explain some of the inconsistencies observed in these studies.

When we evaluated individual weeks of exposure, we observed elevated ORs during weeks 9–12, though no single week stood out as being etiologically important. We note that concentrations between weeks tended to be correlated, thus limiting our ability to detect critical periods of exposure, should they exist. Several other recent studies have conducted analyses of weekly exposure periods. Using a time-series design by Arroyo et al [40], observed positive associations with exposure during week 17 of gestation. [41] and [11] separated PTB into multiple categories based on gestational age and both observed positive and negative associations depending on combined exposure and outcome period [41], with 4-week exposures, and by Rappazzo et al [11] with exposures during individual weeks of pregnancy [42]. examined the relationship between PTB and traffic-related air pollutants, including $PM_{2.5}$ over each trimester, the entire pregnancy, and over the last six weeks of

Table 2
PM_{2.5} concentrations by state and concentrations where average ambient temperature throughout the pregnancy was greater than the 75th percentile

Metric	PM _{2.5} concentrations (μg/m ³)		PM _{2.5} concentrations (μg/m ³) where temp > 75th percentile	
	Cases	Controls	Cases	Controls
Overall				
Minimum	6.6	5.9	6.7	6.2
Q1	11.6	11.7	11.6	11.5
Median	13.7	13.9	13.4	13.8
Q3	16.2	16.4	16.0	16.3
Maximum	31.5	40.2	23.3	30.2
Arkansas				
Minimum	6.7	6.2	10.5	9.9
Q1	9.3	8.6	12.9	12.0
Median	10.6	10.1	13.4	13.5
Q3	12.1	12.2	15.0	14.6
Maximum	18.7	20.0	16.5	17.6
California				
Minimum	9.5	5.9	9.9	8.7
Q1	13.7	14.6	11.2	13.2
Median	18.5	17.7	12.5	14.9
Q3	22.0	22.3	14.1	16.9
Maximum	31.5	40.2	19.2	30.2
New York				
Minimum	10.4	7.8	11.6	8.8
Q1	12.2	11.5	12.5	11.7
Median	12.8	12.5	13.0	12.6
Q3	13.4	13.6	13.2	13.5
Maximum	15.0	17.2	14.1	15.4
Texas				
Minimum	6.6	6.6	9.7	8.9
Q1	9.4	9.4	10.5	10.1
Median	10.3	10.1	11.2	11.1
Q3	11.1	11.0	12.0	11.6
Maximum	12.8	16.3	12.8	16.3
Georgia				
Minimum	13.5	12.9	16.2	13.0
Q1	15.4	15.4	16.9	16.8
Median	16.4	16.8	17.8	17.9
Q3	17.9	18.2	18.5	19.9
Maximum	23.7	25.1	23.3	25.1
North Carolina				
Minimum	10.6	9.5	13.4	11.9
Q1	12.3	12.6	14.4	14.0
Median	14.0	13.7	14.7	14.5
Q3	14.6	14.4	15.8	14.8
Maximum	16.0	16.4	16.0	16.4
Utah				
Minimum	6.7	6.2	6.7	6.2
Q1	9.3	8.6	6.7	7.4
Median	10.6	10.1	7.4	8.1
Q3	12.1	12.2	9.5	9.2
Maximum	18.7	20.0	9.6	12.5

pregnancy and generally observed a positive relationship between PM_{2.5} and PTB in the second trimester and over the entire pregnancy regardless of PTB subtype. Generally, the results of weekly PM_{2.5} exposure analyses and PTB have been inconsistent across studies, and no weekly (or subweekly) period of PM_{2.5} has been identified as etiologically relevant for PTB. Although we recognize that controlling for other exposure windows (e.g., other months of pregnancy) would be preferable, we lacked the sample size to adequately do so. In addition, there is also evidence from experimental and epidemiologic studies demonstrating that PM_{2.5} exposure could result in a coherent series of physiological responses that provide biological plausibility for PTB, including placental oxidative stress and intrauterine inflammation, altered fetal metabolism, altered placental growth, and impaired implantation [43].

