Title: Ambient fine particulate matter and preterm birth in California: identification of critical exposure windows

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Abstract

Exposure to ambient fine particulate matter ≤2.5 μm ($PM_{2.5}$) during pregnancy is associated with preterm birth (PTB), a leading cause of infant morbidity and mortality. Studies attempting to identify etiologically relevant exposure periods of vulnerability have been inconsistent, possibly due to failure to consider the time-to-event nature of the outcome and the cumulative and lagged exposure effects of $PM_{2.5}$. This study aims to identify critical exposure windows for weekly $PM_{2.5}$ exposure and PTB in California. Associations were assessed using multi-level distributed lag Cox proportional hazard models. We assessed effect measure modification by race/ethnicity by calculating the weekly relative excess risk due to interaction (RERI). For a 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure over the entire gestation, PTB risk increased by 11% (HR: 1.11, 95% CI 1.09, 1.14). Gestational weeks 17-24 and 36 were associated with increased vulnerability to $PM_{2.5}$ exposure. We find that non-Hispanic Black mothers may be more susceptible to $PM_{2.5}$ exposure effects when compared with non-Hispanic White mothers, particularly at the end of pregnancy. These findings extend our knowledge about the existence of specific exposure periods during pregnancy that have the greatest impact on preterm birth and can inform prevention efforts and etiologic research in adverse birth outcomes.

Introduction

Preterm birth (PTB) is defined as birth occurring before 37 completed weeks gestation. PTB is a leading cause of infant morbidity and mortality, and is associated with an increased risk of disability during childhood and poor health outcomes as an adult (1). Among modifiable determinants of PTB, maternal exposure to ambient fine particulate matter $\leq$ 2.5 microns ($PM_{2.5}$) during pregnancy is associated with an increased risk of preterm birth (2-11). $PM_{2.5}$ refers to a mixture of constituents that can include heavy metals and toxic organic compounds and may affect birth outcomes directly or indirectly (12). A recent study estimates that PTB attributable to $PM_{2.5}$ exposure ranges from 12-24% globally (13). The direct etiologic mechanism for this association is unknown. However, it is hypothesized that the small particle size could allow for infiltration into the circulatory and reproductive organs, increasing potential for oxidative stress and inflammatory response which can affect adverse birth outcomes (14-17).

Many studies have demonstrated the influence of exposure to $PM_{2.5}$ during pregnancy on risk of PTB, with some attempting to identify windows of increased susceptibility. Identifying these windows is critical to assist in understanding the etiologic mechanisms involved in the $PM_{2.5}$ - PTB relation and would allow for the development of targeted clinical and public health interventions. Results from these previous studies are largely inconsistent, with some finding no associations (18-22), and others making varying conclusions about important periods of susceptibility (2-4, 6, 23-26). These studies have found that $PM_{2.5}$ exposure during the first trimester, second trimester, and the last month of pregnancy is associated with increased risk of PTB. These inconsistent findings could arise due to methodological considerations such as differences in the time period of exposure classification (e.g. exposure averaged over the entire

gestation vs. trimester-average exposure), the failure to treat PTB as a time-to-event outcome, or the failure to account for $PM_{2.5}$ as a cumulative and delayed response exposure (27, 28).

While studies typically average $PM_{2.5}$ exposure across the entire pregnancy, by trimester, or by pre-specified lag period, recent evidence suggests that this approach does not capture the exposure window of etiologic importance. Assessment of $PM_{2.5}$ over shorter exposure windows (e.g., weeks) may allow for identification of sensitive periods, where pre-defined lag periods may not (29-32). A recent study compared the use of trimester average exposure models with distributed lag models (DLM) in this setting and found that the former models produce biased estimates and identify incorrect windows of vulnerability (33). DLM are a method for identifying sensitive periods that allow for modeling risk that depends on both the intensity and timing of past exposures and are highly applicable for examining this type of cumulative exposure, and can be applied in a time-to-event framework (34, 35). It is necessary to examine risk of PTB in a time-to-event framework to address differences in exposure lengths and person-time at risk between preterm and term pregnancies (4). Few previous studies have used these methods to identify susceptible windows for PTB (4, 26, 36).

