Tiny but Mighty: Association between fine particulate matter ($PM_{2.5}$) and infant mortality in a North Carolina Birth Cohort (2003-2015)

Sonya M. Jampel

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Committee:

Joel Kaufman

Daniel A. Enquobahrie

Thomas J. Luben

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Abstract

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Sonya M. Jampel

Chair of the Supervisory Committee:
Joel Kaufman

Department of Environmental & Occupational Health Sciences
Department of Epidemiology
Department of Medicine

Background: Many studies have quantified the association between fine particulate matter ($PM_{2.5}$) and adult mortality. Several studies have evaluated particulate matter (PM_{10}) and postneonatal mortality, but there are relatively few studies about $PM_{2.5}$ and infant mortality. We investigated the association between long-term $PM_{2.5}$ exposure and all infant mortality, neonatal mortality and postneonatal mortality.

Methods: We conducted an unmatched case-control study of infant mortality sampling 10 controls per case from a North Carolina birth cohort (2003-2015). $PM_{2.5}$ exposure was estimated at the birthing parent's residence based on spatiotemporal modeling of $PM_{2.5}$ concentrations at the census block averaged over 2-week periods. We performed logistic regression with adjustment for birthing parent characteristics, year of birth, infant sex assigned at birth, urbanicity and neighborhood deprivation index (NDI). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for an increase equal to the interquartile range of

$PM_{2.5}$ (4.0 μg/m^3) for five critical exposure periods (each trimester, pregnancy, and first month of life). We conducted additional stratification analyses and a 'leave-one-out' analysis to identify potential confounders.

Results: Our analytical dataset included 1,315,691 infants from which we identified 5,992 cases of infant mortality and sampled 60,000 non-cases to serve as controls for our analytical sample. After adjusting for covariates, the odds of infant mortality increased by 5% (OR: 1.05, 95% CI: 0.95, 1.17) for each 4.0 μg/m^3 increase in $PM_{2.5}$ exposure averaged over the entire pregnancy. We observed a slightly higher increase in odds for postneonatal mortality (OR: 1.09, 95% CI: 0.94, 1.27) and a modest increase in odds for neonatal mortality (OR: 1.03, 95% CI: 0.90. 1.18), although confidence intervals included null values. All adjusted odds included null values but revealed positive point estimates for the association between infant and postneonatal mortality and $PM_{2.5}$ exposure during trimester 1 and trimester 2, and neonatal mortality and $PM_{2.5}$ exposure during trimester 3 and revealed negative or null point estimates for all other exposure periods and outcomes. Leaving out year of birth from the adjusted analysis in pregnancy $PM_{2.5}$ exposure resulted in estimates similar to the unadjusted model, and stratifying by year of birth resulted in highly varied effect estimates by year.

Conclusions: Our results suggest that long-term $PM_{2.5}$ exposure over the full pregnancy is modestly associated with infant mortality and postneonatal mortality with effects across other exposure periods near the null value. Decisions about adjusting for temporal variables appear to greatly influence effect estimates. Future work in this field will be important to inform policies that aim to protect infant's environmental health.

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Introduction

In 2005, the World Health Organization concluded that “the evidence is sufficient to infer a causal relationship between particulate air pollution and respiratory deaths in the postneonatal period” (World Health Organization. Regional Office for Europe and Health 2005). However, most previous work on the association of infant mortality and air pollution exposure involved total suspended particles or larger particles with an aerodiameter ≤ 10 μm (PM_{10}) and did not study fine particulate matter with aerodiameter ≤ 2.5 μm ($PM_{2.5}$) (Bobak and Leon 1999; T. J. Woodruff, Grillo, and Schoendorf 1997). $PM_{2.5}$ is hypothesized to be more harmful to human health than larger particles as the smaller size allows it to travel deeper into the lung, have higher deposition in the alveolar region, and travel further into the bloodstream (Schwartz, Dockery, and Neas 1996). Investigations on health impacts of $PM_{2.5}$ are currently relevant due to recent considerations at the Environmental Protection Agency (EPA) about revising the national standard to a level below 12 $\mu g/m^3$ for the annual average, with consideration given to a level between 9 and 10 $\mu g/m^3$ (US EPA 2022).

Based on findings from studies that investigated the association between long-term exposure to $PM_{2.5}$ and infant mortality, the evidence on the prenatal and postnatal critical exposure windows is mixed. Some studies have found both prenatal and postnatal $PM_{2.5}$ exposure to be associated with higher odds (Goyal, Karra, and Canning 2019; deSouza et al. 2022) and higher risk of infant mortality (Heft-Neal et al. 2018). Other studies observed positive associations for only one exposure period (Khadka and Canning 2022; Son et al. 2017) or neither (Tracey J. Woodruff, Parker, and Schoendorf 2006; Tracey J. Woodruff, Darrow, and Parker 2008).The mixed evidence on the association between prenatal and postnatal exposure to $PM_{2.5}$ may be due to differences in geographic settings, time periods of study, differential measurements of exposure, study populations, and varying analytical strategies (Khadka and Canning 2022).