Our study is novel in its examination of ambient temperature as a potential effect measure modifier of the relationship between

PM_{2.5} exposure and PTB. Recent studies have evaluated the effect of ambient temperature on risk of PTB and have reported greater risks of preterm birth in summer and winter (when temperatures are most extreme) compared to spring and autumn (when temperatures are more moderate) [19]. We are unaware of any studies that have evaluated how temperature could modify the relationship between PM_{2.5} and PTB risk, though by Schifano et al [18] looked at the relationship between PM₁₀ and PTB stratified by season, which is likely a proxy for temperature, and found a potential effect of heat and PM₁₀ exposure on PTB risk. Our results, albeit imprecise, demonstrate the ability of higher temperatures to modify the effect of PM_{2.5} exposure modeled as a continuous variable on risk of PTB. The potential biological mechanisms behind this relationship are unclear; however, limited toxicological evidence suggests that exposure to high ambient temperatures may intensify the effects of environmental pollutants, thus amplifying a relationship between PM_{2.5} and PTB [24]. In addition, physiologic changes in response to higher temperatures, such as increased ventilation, can play a role in increasing the biological dose of an air pollutant that is experienced among exposed populations, so concurrent high temperature and higher PM_{2.5} may result in a higher dose of PM_{2.5} than the mother would have under lower ambient temperatures. Finally, atmospheric processes could mitigate direct effects of temperature on air pollution [44]. For example, temperature inversions are capable of trapping air pollutants, including PM_{2.5}, closer to the ground and increase the potential for exposure [45].

This study has several strengths, including the geographic scope of the NBDPS and the availability of complete residential histories, which aids in reducing exposure misclassification due to residential mobility and relying solely on residence at the time of delivery to assign exposure [46,47]. Centralized geocoding increased the consistency of the data across the NBDPS participating centers and improved the quality control of the geocoded data used to assign exposure. Studying NBDPS controls allowed us to investigate PTB without accompanying birth defects. This is an important consideration as certain birth defects have been observed to be higher among PTBs [48] and excluding infants with birth defects could be removing an important potential confounder, operating under the hypothesis that infants with birth defects are not a mediator on the PTB and PM_{2.5} relationship. In addition, the NBDPS controls have been demonstrated to be representative of their source population [27], improving the generalizability of our results.

Our study also had limitations. Specifically, our study was not able to account for different subsets of PTB, which may have different predominant causes. In addition, our study did not have information on spontaneous compared to iatrogenic PTB; however, we hypothesize only spontaneous PTB would be associated with exposure to PM_{2.5}. Both of these limitations would likely lead to bias toward the null. Our data were also limited by sample size, and a relatively small number of cases overall may have precluded us from seeing a relationship in certain analyses, though we note that it is likely that we would only see effects during biologically relevant periods of exposure, which are unlikely to occur during the entire length of pregnancy. In addition, as in many PTB studies, our study used estimates of gestational age to assign case status, and inaccuracies in predicting gestational age may make it more difficult to identify critical windows of exposure, particularly in our weekly analyses.

Another potential limitation is the inability to distinguish between the potential effects of temperature versus ozone in both the temperature stratified and nonstratified analyses. Although our study both controlled for and stratified by high temperature, it is possible that ozone concentrations may actually be driving the effect measure modification we saw, as ozone and temperature are generally positively associated [49]. To our knowledge, there are no