Recent studies in California (6, 10, 37) report associations between PTB with trimester or gestational average $PM_{2.5}$ exposure during pregnancy, without accounting for cumulative and delayed exposure effects. The methodological limitations in these studies results in a gap in evidence that limits our ability to make specific recommendations to women during their pregnancy and inform further research.

The present study examines the association between residential ambient levels of weekly $PM_{2.5}$ and preterm birth in California from 2005 to 2010 to identify periods of increased vulnerability using a DLM Cox proportional hazards model, treating gestational age as a time-to-

event outcome. To account for potential effect modification by gestational age, analyses are stratified by very preterm and moderate preterm birth. Further, due to widely documented racial/ethnic disparities in the association between $PM_{2.5}$ exposure and PTB (38, 39), we explore effect modification by calculating a weekly relative excess risk due to interaction (RERI) for NH white and NH black mothers.

Methods

Study Population

We identified all live singleton births in California from January 1st 2005 to December 31st 2010 collected from the natality file of the California Department of Health Services (40). Demographic and clinical information were obtained for mother and child, including zip code of residence at the time of giving birth. Women with missing zip code (n=46,129) or gestational age (n=155,041) were excluded from the analyses. We created a cohort defined by date of conception where only births conceived between January 1st 2005 and February 20th 2010 were included. This accounts for "fixed cohort bias" (41) by allowing for births of all gestational lengths to be included in the cohort. The State of California and the University of California, Irvine approved the study (IRB protocol approval #13-06-1,251 and 2013–9716, respectively).

PTB Definition

PTB was defined as birth before 37 weeks completed gestation in accordance with the World Health Organization (42) definition. PTB was further categorized into moderate preterm (MPTB) (33 – 37 weeks), very preterm (VPTB) (28 – 32 weeks) and extremely preterm birth (EPTB) (less than 28 weeks). Births that occurred before 28 weeks were excluded (n=8,877) due to hypothesized differences in the etiologic mechanism causing birth before 28 weeks (43, 44).

Gestational age was determined from birth certificates by ultrasound and/or clinical estimate. In California in 2005 and 2006 gestational age was recorded using estimate based on last menstrual period (LMP). However, most women in California had at least one ultrasound during these years, allowing clinicians to verify menstrual dates with ultrasound estimates (45, 46). We would expect some degree of measurement error for births in 2005 and 2006 with LMP estimate only. Conception date was then calculated using gestational age on the birth certificate.

Air Pollution Ascertainment

Maternal zip code of residence reported on the birth certificate was linked to air pollution monitoring data to ascertain weekly $PM_{2.5}$ ($\mu g/m^3$) exposure during pregnancy. We used data provided by the US Environmental Protection Agency (EPA) and the California Air Resources Board (CARB) to assign ambient air pollution exposures by zip code and gestational week for each woman. $PM_{2.5}$ estimates for each zip code was interpolated using an inverse-distance weighting approach using measurements from the three nearest fixed-site monitoring stations within 20 km of the zip code centroid (47). A map of fixed-site monitoring station locations in California is available at the CARB website (48). Zip codes without at least three monitors within 20 km were excluded from analysis. If a daily value from a monitoring station was missing, the mean of the two closest values within 7 days before and after the missing date was used to impute the missing value. If there were any missing days after initial daily imputation, the week was recorded as missing. Mothers with missing $PM_{2.5}$ data for more than one consecutive week were excluded from analysis (n=343,793).