Further, the under-researched association between infant mortality and $PM_{2.5}$ exposure has some previous evaluation of potential confounders but lacks extensive evaluation of effect modifiers. Most previous studies adjusted for race as a proxy for racism because race is associated with exposure to $PM_{2.5}$ in North Carolina (Gray, Edwards, and Miranda 2013); and several studies have identified differences in infant mortality by race (Wallace et al. 2017; Bishop-Royse et al. 2021). Although race is not fundamentally based on biological differences, the variable can be used as a proxy for unmeasurable confounders such as access to health care, exposure to structural racism, racial inequity in unemployment and education, and residential segregation (Wallace et al. 2017; Bishop-Royse et al. 2021; Benmarhnia, Hajat, and Kaufman 2021). Effect modification by race, as a proxy for racism, of the association between infant mortality and $PM_{2.5}$ exposure has not been researched thoroughly. One study found an increased effect among Black individuals between $PM_{2.5}$ and cardiovascular disease (CVD) and respiratory mortality among 53 million U.S. Medicare beneficiaries (Wang et al. 2020). A study in North Carolina also found Black people in poorer communities to have the highest $PM_{2.5}$ mortality estimate (Son et al. 2020). We hypothesize effect modification by race in our study may be due to psychosocial pathways like perceived stress and biological markers of chronic stress (Son et al. 2020). If there is effect modification, individuals experiencing higher levels of stress due to racism or other social factors might be more susceptible to the effect of $PM_{2.5}$ exposure resulting in increased odds of infant mortality. Assessing differences in the effect of air pollution on infant mortality based on exposure to racism is vital in any analysis hoping to bring an environmental justice lens and evaluate disparities in health outcomes; although, great care must be taken (Benmarhnia, Hajat, and Kaufman 2021).

Previous studies report effect modification by sex for the association between infant mortality and $PM_{2.5}$ exposure. One found increased infant mortality in males (Jung et al. 2020) and others showed increased infant mortality in females (deSouza et al. 2022; He et al. 2022). The effect modification may be due to sex-specific differences in fetal growth patterns, hormone

metabolism, and placental response to exposure (Broere-Brown et al. 2016; Rosenfeld 2015; DiPietro and Voegtline 2017).

We conducted a case-control study within a North Carolina birth cohort to analyze the association between increased long-term $PM_{2.5}$ exposure and infant mortality. North Carolina provided a population with racial diversity and urban and rural settings to assess this under-researched relationship using precise locations by census block and a large analytical dataset. We completed important effect modification analyses for race (a surrogate for racism) and sex assigned at birth as well as a threshold analysis of policy relevant $PM_{2.5}$ concentrations.

Methods

Study Population

We used birth certificate data from the State Center for Health Statistics of the North Carolina Department of Health and Human Services linked with data from the Birth Defects Monitoring Program (NC BDMP) to create a birth cohort of all infants born in North Carolina (NC) between 2003-2015. The NC BDMP is an active surveillance system that follows NC births to obtain birth defect diagnoses up to 1 year after the date of birth. As part of this, they also identify infant deaths during the first year of life and information from the death certificate (i.e., date of death, cause of death). We identified all live singleton births (20-44 weeks gestation) recorded in the years 2003-2009 and 2011-2015 with birthing parent residence in North Carolina at time of delivery. We excluded births in 2010 due to changes in the birth certificate form which led to missing data in important covariates such as smoking, education, and diabetes. We further excluded births where birthing parent age was less than 15 years, greater than 50 years or unknown, births less than 500 g and births where birthing parent address was unable to be geocoded to point or street address. We also excluded infants who died from external causes (V030-V892; W06-W92; X00-X99; Y069-Y848) because $PM_{2.5}$ exposure can be

eliminated as a causal mechanism. The remaining births comprised our analytic dataset (Supplementary Figure S1). The Institutional Review Boards (IRB) of the University of North Carolina-Chapel Hill (09-0828) and the University of Washington (00016823) approved this research.

Study Design

Due to the relatively rare incidence of infant mortality, we conducted an unmatched case-control study. From the analytic dataset, we first identified all cases of infant mortality, defined as infant death within the first year of life. From the remaining births in the analytic dataset, we randomly sampled 60,000 non-cases to serve as controls in our analytic sample (for an approximate case:control ratio of 1:10).