Table 3
Crude and adjusted odds ratios of PM_{2.5} and preterm birth

Month of pregnancy	Crude model,* OR (95% CI)	Partial model,† OR (95% CI)	Full model,‡ OR (95% CI)
Month 1§			
Q2	0.69 (0.24, 1.70)	0.67 (0.23, 1.81)	0.68 (0.22, 1.65)
Q3	1.15 (0.49, 2.31)	1.09 (0.41, 2.27)	1.13 (0.46, 2.32)
Q4	1.02 (0.54, 1.80)	0.95 (0.48, 1.75)	0.95 (0.51, 1.72)
Continuous	0.93 (0.76, 1.15)	0.96 (0.77, 1.18)	0.96 (0.77, 1.19)
Month 2§			
Q2	1.16 (0.44, 2.46)	1.14 (0.53, 2.22)	1.11 (0.44, 2.80)
Q3	1.09 (0.42, 2.47)	1.08 (0.40, 2.60)	1.06 (0.34, 2.44)
Q4	1.13 (0.62, 2.10)	1.09 (0.56, 1.84)	1.11 (0.57, 2.10)
Continuous	0.99 (0.82, 1.2)	1.03 (0.85, 1.26)	1.03 (0.84, 1.25)
Month 3§			
Q2	0.98 (0.38, 2.22)	0.96 (0.32, 2.10)	1.00 (0.35, 2.18)
Q3	1.19 (0.44, 2.72)	1.11 (0.40, 2.44)	1.14 (0.44, 2.59)
Q4	1.50 (0.83, 2.56)	1.47 (0.80, 2.66)	1.49 (0.82, 2.68)
Continuous	1.09 (0.91, 1.31)	1.14 (0.94, 1.36)	1.15 (0.95, 1.38)
Month 4§			
Q2	1.34 (0.60, 2.71)	1.29 (0.55, 2.89)	1.31 (0.56, 2.91)
Q3	1.62 (0.69, 3.35)	1.56 (0.58, 3.25)	1.62 (0.70, 3.32)
Q4	1.35 (0.67, 2.43)	1.30 (0.70, 2.33)	1.32 (0.69, 2.25)
Continuous	1.04 (0.87, 1.25)	1.05 (0.87, 1.26)	1.06 (0.87, 1.27)
Month 5§			
Q2	0.96 (0.42, 1.96)	0.95 (0.41, 1.99)	0.95 (0.32, 2.38)
Q3	0.77 (0.26, 1.67)	0.73 (0.24, 1.88)	0.71 (0.23, 1.76)
Q4	1.13 (0.56, 1.96)	1.13 (0.60, 1.99)	1.12 (0.60, 1.87)
Continuous	1.08 (0.90, 1.29)	1.07 (0.88, 1.28)	1.07 (0.89, 1.29)
Month 6§			
Q2	1.12 (0.46, 2.37)	1.16 (0.44, 2.42)	1.13 (0.49, 2.37)
Q3	0.88 (0.33, 2.17)	0.82 (0.27, 2.23)	0.81 (0.28, 1.78)
Q4	1.09 (0.55, 2.09)	1.11 (0.59, 1.92)	1.07 (0.57, 1.89)
Continuous	1.05 (0.88, 1.26)	1.01 (0.85, 1.23)	0.99 (0.83, 1.20)
Month 7§			
Q2	0.80 (0.33, 1.80)	0.83 (0.28, 1.80)	0.82 (0.25, 1.82)
Q3	1.01 (0.40, 2.30)	1.03 (0.39, 2.14)	0.99 (0.41, 2.29)
Q4	1.02 (0.55, 1.80)	1.10 (0.59, 1.93)	1.07 (0.57, 1.91)
Continuous	1.06 (0.87, 1.27)	1.02 (0.83, 1.23)	1.02 (0.83, 1.22)

CI = credible interval.

* Crude model: PM_{2.5}.

† Partial model: PM_{2.5}, adjusted for temperature.

‡ Full model: PM_{2.5}, adjusted for temperature, maternal age at delivery, household income, maternal education, maternal birthplace, maternal race, maternal smoking status, parity.

§ In all models that look at categorical levels of exposure, Q1 is the referent group.

|| Continuous results are presented per 10 µg/m³ unit increase.

studies that have examined ozone as a potential effect measure modifier in the PM_{2.5} and PTB relationship, and studies that have looked at the ozone and preterm birth relationship directly show mixed results [6,50,51].