Covariates

We considered the following covariates also collected from the birth certificate as potential confounders, given their documented association with PTB (1) : maternal age (continuous), parity (1, 2 , ≥ 3), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, American Indian/Alaskan native, Asian, Hawaiian/Pacific islander, Hispanic, other/unknown), maternal education (less than high school, high school graduate or equivalent, and any college or beyond), Medicaid insurance status (yes/no), infant sex (male/female), an indicator for season of conception, and an indicator for year of conception to account for temporal variability.

Statistical Analysis

We applied DLM multilevel Cox proportional hazards models with a random effect at the maternal zip code level (to account for potential clustering and spatial patterns) to estimate hazard ratios (HR) and 95% confidence intervals (CI) for risk of PTB per 10 $\mu g/m^3$ increase of $PM_{2.5}$ exposure by gestational week. The proportional hazards assumption was tested for all models by adding time-by-covariate interaction terms in the final models and indicated non violation (49). All models were adjusted for all potential confounders defined using a directed acyclic graph. We additionally estimated traditional Cox proportional hazards models using trimester and gestational average exposure models to identify differences in conclusions between the weekly exposure DLM and traditional average exposure models. The analysis was conducted for overall PTB, moderate PTB, and very PTB separately.

In weekly exposure models the hazard rate was modeled at week *t* including an interaction of exposure at week *t* with the cumulative exposure up until week *t* using a DLM. For each gestational week *t*, *t-s* weeks were included to represent the cumulative exposure (where *s* represents the previous gestational weeks). Exposure weeks post-birth are not included in the

model. An inverse weighting approach was used in calculating the weighted cumulative average, where *t-s* weekly exposure contribution is weighted inversely to its distance from week *t*. This non-parametric approach allows exposure effects to vary across exposure weeks, and accounts for the effect of exposure in previous weeks giving more weight to closest weeks. This approach allows us to consider that the closer a week is to week *t*, the higher its cumulative contribution may be for the effect of exposure at week *t*. We tested for departures from linearity in our continuous variable, age.

The final model is as follows:

$$\lambda_{i,j}(t|x,C) = \lambda_0(t)\exp(\beta x_t \sum_{s=1}^{t} \beta_1 w_{t-s} + \beta'_2 C + a_j)$$

Where for the ith subject within the jth zip code x represents ambient weekly air pollution exposure at week *t*, C represents the set of covariates described above, and $\lambda_0(t)$ represents the baseline PTB hazard at week t (i.e., the hazard function for a woman whose covariates are all equal to zero). w_{t-s} represents the inversely weighted lagged exposure during *t-s* previous weeks. The a_j denotes the zip-code-specific random effects.

We evaluated potential effect measure modification by race in a subset analysis including only NH white and NH black mothers (n=698,942). We assess additive interaction by calculating the relative excess risk due to interaction (RERI) for each week for overall preterm birth with associated standard errors using the delta method (50-52). NH Black was considered the 'exposed' group and $PM_{2.5}$ was treated as a continuous exposure. An RERI > 0 in this analysis indicates that the public health consequence of an intervention on $PM_{2.5}$ exposure would be larger among NH Black when compared with NH White mothers.As an exploratory analysis we

used the same approach to examine effect modification among NH White and Hispanic mothers (n=1,837,357).

Sensitivity analyses were performed to test assumptions that were made. We performed the overall PTB analysis including births before 28 weeks to account for potential selection bias by excluding births that may result from air pollution exposure. We additionally performed the overall PTB analyses without any weighting for cumulative exposure (i.e. flat weighting). All analyses were conducted using SAS 9.4.

Results

Our study population included 2,293,218 singleton live births in California between 2005 and 2010. Overall, 8.2% of births were preterm. Moderate PTB accounted for 6.9% and very PTB accounted for 1.2% of all births. The distribution of maternal and child characteristics is shown in **Table 1**. The average age of mothers was 28 years (SD 6.3), and 46% of mothers had at least some college education. The majority were Hispanic (55%), followed by non-Hispanic white (25%). 39% reported this birth as their first child and 51% of babies born were male. Almost half (49%) of the population reported receiving Medicaid insurance.