Exposure

We used a validated spatiotemporal model to assign exposure to fine particulate matter ≤2.5 μm in diameter ($PM_{2.5}$) over critical prenatal and postnatal time periods (Kirwa 2021). The prediction model used data from research and regulatory monitors as well as a large (>200) array of geographic covariates to create fine scale spatial and temporal predictions. The model estimates at precise point locations rather than a grid of concentrations, and the centroid of each census block in North Carolina was used to calculate predicted concentrations. The model has a cross-validated R^2 of 0.89 for $PM_{2.5}$ (Kirwa et al. 2021). The exposure model estimated 2-week average $PM_{2.5}$ concentrations at each birthing parent's census block determined by residential address listed on the birth certificate. If the residential address was missing, the mailing address was used. We examined critical periods by computing a weighted average of the 2-week average of $PM_{2.5}$ estimates during the 1st trimester (conception -12 weeks), 2nd trimester (13 to 26 weeks), 3rd trimester (27 weeks to birth), entire pregnancy, and first month (0 to 28 days) after birth. We used the birth date and the clinical estimate of gestational age to

estimate the date of conception, and then used this to define each of the critical exposure periods. Individuals were excluded from analyses for a specific exposure window if they had less than 11 days in that window, which impacted the sample size for trimester 3 and month 1 exposure periods.

Outcome

The outcome of infant mortality was defined as death within the first year of life. We additionally conducted separate secondary analyses for neonatal (0-28 days) and postneonatal (29 days to 1 year) mortality.

Covariates

Individual covariates in the model are birthing parent age (15-19, 20-23, 25-34, 35-39, 40-50), education (greater than high school education, high school education, less than high school education), smoking status (any number of cigarettes during pregnancy, nonsmoker), parity (0, 1, 2, 3+ previous births), prenatal care in first trimester (yes, no), marital status (married, unmarried), diabetes during pregnancy (gestational or pregestational diabetes, no), Medicaid (yes, no), year of birth (2003, 2004, 2005, 2006, 2007, 2008, 2009, 2011, 2012, 2013, 2014, 2015), infant sex assigned at birth (male, female) and race/ethnicity. Race/ethnicity of birthing parent was self-reported on the birth certificate by birthing parent with an ability to choose one of the following categories (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian/Pacific Islander, American Indian, Other/Unknown). Race/ethnicity of the birthing parent was adjusted for as an indicator variable with Non-Hispanic White as reference group since this was the largest group. We adjusted for race/ethnicity as a crude proxy for exposure to racism during birthing parent lifetime. We adjusted for the year of birth as an indicator variable to account for decreasing $PM_{2.5}$ concentrations and decreasing infant mortality rates over time.

Urbanicity was assessed using 2010 Rural-Urban Commuting Area (RUCA) codes from the US Department of Agriculture ("USDA ERS - Rural-Urban Commuting Area Codes" 2010). We based the assignment on the 2010 census tracts grouped into metropolitan (census tract with urbanized area (UA) (> 50,000 inhabitants) or primary flow ≥ 10% to UA), micropolitan (census tract with large urban cluster (large UC) (10,000 to 49,999 inhabitants) or primary flow ≥ 10% to large UC), small town (census tract with small urban cluster (small UC) (2,500 to 9,999 inhabitants) or primary flow ≥ 10% to small UC), and rural (primary flow to census tract outside a UA or UC).

Neighborhood socioeconomic status was measured by a neighborhood deprivation index (NDI) at the census tract based on North Carolina data from the 2013-2017 American Community Survey (ACS). NDI uses eight previously identified socio-demographic variables representing five domains – poverty, housing, employment, occupation, and education (Messer et al. 2006).

Data Analysis

We conducted a case-control study of 60,000 randomly sampled controls (approximately 10 times the number of cases) and all cases. We ran a stepwise logistic regression with covariates determined a priori. We conducted regression with an unadjusted model, a partially adjusted model which was adjusted for individual-level covariates (age, education, smoking status, parity, prenatal care in first trimester, marital status, diabetes, race/ethnicity, Medicaid, year of birth, infant sex assigned at birth), and fully adjusted (which also included community level covariates of urbanicity and NDI).

We calculated odds ratios per 4.0 $\mu g/m^3$ increase in $PM_{2.5}$; this unit increase is approximately equivalent to the interquartile range (IQR) of $PM_{2.5}$ exposures assigned to individuals in our study. We next conducted logistic regression models for controls and all neonatal mortality and then controls and all postneonatal mortality to allow for comparability to

other studies. Neonatal mortality often occurs in hospitals and might depend more on birth defects, pregnancy complications, or other adverse birth outcomes making a secondary analysis worthwhile.

Secondary and Sensitivity Analyses

We subsetted the analytical sample to include all cases and controls with $PM_{2.5}$ exposure < 8 $\mu g/m^3$, < 10 $\mu g/m^3$ and < 12 $\mu g/m^3$ of $PM_{2.5}$ in each exposure window. We then ran the continuous regression on these subsetted datasets to evaluate the association between infant mortality and $PM_{2.5}$ concentrations under potentially policy-relevant levels.