With regard to our temperature-stratified analyses, we only stratified by high temperature; however, if very low temperature

days also acts as an effect measure modifier on the PTB and PM_{2.5} relationship, then it is possible that in certain cases (i.e., during very cold winters), high temperature could be protective in the winter. If this is the case, we would expect to see our high temperature strata biased toward the null, as both summer and winter months are included in the analysis.

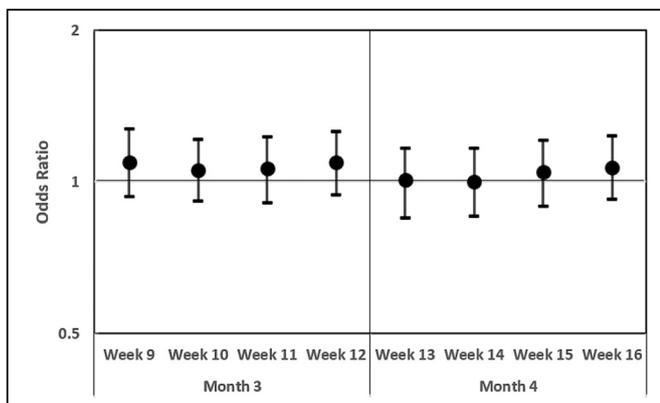


Fig. 1. The relationship between preterm birth and PM_{2.5} using weekly, continuous estimates of exposure. Circles represent odds ratios; lines represent 95% credible intervals. Numbers reported per 10 µg/m³ increase of PM_{2.5}.

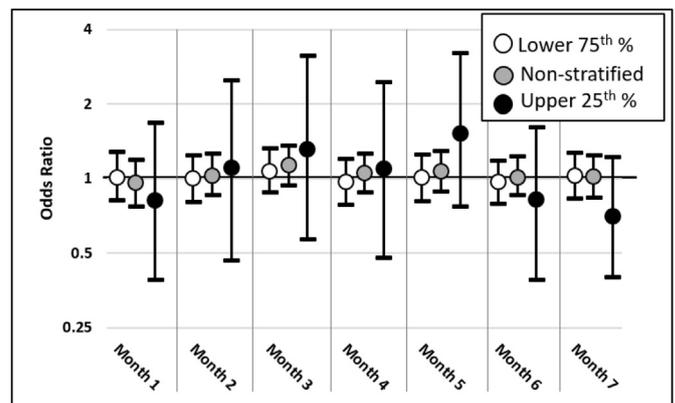


Fig. 2. The relationship between preterm birth and PM_{2.5} stratified by ambient temperature averaged over the pregnancy. Circles represent odds ratios; lines represent 95% credible intervals. Numbers reported per 10 µg/m³ increase of PM_{2.5}.

An additional limitation is our assumption of independence for our models, as we recognize that the preceding month and preceding months of interest are likely associated with the month analyzed (e.g., the exposure in month 3 is likely correlated with the exposure in months 2 and 4). This limits our ability to draw conclusions about any individual month as a critical window of exposure. Nevertheless, although we are not able to fully parse out that a single month of exposure is more strongly associated with PTB, we do see a pattern of increasing ORs during specific adjacent months, suggesting that a critical window, should one exist, may be contained in those months.

To ensure that we captured the largest amount of study population possible, while still using monitors that could presumably capture or be correlated with a person's true exposure, we used monitors up to 50 km away; however, this large distance has the potential for increased exposure measurement error, particularly if the monitors used are not correlated with the true exposure concentrations. Previous work has demonstrated that risk estimates based on the nearest monitor may be more biased than those based on land use regression models or kriging [52]. Despite choosing a 50 km monitor distance, a portion of participants had to be excluded because of missing exposure data ($n = 2872$). We anticipate that this may lead to bias toward the null; however, if the lack of monitor data within 50 km was systematically due to something that was related to both exposure and outcome (e.g., if the excluded participants consistently had lower exposures to $PM_{2.5}$ during relevant time periods and higher rates of PTB), it is possible that the bias could be away from the null. We further note that although we tried to use the largest study population possible, a portion of the participants had to be excluded because of missing covariate data ($n = 629$), which has the potential to bias results if important covariates differ substantially between the included and excluded subjects. Finally, if mothers mediate their exposure to stay inside, then ambient, outdoor $PM_{2.5}$, and temperature concentrations may not be associated with their true exposure, leading to bias toward the null.