The average $PM_{2.5}$ over the entire pregnancy for all mothers was 13.5 $\mu g/m^3$ with an interquartile range of 4.4 $\mu g/m^3$. Average $PM_{2.5}$ for term births and preterm births was 13.5 $\mu g/m^3$ and 13.8 $\mu g/m^3$, respectively. The range of weekly average $PM_{2.5}$ observed in this study population was 1.0 – 117.6 $\mu g/m^3$. The distribution of average $PM_{2.5}$ by week, trimester and entire gestation is shown in **Table 1S**.

The crude and adjusted HRs and 95% CIs for trimesters and gestational average exposure for overall, moderate, and very PTB are shown in **Table 2**. In adjusted models, a 10 $\mu g/m^3$

increase in $PM_{2.5}$ exposure over the entire pregnancy (HR 1.12, 95% CI: 1.09, 1.14), trimester 2 (HR 1.04, 95% CI: 1.03, 1.06), and trimester 3 (HR 1.05, 95% CI: 1.04, 1.07) was associated with an increased risk of overall PTB. Results for moderate PTB were similar. For very PTB, 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure over the entire pregnancy was associated with greater increased risk of PTB than for overall PTB (HR 1.19, 95% CI: 1.14, 1.25), as well as greater increased risk during trimesters 2 (HR 1.08, 95% CI: 1.04, 1.12) and 3 (HR 1.15, 95% CI: 1.11, 1.19). We did not find any increase in risk associated with $PM_{2.5}$ exposure during trimester 1 across all categories of PTB.

Figure 1 shows adjusted HRs and 95% CIs for overall, moderate, and very PTB for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure by gestational week (specific HRs and 95% CI for each week are presented in Table 2S). We identified two periods of increased vulnerability to $PM_{2.5}$ for overall PTB. The initial increase in risk occurred for exposures during weeks 17 through 24. During this period, we observed the greatest increase in risk at week 19 (HR 1.04, 95% CI: 1.03, 1.05. We also see an increase in risk associated with exposure during week 36 (HR 1.03, 95% CI: 1.01, 1.04). Results are similar for MPTB, with windows of increased susceptibility occurring between 19-24 (Week 19 HR 1.04, 95% CI: 1.03, 1.05) and week 36 (HR 1.03, 95% CI: 1.01, 1.04). There was only one period of vulnerability identified for VPTB, weeks 19 and 20. The magnitude of the association during these weeks is similar to what is found for week 19 in overall and moderate PTB, and slightly stronger for week 20 (HR 1.04, 95% CI 1.01, 1.06 & HR 1.04, 95% CI 1.01, 1.06, respectively). HR and 95% CI for all models are shown in **Tables 2S-4S**.

Figure 2 shows the RERI for NH Black compared with NH White mothers for each week of gestation. There is evidence of effect modification by race, specifically in weeks 27-33. This

indicates that NH Black mothers may be more susceptible to $PM_{2.5}$ exposure effects when compared with NH White mothers, particularly at the end of pregnancy. We find a smiliar pattern, with decreased magnitude, when comparing Hispanic to NH White mothers (**Figure 1S**).

After adding births before 28 weeks back into the analysis for overall PTB, the identified periods of susceptibility and magnitudes of association did not change (**Figure 2S, Table 5S**). When the inverse weighting approach for cumulative exposure was exchanged for a flat weight, weeks 19 to 24 remained windows of susceptibility, and the association for weeks 34-35 increased slightly (**Figure 3S, Table 6S**). The descriptive statistics for mothers who were excluded for missing air pollution, zip code, or gestational age (n=544,962) are shown in **Table 7S**. These mothers have similar age and parity distributions as the included mothers, but are slightly more educated, a higher proportion are NH White, and a lower proportion report receiving Medicaid insurance.