We assessed effect modification for race/ethnicity, infant's sex assigned at birth, term birth, and cause of death. We did not include the "Other/Unknown" group for race/ethnicity in effect modification analysis due to small counts. To assess effect modification, we compared stratified estimates to unstratified estimates from the main analysis. By running the regression with only full-term births (greater than or equal to 37 weeks), we could observe the direct effects of $PM_{2.5}$ exposure on infant mortality not working through the preterm birth pathway. This sensitivity analysis allowed us to assess preterm birth working as a confounder or a mediator. For cause of death, we assessed deaths from Sudden Infant Death (SIDS) (R95) or Respiratory death which included "Diseases of the Respiratory System" (J000-99) and "Bronchopulmonary dysplasia (BPD)" (P27.1) based on categories from a previous study (Tracey J. Woodruff, Darrow, and Parker 2008).

We then evaluated model specification by identifying influential confounders using a 'leave-one-out' analysis for entire pregnancy exposure to $PM_{2.5}$ and all infant mortality. This involved repeatedly performing the fully adjusted regression without one of the covariates. After identifying year of birth as an important confounder, we ran the analysis with year of birth and each of the covariates independently as the only adjustment variables. We also tested the year of birth as a spline with 2 and 3 degrees of freedom. We conducted analyses without the

covariates of smoking, parity, and prenatal care due to concerns of data quality. Next, we ran the fully adjusted model separately for births from 2003-2008 and from 2012-2015. These periods were selected to represent years with similar $PM_{2.5}$ values as there were observed decreasing trends in $PM_{2.5}$ concentrations over time. We then ran new analyses with 2003-2008 and 2012-2015 as indicator variables in separate regressions. Lastly, we stratified the analysis by each year separately to look at the relationship between $PM_{2.5}$ exposure during pregnancy and infant mortality in each year.

All data analysis was conducted in R Version 4.2.2 (R Core Team 2022).

Results

We identified 1,424,66 live singleton (20-44 weeks gestation) recorded in the years 2003-2009 and 2011-2015 with birthing parent residence in North Carolina at time of delivery. After exclusions, our analytical dataset included 1,315,691 infants from which we identified 5,992 cases of infant mortality of which 2,460 were postneonatal mortality (Supplementary Figure S1). From the remaining live births, we sampled 60,000 non-cases to serve as our controls. We were unable to assign exposure estimates to two of the selected controls due to missing census block assignment, leaving a total of 59,998 controls in our analytic sample.

Birthing parents of cases were more likely to be younger, less educated, Black Non-Hispanic and American Indian Non-Hispanic, smokers and on Medicaid. 70.1% of birthing parents of cases received prenatal care in the first trimester compared to 77.4% of birthing parents of controls. Cases were more likely to be male, lower birth weight, preterm and have chromosomal defects. 59.1% of cases were categorized as low birth weight (<2500 g) compared to 7.0% of controls. Cases were more likely to live in micropolitan areas and small towns as well as census tracts that had a higher NDI. Of the total 288,987 census blocks in North Carolina, individuals in the full study population were assigned to 137,865 unique census

blocks based on residence at delivery. In our analytical sample, sampled controls were assigned to 36,141 unique census blocks and cases were assigned to 5,394 unique census blocks (Table 1, Supplemental Table S1). Sampled non-cases or controls (n = 60,000) appear representative of all non-cases in the analytical dataset (n = 1,309,699) based on descriptive statistics (Supplemental Table S1).

The mean $PM_{2.5}$ exposure during pregnancy in cases was 10.7 $\mu g/m^3$ (SD: 2.6) compared to 10.6 $\mu g/m^3$ (SD: 2.4) in controls and 10.6 $\mu g/m^3$ (SD: 2.4) in the complete analytical dataset. The cases had higher median and mean $PM_{2.5}$ exposure than the controls for all exposure windows, although the range of exposures was generally similar and overlapping for cases and controls (Table 2, Supplemental Figure S2). Mean $PM_{2.5}$ exposure decreased substantially over the study period in the sample population for pregnancy exposure from 12.5 $\mu g/m^3$ (SD: 1.5) in 2003 to 7.8 $\mu g/m^3$ (SD: 0.7) in 2015 (Supplemental Figure S3). The estimates for exposure averaged over the full pregnancy period had a narrower distribution due to the longer time period and the greater number of 2-week averages included in estimating exposure for the full pregnancy period. We estimated associations between $PM_{2.5}$ and infant mortality for fewer individuals when examining the month 1 and trimester 3 exposure windows because some individuals contributed fewer than 11 days to these exposure windows and were thus excluded from the analysis (Table 2).

In unadjusted models, the odds of infant mortality increased by 12% (95% CI: 1.06, 1.17) for each 4.0 $\mu g/m^3$ increase in $PM_{2.5}$ exposure averaged over the entire pregnancy. After adjusting for covariates, the odds of infant mortality were attenuated and the confidence interval included the null value but the point estimate suggested that the odds slightly increased by 5% (95% CI: 0.95, 1.17) for each 4.0 $\mu g/m^3$ increase in $PM_{2.5}$ exposure over the entire pregnancy. We observed a slightly higher increase in odds for postneonatal mortality (OR: 1.09, 95% CI: 0.94, 1.27) and a modest increase in odds for neonatal mortality (OR: 1.03, 95% CI: 0.90. 1.18), although confidence intervals included null values. For month 1 exposure, the increased odds of

infant mortality was 4% (95% CI: 1.00, 1.08) and the increased odds of postneonatal mortality was 3% (95% CI: 0.98, 1.08) for each 4.0 μg/m^3 increase in $PM_{2.5}$ exposure in unadjusted models; however, adjustment of the model attenuated the effect to the null value (Table 3, Figure 1, Supplemental Table S3).