In addition to spatial scale, we recognize that the temporal scales we used (i.e., months and weeks) may bias results, particularly given that we do not yet have a firm understanding of the critical exposure window [53]. Nevertheless, we tried to choose temporal averaging windows that we thought would be the most sensitive to our outcome based on the toxicological and epidemiologic information currently available, and less sensitive to variations in $PM_{2.5}$. Thus, in our main analysis, instead of focusing on the trimester, which we anticipated may mask an effect or the week, we focused instead on the month. We expect this bias related to our temporal window choices to be nondifferential with regard to outcome status.

Overall, we observed elevated risks of PTB associated with $PM_{2.5}$ exposures during months 3 and 4 of pregnancy. These risks became more apparent when the exposure period coincided with periods of higher ambient temperatures in stratified analyses, suggesting that temperature may modify the relationship between PTB and $PM_{2.5}$, though we note that results were imprecise and any interpretations as to the true relationship between these covariates must be made with caution.

Acknowledgment

The authors thank the California Department of Public Health Maternal Child and Adolescent Health Division for providing data, and Adam Benson and Kristen Rappazzo for comments of early versions of this manuscript.

This project was supported through funding from the Centers for Disease Control and Prevention (CDC) to the North Carolina Center for Birth Defects Research and Prevention at the University

of North Carolina at Chapel Hill (grant number U01DD001231), and through CDC cooperative agreements under PA #96043, PA #02081, FOA #DD09-001, FOA #DD13-003, and NOFO #DD18-001 to the Centers for Birth Defects Research and Prevention participating in the National Birth Defects Prevention Study (NBDPS) and/or the Birth Defects Study To Evaluate Pregnancy exposures (BD-STEPS).