Discussion

This study finds specific periods of vulnerability to $PM_{2.5}$ exposure for risk of PTB. We identified increased risk associated with $PM_{2.5}$ exposure during gestational weeks 17-24 and week 36. Identification of these windows could allow for the development of specific clinical and public health interventions to reduce risk of PTB, as well as inform research about the underlying etiologic mechanisms involved in the $PM_{2.5}$ - PTB relation. We find evidence of increased vulnerability among NH Black and Hispanic mothers when compared with NH White mothers, and we encourage additional exploration of the $PM_{2.5}$ - PTB relation among specific racial/ethnic groups. This study demonstrates the need for appropriate methods to estimate the relation between time varying exposures with both delayed and cumulative exposure effects and a time-to-event outcome to identify critical periods of vulnerability.

Previous research documents heightened fetal sensitivity to clinically invasive external stimuli beginning at the 18th week and lasting at least to the 24th week of gestation (53-58). $PM_{2.5}$ may similarly elicit sensitive fetal reactivity that mirrors this 2nd trimester stress reactivity observed in previous research and disrupts the maternal clock of the timing of parturition (59) . The sensitivity during week 36 is similar to that observed in the late 3rd trimester with warm temperatures in California and the risk of PTB (60). Although the mechanistic nature of this acute "trigger" remains unclear, $PM_{2.5}$ may accelerate parturition by a few days of pregnancies on the cusp of term delivery. We speculate that such "trigger" mechanisms fundamentally differ from those during 17-24 weeks that affect the risk of PTB.

Previous studies in California have evaluated this association treating PTB as a binary outcome in trimester and gestational average models. A recent study used logistic regression models and found a 16.4% increase in odds of PTB per IQR increase in gestational average $PM_{2.5}$ exposure (8). A second study in California found similar results using a matched case control design and conditional logistic regression, with a total pregnancy $PM_{2.5}$ (OR 1.15), and increased odds of PTB associated with exposure during first month (OR 1.21), and last 2 weeks (OR 1.17) (6). The gestational average and predefined lag period associations from these studies are similar in magnitude to our results. However, we did not see an association in the first month of gestation, which is possibly due to the treatment of PTB as a time-to-event outcome in the present study.

Methods that account for cumulative and lagged exposure effects in time-to-event models have been used outside of California to identify specific periods of vulnerability to $PM_{2.5}$ during gestation. Chang et al. examined the risk of cumulative and lagged average $PM_{2.5}$ exposure in North Carolina using a discrete time survival model and found that an IQR increase in

cumulative $PM_{2.5}$ was associated with 6.8% increased risk of PTB, and found increased risk associated with exposure in trimesters 1 and 2 (3). This study accounted for cumulative and lagged exposure effects in a time-to-event model but assessed exposure over trimester specific and predefined lag periods. Chang et al. presented a Bayesian hierarchical model with PTB as a time-to-event outcome applied to a dataset of births in Atlanta where they found associations between $PM_{2.5}$ and PTB during early and mid-pregnancy. They found the strongest evidence for an association during trimester 2 (RR per IQR 1.03) (4). Warren et al. developed a Bayesian spatial model to identify susceptible windows applied in Texas, and found increased susceptibility to PM2.5 during the middle of the first trimester through the middle of the second trimester, with the largest estimated effect at week 14 (26). Most recently, a study in China used a distributed lag model approach and found an increase in risk associated with $PM_{2.5}$ exposure during weeks 20-28 (61). They found a narrower window of susceptibility associated with very PTB, similar to what was found in the present study. The associations in the second trimester from these studies are largely consistent with what was found in the present study, while differences may be due to the use of predefined lag periods, air pollution exposure estimation, and differences in overall magnitude of $PM_{2.5}$ exposure.