For all infant mortality, neonatal mortality and postneonatal mortality, the associations with the highest magnitude were for the pregnancy exposure window. All unadjusted models for all five critical periods and all mortality and subsetted mortality have positive associations except for the associations for trimester 3 and postneonatal mortality. Partially adjusted models that did not adjust for NDI and urbanicity were similar to the fully adjusted model and are reported in the supplemental material (Supplemental Table S4, Supplemental Figure S4). There appeared to be larger effects for exposures averaged over trimesters 1 and 2 than trimester 3. Neonatal mortality results appear to be similar to all mortality and postneonatal results (Supplemental Table S3, Supplemental Figure S4). We focused subsequent analyses on postneonatal mortality as it is less likely to occur due to birth complications in the hospital.

For sensitivity and secondary analyses, we present the fully adjusted model and the association between $PM_{2.5}$ exposure and all infant mortality and postneonatal mortality for the critical periods of pregnancy and month 1. Additionally, analysis for all critical periods, outcomes, and models can be found in Supplemental Table S3.

Among those with an exposure <12 μg/m^3 $PM_{2.5}$ during pregnancy, an increase of $PM_{2.5}$ of 4.0 μg/m^3 was associated with a decrease in odds of infant mortality of 34% (OR 95% CI: 0.55, 0.78). There was a similar trend of a decreased odds of infant mortality and postneonatal mortality and all mortality with increased concentration of $PM_{2.5}$ when restricting average exposure to <10 μg/m^3 and <8 μg/m^3 $PM_{2.5}$ exposure (Figure 2a, Supplemental Table S3).

Males had a decreased odds of infant mortality compared to females for $PM_{2.5}$ exposure averaged over the entire pregnancy, but an increased odds for the month 1 postnatal exposure (Figure 2b, Supplemental Table S3).

For the entire pregnancy exposure window, the odds of infant mortality are higher for White Non-Hispanic and Black Non-Hispanic birthing parents (OR: 1.12, 95% CI: 0.96, 1.29; OR: 1.08, 95% CI: 0.91, 1.28, respectively) and lower for Hispanic, American Indian Non-Hispanic and Asian/Pacific Islander Non-Hispanic birthing parents (OR: 0.98, 95% CI: 0.74, 1.31; OR: 0.72, 95% CI: 0.29, 1.82; OR: 0.66, 95% CI: 0.33, 1.31, respectively) compared to the results for the full analytic sample, although all confidence intervals overlapped with the null values. For the postnatal month 1 exposure window, the odds of infant mortality are higher for Black Non-Hispanic, Hispanic, and American Indian birthing parents and lower for White Non-Hispanic and Asian/Pacific Islander birthing parents compared to the results for the full analytic sample. However, all estimates lack precision especially for infants of Asian/Pacific Islander NH and American Indian NH birthing parents. Black Non-Hispanic birthing parents are the only group that has an odds of infant mortality and infant postneonatal mortality higher or the same compared to the non-restricted model for all time periods (Figure 2c, Supplemental Table S3).

Restricting the analyses to full-term births slightly increased the odds ratio estimate for the entire pregnancy but decreased the estimate for postnatal month 1, however all confidence intervals included null values. Interestingly, adjusting for covariates in the full-term model for pregnancy increased the effect estimate compared to the unadjusted model which is the opposite of what happened in the main model (Figure 2d, Supplemental Table S3).

When evaluating cases for which SIDS was listed as the cause of death, $PM_{2.5}$ exposure was associated with a decreased odds of infant mortality in the fully adjusted model but an increased odds of mortality in the unadjusted model. While the month 1 exposure odds ratio estimates overlapped with the null hypothesis, the odds ratio estimates for entire pregnancy exposure did not. The estimates are imprecise for respiratory illness as a cause of death (Figure 2e, Supplemental Table S3).