References

- [1] Centers for Disease Control and Prevention. Births: Final Data for 2016. Atlanta, GA: National Center for Health Statistics; 2018.
- [2] Behrman RE, Butler AS, editors. Preterm Birth: Causes, Consequences, and Prevention. Washington (DC): National Academies Press; 2007.
- [3] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84.
- [4] Prevention CfDCA. Premature Birth. 2018. Available from, <https://www.cdc.gov/features/prematurebirth/index.html>. [Accessed 21 September 2018].
- [5] Warren J, Fuentes M, Herring A, Langlois P. Spatial-temporal modeling of the association between air pollution exposure and preterm birth: identifying critical windows of exposure. *Biometrics* 2012;68:1157–67.
- [6] Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JK. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. *Am J Epidemiol* 2007;166:1045–52.
- [7] Huynh M, Woodruff TJ, Parker JD, Schoendorf KC. Relationships between air pollution and preterm birth in California. *Paediatr Perinat Epidemiol* 2006;20:454–61.
- [8] Lee PC, Roberts JM, Catov JM, Talbott EO, Ritz B. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. *Matern Child Health J* 2013;17:545–55.
- [9] EPA US. The Integrated Science Assessment for Particulate Matter (External Review Draft, 2018). Research Triangle Park, NC: The US Environmental Protection Agency; 2018.
- [10] Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res* 2012;117:100–11.
- [11] Rappazzo KM, Daniels JL, Messer LC, Poole C, Lobdell DT. Exposure to fine particulate matter during pregnancy and risk of preterm birth among women in New Jersey, Ohio, and Pennsylvania, 2000–2005. *Environ Health Perspect* 2014;122:992–7.
- [12] Hansen C, Neller A, Williams G, Simpson R. Maternal exposure to low levels of ambient air pollution and preterm birth in Brisbane, Australia. *BJOG* 2006;113:935–41.
- [13] Gehring U, Wijga AH, Fischer P, de Jongste JC, Kerkhof M, Koppelman GH, et al. Traffic-related air pollution, preterm birth and term birth weight in the PIAMA birth cohort study. *Environ Res* 2011;111:125–35.
- [14] Darrow LA, Klein M, Flanders WD, Waller LA, Correa A, Marcus M, et al. Ambient air pollution and preterm birth: a time-series analysis. *Epidemiology* 2009;20:689–98.
- [15] 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;113:1212–21.
- [16] Strand LB, Barnett AG, Tong S. Maternal exposure to ambient temperature and the risks of preterm birth and stillbirth in Brisbane, Australia. *Am J Epidemiol* 2012;175:99–107.
- [17] Kuehn L, McCormick S. Heat exposure and maternal health in the face of climate change. *Int J Environ Res Public Health* 2017;14:853.
- [18] Schifano P, Lallo A, Asta F, De Sario M, Davoli M, Michelozzi P. Effect of ambient temperature and air pollutants on the risk of preterm birth, Rome 2001–2010. *Environ Int* 2013;61:77–87.
- [19] Strand LB, Barnett AG, Tong S. The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature. *Environ Res* 2011;111:451–62.
- [20] Saenen ND, Vrijens K, Janssen BG, Madhloum N, Peusens M, Gyselaers W, et al. Placental nitrosative stress and exposure to ambient air pollution during gestation: a population study. *Am J Epidemiol* 2016;184:442–9.
- [21] Backes CH, Nelin T, Gorr MW, Wold LE. Early life exposure to air pollution: how bad is it? *Toxicol Lett* 2013;216:47–53.
- [22] Bobak M. Outdoor air pollution, low birth weight, and prematurity. *Environ Health Perspect* 2000;108:173–6.
- [23] Kannan S, Misra DP, Dvonch JT, Krishnakumar A. 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;114:1636–42.
- [24] Gordon CJ. Role of environmental stress in the physiological response to chemical toxicants. *Environ Res* 2003;92:1–7.
- [25] Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. The national birth defects prevention study. *Public Health Rep* 2001;116(Suppl.1):32–40.
- [26] Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, et al. The National Birth Defects Prevention Study: A review of the methods. *Birth Defects Res A Clin Mol Teratol* 2015;103:656–69.