Several limitations of this study should be considered. $PM_{2.5}$ was assigned at the zip code level, which may reduce variability in air pollution exposure at the individual level. Because air pollution exposure was ascertained using zip code from the birth certificate, we assumed that mothers did not move during the duration of their pregnancy. This may be an important assumption if a large proportion of the study population moved to a zip code with a different air pollution level during pregnancy. However, a recent simulation effort demonstrates that effect estimates do not differ after accounting for residential mobility during pregnancy (62, 63).

Further, zip code was included in the model as a random effect, which does not proportionately account for the relatedness of zip codes that are spatially near each other. Future work could investigate the spatial clustering regarding the weekly specific impact of air pollution on PTB. Air pollution was assigned using fixed site monitors, which are not evenly spaced across the state of California. This may result in differential measurement precision of exposure by region, specifically in rural areas where there are fewer monitors. For these specific remote areas, future studies need to rely on specific campaigns to improve exposure measurement (64).

There was missingness of zip code, daily air pollution values and gestational age in this study population. The exclusion of these participants may reduce generalizability of this study to the entire state of California if missingness was differential by zip code. We find that overall the distribution of measured covariates of included and excluded mothers is similar, although excluded mothers are more likely to be NH white, have completed some college, and report not receiving Medicaid insurance.

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Conclusion

Exposure to $PM_{2.5}$ was associated with an increased risk of overall, moderate, and very PTB in this study population, and periods of increased vulnerability were identified during weeks 17-24 and week 36 for overall PTB. The observed associations were consistent for moderate PTB, with a smaller window of susceptibility for very PTB. We find evidence of increased vulnerability to $PM_{2.5}$ exposure among NH Black mothers when compared with NH White mothers. These findings provide evidence for specific periods of vulnerability to $PM_{2.5}$ during pregnancy and should inform public health recommendations, policy development, and future etiologic research.

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Tables and Figures

Table 1. Study Population Characteristics of Singleton Live Births in California from 2005-2010 (n= 2,293,218)				
			Average $PM_{2.5}$	
	N	(%)	Mean	SD
Full Term Birth	2,105,943	91.8	13.5	3.3
Overall Preterm Birth	187,275	8.17	13.8	3.4
Moderate Preterm Birth	159,192	6.94	13.8	3.4
Very Preterm Birth	28,083	1.22	13.7	3.6
Education				
Less than high school	662,532	28.9	14.1	3.4
High school / equivalent	569,341	24.8	13.6	3.3
Any college and beyond	1,061,345	46.3	13.1	3.2
Age Category				
<18	72,345	3.15	14.1	3.4
18-25	780,015	34.0	13.8	3.4
26-34	1,050,458	45.8	13.4	3.3
35+	390,400	17.0	13.2	3.1
Race				
American Indian / Alaskan Native	6,471	0.28	13.2	3.9
Asian	275,417	12.0	12.7	3.0
Hawaiian / Pacific Islander	10756	0.47	12.2	3.1
Hispanic	1,262,109	55.0	14.0	3.3
NH Black	127,121	5.54	13.6	3.3
NH White	571,821	24.9	13.0	3.3
Other	39,523	1.72	12.7	3.2
Medicaid				
No	1,180,706	51.5	13.2	3.2
Yes	1,112,512	48.5	13.9	3.4
Parity				
1	896,037	39.1	13.4	3.3
2	715,699	31.2	13.4	3.3
3 or greater	681,482	29.7	13.8	3.4
Sex of neonate				
Male	1173663	51.2	13.5	3.3
Female	1119555	48.8	13.5	3.3

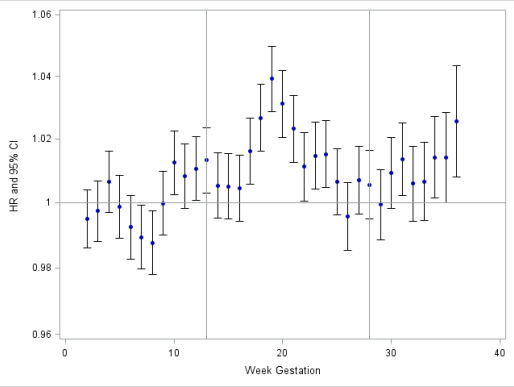
Table 2. Crude and Adjusted Associations Between $PM_{2.5}$ Exposure and Risk of Preterm Birth by Total Pregnancy and Trimester Average Exposure in California, 2005-2010