The following analyses were completed with exposure to $PM_{2.5}$ during the entire pregnancy and all infant mortality. In our exploratory analysis to evaluate influential

confounders, we excluded each adjustment variable separately from the fully adjusted model and found that removing year of birth led to an odds ratio that most resembled the unadjusted analysis (OR: 1.12, 95% CI: 1.06, 1.17; Supplemental Table S4b). To further examine the structure of this influential variable, we replaced year of birth as an indicator variable with a spline with 2 or 3 degrees of freedom, which did not change the model significantly (Supplemental Table S4c). Including only year of birth and each covariate variable separately in the model resulted in the models with year of birth and marital status (OR: 1.04, 95% CI: 0.94, 1.14), year of birth and race/ethnicity (OR: 1.02, 95% CI: 1.93, 1.12), and year of birth and NDI (OR: 1.02, 95% CI: 1.93, 1.12) having an odds ratio closest to the null. Including only year of birth and RUCA score in the model as adjustment terms resulted in an estimate farthest from the null (OR: 1.19, 95% CI: 1.08, 1.31) (Supplemental Table S4d). Stratifying analyses for full pregnancy exposure for infants born in 2003-2008 resulted in a positive effect estimate (OR: 1.13, 95% CI: 1.01, 1.27) compared to analyses for infants born 2012-2015 which resulted in a negative effect estimate (OR: 0.97, 95% CI: 0.74, 1.27) (Supplemental Table S4e). Further stratification by year of birth yielded varied effect estimates with 2004 and 2005 having the highest magnitude positive estimates (OR: 1.44, 95% CI: 1.06, 1.94; OR: 1.63, 95% CI: 1.20, 2.22) (Supplemental Table S4f).

Discussion

Our study expanded upon previous research on long-term $PM_{2.5}$ exposure and infant mortality using an unmatched case-control study design with data from a large birth cohort in North Carolina from 2003-2015. We observed prenatal exposure to $PM_{2.5}$ to have a modest positive association with infant mortality, postneonatal mortality and neonatal mortality, though confidence intervals were imprecise, and all adjusted unstratified odds included the null value. Point estimates suggest a positive association between $PM_{2.5}$ exposure in trimesters 1 and 2

and infant mortality and postneonatal mortality and a null or negative association with $PM_{2.5}$ exposure in trimester 3. The wide confidence intervals that overlap with null values may be due to power issues especially for postneonatal mortality where the number of cases was more than halved.

Some studies have found both prenatal and postnatal critical exposure windows of $PM_{2.5}$ to be associated with increased risk or odds of infant mortality (Goyal, Karra, and Canning 2019; Heft-Neal et al. 2018; deSouza et al. 2022). In contrast, other studies have found only prenatal exposure (Khadka and Canning 2022; Jung et al. 2020) or postnatal exposure (Son et al. 2017) to $PM_{2.5}$ to be associated with a greater risk of infant mortality. Studies in California (Tracey J. Woodruff, Parker, and Schoendorf 2006) and the entire United States (Tracey J. Woodruff, Darrow, and Parker 2008) examined postnatal $PM_{2.5}$ exposure and overall postneonatal mortality and observed null associations. However when restricting to respiratory-related postneonatal mortality, they found an association with postnatal $PM_{2.5}$ exposure (Tracey J. Woodruff, Parker, and Schoendorf 2006). There is variation in classification of postnatal $PM_{2.5}$ exposure with the first study defining exposure from birth to postneonatal death and matching the same exposure time for controls (Tracey J. Woodruff, Parker, and Schoendorf 2006) and the second study defining exposure as the first two months of life (Tracey J. Woodruff, Darrow, and Parker 2008). We chose to define postnatal exposure as the first month of life as all postneonatal deaths and controls would then have the same exposure length. Differences in categorization of postnatal exposure could lead to different conclusions. Differences in study conclusions could also be due to different geographic settings, exposure assessment, study population, analytical strategies, and study time period (Khadka and Canning 2022).

Given the robust epidemiological evidence and biological explanation of $PM_{2.5}$ exposure and adult mortality, we would expect gestational and early-life $PM_{2.5}$ exposure to have a similar, if not stronger, effects on infant mortality. Different physiologic characteristics of infants including developing lungs and immune systems may result in higher health risks (Glinianaia et

al. 2004; Scheers et al. 2011). Prenatal exposure to $PM_{2.5}$ is associated with higher levels of adverse birth outcomes such as low birth weight (Stieb et al. 2016; Quraishi et al. 2022), preterm birth (Hao et al. 2016) and small for gestational age (Stieb et al. 2016). $PM_{2.5}$ may cause an imbalance in the autonomic nervous system leading to oxidative stress in pregnant people which then affects maternal and fetal health (Brook et al. 2010). A previous study found carbonaceous air pollution particles, an important part of $PM_{2.5}$, to cross the placental barrier and appear in fetal tissues (brain, lung, fetal liver, and preterm placenta) which could affect development as well (Bongaerts et al. 2022). Prenatal exposure to $PM_{2.5}$ may affect infant mortality through the same mechanisms by which it affects other adverse birth outcomes, which are associated with higher levels of infant mortality ("Infant Mortality | Maternal and Infant Health | Reproductive Health | CDC" 2022).