- [27] Cogswell ME, Bitsko RH, Anderka M, Caton AR, Feldkamp ML, Hockett Sherlock SM, et al. Control selection and participation in an ongoing, population-based, case-control study of birth defects: the National Birth Defects Prevention Study. *Am J Epidemiol* 2009;170:975–85.
- [28] Stingone JA, Luben TJ, Daniels JL, Fuentes M, Richardson DB, Aylsworth AS, et al. Maternal exposure to criteria air pollutants and congenital heart defects in offspring: results from the national birth defects prevention study. *Environ Health Perspect* 2014;122:863–72.
- [29] Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10:37–48.
- [30] Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2016;45:1887–94.
- [31] Bravo MA, Fuentes M, Zhang Y, Burr MJ, Bell ML. Comparison of exposure estimation methods for air pollutants: ambient monitoring data and regional air quality simulation. *Environ Res* 2012;116:1–10.
- [32] Mikati I, Benson AF, Luben TJ, Sacks JD, Richmond-Bryant J. Disparities in distribution of particulate matter emission sources by race and poverty status. *Am J Public Health* 2018;108:480–5.
- [33] Development NEKSNioCHaH. What are the risk factors for preterm labor and birth? U.S. Department of Health and Human Services; 2017. Available from, https://www.nichd.nih.gov/health/topics/preterm/conditioninfo/who_risk. [Accessed 21 September 2018].
- [34] Health DoR. Preterm Birth. Centers for Disease Control and Prevention; 2018. Available from, <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm>. [Accessed 21 September 2018].
- [35] Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. *Am J Epidemiol* 2010;172:1108–17.
- [36] Chang HH, Warren JL, Darrow LA, Reich BJ, Waller LA. Assessment of critical exposure and outcome windows in time-to-event analysis with application to air pollution and preterm birth study. *Biostatistics* 2015;16:509–21.
- [37] Ha S, Hu H, Roussos-Ross D, Haidong K, Roth J, Xu X. The effects of air pollution on adverse birth outcomes. *Environ Res* 2014;134:198–204.
- [38] Pereira G, Evans KA, Rich DQ, Bracken MB, Bell ML. Fine particulates, preterm birth, and membrane rupture in Rochester, NY. *Epidemiology* 2016;27:66–73.
- [39] Hao H, Chang HH, Holmes HA, Mulholland JA, Klein M, Darrow LA, et al. Air pollution and preterm birth in the U.S. State of Georgia (2002–2006): Associations with Concentrations of 11 Ambient Air Pollutants Estimated by Combining Community Multiscale Air Quality Model (CMAQ) simulations with stationary monitor measurements. *Environ Health Perspect* 2016;124:875–80.
- [40] Arroyo V, Diaz J, Ortiz C, Carmona R, Saez M, Linares C. Short term effect of air pollution, noise and heat waves on preterm births in Madrid (Spain). *Environ Res* 2016;145:162–8.
- [41] Symanski E, Davila M, McHugh MK, Waller DK, Zhang X, Lai D. Maternal exposure to fine particulate pollution during narrow gestational periods and newborn health in Harris County, Texas. *Matern Child Health J* 2014;18:2003–12.
- [42] Padula AM, Mortimer KM, Tager IB, Hammond SK, Lurmann FW, Yang W, et al. Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California. *Ann Epidemiol* 2014;24:888–895e884.
- [43] EPA US. Integrated Science Assessment (ISA) for Particulate Matter (External Review Draft). Washington, DC: U.S. Environmental Protection Agency; 2018.
- [44] Gordon CJ, Johnstone AF, Aydin C. Thermal stress and toxicity. *Compr Physiol* 2014;4:995–1016.
- [45] Wallace J, Kanaroglou P. The effect of temperature inversions on ground-level nitrogen dioxide (NO₂) and fine particulate matter (PM_{2.5}) using temperature profiles from the Atmospheric Infrared Sounder (AIRS). *Sci Total Environ* 2009;407:5085–95.
- [46] Miller A, Siffel C, Correa A. Residential mobility during pregnancy: patterns and correlates. *Matern Child Health J* 2010;14:625–34.
- [47] Chen L, Bell EM, Caton AR, Druschel CM, Lin S. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. *Environ Res* 2010;110:162–8.
- [48] Honein MA, Kirby RS, Meyer RE, Xing J, Skerretre NI, Yuskiv N, et al. The association between major birth defects and preterm birth. *Matern Child Health J* 2009;13:164–75.
- [49] U.S. EPA. Integrated Science Assessment (ISA) of Ozone and Related Photochemical Oxidants (Final Report, Feb 2013). Washington, D.C.: U.S. Environmental Protection Agency; 2013.
- [50] Mendola P, Wallace M, Hwang BS, Liu D, Robledo C, Mannisto T, et al. Preterm birth and air pollution: Critical windows of exposure for women with asthma. *J Allergy Clin Immunol* 2016;138:432–440.e5.
- [51] Qian Z, Liang S, Yang S, Trevathan E, Huang Z, Yang R, et al. Ambient air pollution and preterm birth: A prospective birth cohort study in Wuhan, China. *Int J Hyg Environ Health* 2016;219:195–203.
- [52] Kim SY, Sheppard L, Kim H. Health effects of long-term air pollution: influence of exposure prediction methods. *Epidemiology* 2009;20:442–50.
- [53] Tanner JP, Salemi JL, Stuart AL, Yu H, Jordan MM, DuClos C, et al. Uncertainty in maternal exposures to ambient PM_{2.5} and benzene during pregnancy: Sensitivity to exposure estimation decisions. *Spat Spatiotemporal Epidemiol* 2016;17:117–29.