		Crude		Adjusted[±]	
		Hazard Ratio	95% CI	Hazard Ratio	95% CI
Overall PTB	Total Pregnancy	1.238	1.222, 1.255	1.115	1.089, 1.142
	Trimester 1	1.091	1.081, 1.102	0.990	0.977, 1.004
	Trimester 2	1.136	1.125, 1.148	1.042	1.026, 1.058
	Trimester 3	1.115	1.105, 1.125	1.051	1.037, 1.065
Moderate PTB	Total Pregnancy	1.253	1.235, 1.271	1.114	1.086, 1.142
	Trimester 1	1.103	1.092, 1.114	1.001	0.986, 1.016
	Trimester 2	1.145	1.132, 1.158	1.045	1.028, 1.063
	Trimester 3	1.114	1.103, 1.125	1.042	1.028, 1.056
Very PTB	Total Pregnancy	1.202	1.162, 1.244	1.193	1.135, 1.254
	Trimester 1	1.048	1.023, 1.074	0.990	0.957, 1.023
	Trimester 2	1.112	1.083, 1.142	1.083	1.044, 1.123
	Trimester 3	1.129	1.102, 1.156	1.148	1.112, 1.186

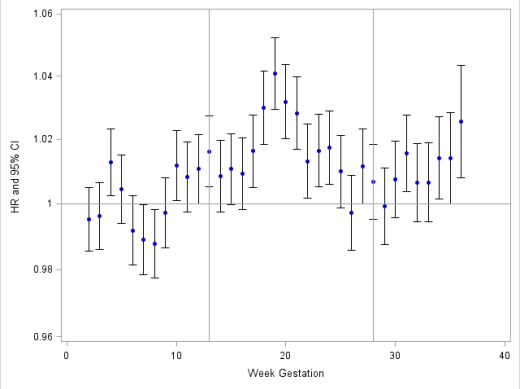
[±] Adjusted for maternal age (continuous), parity (1, 2 , ≥ 3), maternal race (non-Hispanic white, non-Hispanic black, American Indian/Alaskan native, Asian, Hawaiian/Pacific islander, other/mixed, Hispanic), maternal education (less than high school, high school graduate or equivalent, and any college or beyond), Medicaid insurance status (yes/no), infant sex (male/female), season of conception, year of conception

Figure 1. Adjusted Hazard Ratios and 95% Confidence Intervals for a 10 μg/m^3 Increase in $PM_{2.5}$ Exposure on Preterm Birth by Gestational Week Fitted from Distributed Lag Cox Proportional Hazards Models

A). Overall PTB



B). Moderate PTB



C). Very PTB

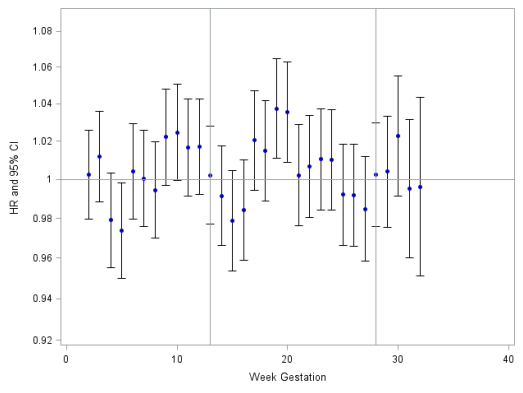


Figure 2. Relative Excess Risk Due to Interaction (RERI) and 95% Confidence Intervals by Gestational Week for NH Black compared with NH White mothers (n=698,942)