$PM_{2.5}$ exposure might work directly to affect infant mortality or indirectly through mediators like preterm birth or low birthweight (Khadka and Canning 2022). In the main analysis, when including preterm births, we analyzed the total (direct and indirect effects together) of $PM_{2.5}$ exposure on infant mortality. In the secondary analysis restricting to only full-term births, we were able to look at the association when the potential for the preterm birth pathway is excluded. This restriction also allowed us to compare similar length exposure periods for trimester 3 and entire pregnancy exposure. In the unadjusted model for entire pregnancy exposure restricting to full term births, the effect on infant mortality is attenuated; but in the fully adjusted model, the point estimate appears slightly larger than the unrestricted model. However, all confidence intervals are overlapping. A cohort study across the United States found that over 50% of the association between prenatal $PM_{2.5}$ exposure and infant mortality was explained by the direct pathway suggesting there are other mechanisms besides low birthweight and preterm birth to allow $PM_{2.5}$ exposure to affect infant death risk (Khadka and Canning 2022). Given the relatively few studies on $PM_{2.5}$ and infant mortality, further complete

mediation analysis will be necessary to discern between direct and indirect effects and address other mediators such as low birthweight.

Postnatal exposure to $PM_{2.5}$ might also cause infant mortality by acting through similar pathways as in adults. Given infants have less developed pulmonary and immune system, the adverse outcomes might be as or more extreme resulting in infant death (Heinrich and Slama 2007). We report no association infant mortality, postneonatal mortality or neonatal mortality although all estimates lack strong precision. Given many neonatal deaths occur in the hospital within the first few days of life, these deaths might not be due to postnatal air pollution exposure.

After adjusting for covariates in our study, we found possible slight positive associations for $PM_{2.5}$ exposures averaged over trimesters 1, 2, and the entire pregnancy and postneonatal mortality and all infant mortality although estimates included null values. Similarly, one study in South Korea observed positive associations over the whole pregnancy and trimesters 1 and 2 separately but not in trimester 3 or the postnatal period (from birth to death or age 1) (Jung et al. 2020). On the other hand, a study in the United States reported infant death to be positively associated with $PM_{2.5}$ in all three trimesters and strongest in the third trimester (Khadka and Canning 2022). Timing of exposure influences fetal susceptibility and can be important in determining the magnitude of the adverse effects of $PM_{2.5}$ on preterm birth (J. L. Warren et al. 2019; J. Warren et al. 2012). Future work will be useful to parse out the mechanisms in each trimester of exposure and better quantify the effect on infant mortality.

Our results suggest that there might be a threshold effect with exposures less than 8 $\mu g/m^3$, 10 $\mu g/m^3$, and 12 $\mu g/m^3$ for entire pregnancy exposure no longer having a positive association with infant mortality (Figure 2a). The literature on threshold effects on $PM_{2.5}$ and infant mortality is sparse. A study in Burkina Faso examining $PM_{2.5}$ from dust storms and neonatal mortality found no association in $PM_{2.5}$ levels measured in count of days <30 $\mu g/m^3$ (Karimi et al. 2020). Conversely, other studies on the effect of $PM_{2.5}$ on all-cause adult mortality reported positive effect estimates at lower $PM_{2.5}$ levels (<10 $\mu g/m^3$) (Pope and Dockery 2006;

Wang et al. 2020; Pinault et al. 2016). Generally, analyses of the concentration response (C-R) relationship between long-term $PM_{2.5}$ exposure and total (non-accidental) mortality support a linear, no-threshold relationship (US EPA 2019). Research points to possible differences in the shape of the C-R function for different health outcomes and causes of adult mortality. For example, research suggests a supra-linear C-R function for cardiovascular mortality and a sub-linear C-R function for other causes of adult mortality (US EPA 2019). Given the literature on all adult mortality indicating no safe threshold of $PM_{2.5}$ exposure, different C-R relationships for different outcomes and sparse literature on infant mortality, future work should explore this area.

Our results show possible differential effects of $PM_{2.5}$ on infant mortality by race/ethnicity categories with Black NH individuals being the only group where the odds of infant mortality and postneonatal mortality is higher or the same compared to the non-restricted model for all exposure periods, although confidence intervals overlap with the unrestricted model. Other race/ethnicity groups are higher in some critical periods and not others with very wide confidence intervals. This study population included disparities by race/ethnicity in infant mortality rates, but $PM_{2.5}$ exposure does not appear to explain these disparities in our study with confidence. While no studies have quantified effect modification by race for $PM_{2.5}$ and infant mortality, previous studies have shown increased risk for Black individuals when exposed to $PM_{2.5}$ for all-cause adult mortality (Wang et al. 2020) and all-cause adult mortality if the individuals are also poor (Son et al. 2020). Another study found effect estimates for the association between $PM_{2.5}$ and low birth weight were higher for infants of black mothers compared to white mothers (Bell, Ebisu, and Belanger 2007). Increased risk may work through psychosocial pathways such as perceived and biological markers of chronic stress (Son et al. 2020).