Appendix A**Table A1**

Effect estimates for [Figure 1](#): the relationship between preterm birth and PM_{2.5} using weekly, continuous estimates of exposure

Week	Odds ratios*
Week 9	1.09 (0.94, 1.27)
Week 10	1.06 (0.91, 1.21)
Week 11	1.06 (0.91, 1.23)
Week 12	1.09 (0.94, 1.26)
Week 13	1.01 (0.85, 1.17)
Week 14	1.00 (0.86, 1.16)
Week 15	1.04 (0.89, 1.21)
Week 16	1.07 (0.92, 1.23)

* Effects per 10 µg/m³ increase.

Table A3

Average temperature across pregnancy by state (degrees Fahrenheit)

Metric	Cases*	Controls*
Overall		
Minimum	36.8	36.3
Q1	53.9	54.2
Median	60.7	59.3
Q3	67.3	65.9
Maximum	83.4	83.2
Arkansas		
Minimum	47.3	48.0
Q1	55.9	57.3
Median	59.8	61.0
Q3	68.3	66.6
Maximum	73.0	74.3
California		
Minimum	50.9	51.4
Q1	59.9	59.4
Median	64.4	64.2
Q3	68.8	68.3
Maximum	74.7	74.4
New York		
Minimum	36.8	36.7
Q1	43.2	44.7
Median	51.3	50.3
Q3	57.5	56.3
Maximum	63.0	62.9
Texas		
Minimum	39.0	43.2
Q1	65.3	67.0
Median	70.6	71.2
Q3	77.0	75.4
Maximum	83.4	83.2
Georgia		
Minimum	50.8	49.7
Q1	56.2	55.7
Median	61.7	61.4
Q3	67.2	66.0
Maximum	72.5	71.2
North Carolina		
Minimum	49.4	43.4
Q1	52.1	54.2
Median	62.0	59.2
Q3	67.1	64.5
Maximum	70.0	78.0
Utah		
Minimum	42.5	36.3
Q1	44.6	45.0
Median	51.2	52.3
Q3	56.9	58.1
Maximum	62.4	63.9

* Temperature reported in degrees Fahrenheit.

Table A2

Effect estimates for [Figure 2](#): the relationship between preterm birth and PM_{2.5} stratified by ambient temperature averaged over the pregnancy

Month	High temperature (>75%), OR (95% CI)	Low temperature (<75%) (OR (95% CI)
Month 1	0.81 (0.39, 1.67)	1.01 (0.81, 1.28)
Month 2	1.12 (0.46, 2.48)	1.00 (0.80, 1.24)
Month 3	1.31 (0.57, 3.12)	1.07 (0.87, 1.32)
Month 4	1.10 (0.48, 2.44)	0.97 (0.78, 1.19)
Month 5	1.52 (0.77, 3.20)	1.01 (0.80, 1.25)
Month 6	0.82 (0.39, 1.60)	0.97 (0.79, 1.18)
Month 7	0.70 (0.40, 1.22)	1.03 (0.83, 1.27)

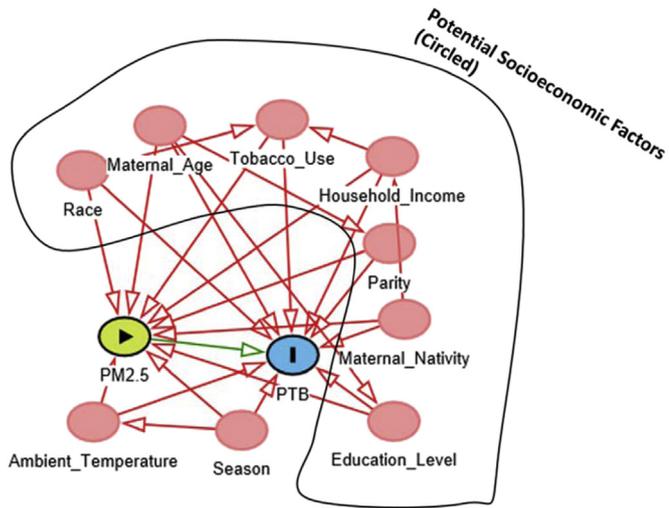


Fig. A1. Directed acyclic graph used for analysis.