While we observed an association of reduced risk between $PM_{2.5}$ and SIDS for the prenatal exposure window, there is mixed evidence in the literature. Previous studies on $PM_{2.5}$ exposure and SIDS reported null associations (Son, Bell, and Lee 2011; Tracey J. Woodruff,

Parker, and Schoendorf 2006; Tracey J. Woodruff, Darrow, and Parker 2008) but other studies on PM_{10} and SIDS found a positive association (Kihal-Talantikite, Marchetta, and Deguen 2020; T. J. Woodruff, Grillo, and Schoendorf 1997; Hwang, Cheong, and Kim 2019). Little is known about the biological mechanism responsible for SIDS but it is hypothesized to involve disruptions in autonomic control (Lavezzi 2015). Young infants who are rapidly developing and more vulnerable infants might be even more susceptible to air pollution (Hwang, Cheong, and Kim 2019). It is possible that deaths from SIDS may occur via a mechanism that is not related to environmental pollutants in which we would observe a null effect and could explain the mixed results. Future work should further examine the mechanisms for how SIDS might be affected by $PM_{2.5}$.

Our results suggest different critical exposure periods for female and male infants with females more susceptible over the prenatal period and males more susceptible over the postnatal period although all confidence intervals overlapped with the null. Similarly, a study in Massachusetts found higher effect estimates for all mortality in female infants in the postnatal period, but they did not provide a biological explanation (Son et al. 2017). On the other hand, a South Korean study found male infants more susceptible in the prenatal period (Jung et al. 2020) and hypothesized that it was due to a delay in fetal lung development in males (Torday et al. 1981; Lin et al. 2022)

Our study had many strengths and weaknesses. Our study has precise spatiotemporal exposure estimates by census block and 2-week averages whereas previous studies on this association assessed exposure with less spatiotemporal precision. There was still potential for exposure misclassification as the classification does not account for changes in residential address during pregnancy or the first month of life. However, previous studies suggest that when pregnant people move the median distance traveled is under 10 kilometers (Bell and Belanger 2012; Saadeh et al. 2013). The model also does not account for how much time is spent indoors or the presence of an air filter which would influence exposure levels. Additionally,

census blocks can vary in size depending on urbanicity or rurality which might affect the precision of predictions. We chose to assess postnatal exposure as exposure in the first month of life as a proxy for exposure between birth and death or first birthday. Other studies categorize postnatal exposure as from birth to death or first birthday (Tracey J. Woodruff, Parker, and Schoendorf 2006; Son et al. 2017; Jung et al. 2020), first two months of life (Tracey J. Woodruff, Darrow, and Parker 2008) or end of nine-month prenatal period to twelve months after (Khadka and Canning 2022). By only assessing the first month of life exposure, the window of exposure could be the same for controls and postneonatal infant mortality cases and avoid issues with seasonal and secular trends applied differently on different lengths of follow up. However, there is a possibility for exposure measurement error by using a one month exposure to represent an exposure window of variable length.

Although our exposure model has spatial and temporal precision, our exposure model has several important limitations including not analyzing other pollutants, using only a linear model, and failing to disaggregate type of $PM_{2.5}$. We chose to focus on $PM_{2.5}$ and infant mortality and conducted race/ethnicity, infant sex, cause of death and threshold additional analyses because relatively little is known about this relationship. While previous studies have found associations with $PM_{2.5}$ to be robust to inclusion of co-occurring pollutants (US EPA 2019), further work could include pollutants such as O_3, NO_2, SO_2, CO and PM_{10} to examine joint effects on infant mortality. We chose a linear model since little is known about the shape of the concentration-response relationship of $PM_{2.5}$ and infant mortality. Future research might consider non-linear models because of recent evidence of a potential non-linear concentration-relationship between $PM_{2.5}$ and adult cardiovascular mortality (US EPA 2019). The threshold findings in our work also suggest a non-linear effect though not the supralinear effect suggested in the adult mortality literature. Given the high heterogeneity by region and season of particulate matter composition in the United States (Bell et al. 2007), an analysis taking into account this kind of heterogeneity may be worthwhile. Studies suggest that exposure to carbonaceous $PM_{2.5}$

increases the risk of infant mortality while exposure to $PM_{2.5}$ from mineral dust or sea salt does not (Goyal, Karra, and Canning 2019). Although our study has strong spatiotemporal precision, future studies could address issues in exposure assessment to reduce misclassification and evaluate pollutant mixture effects, $PM_{2.5}$ composition, and non-linear relationships.

Another strength of our study was the large analytic dataset of over 1.3 million births over twelve years. We performed a case-control study to increase computational efficiency without compromising statistical power, since we could maintain a 1:10 ratio of cases and controls and the sampled controls were representative of all non-cases. Infant mortality is a rare outcome which makes odds ratios good approximations for relative risks. Using data from the same study population, Slawsky et al. used a similar method in their study on brownfields and birth defects (Slawsky et al. 2022). However, the null results in our study may have been due to being underpowered for ORs less than 1.10 in the main analysis and even more so for sensitivity analyses, which included fewer cases. A decision to select additional controls to increase overall sample size would not have greatly improved our power because we would have the same number of cases. Additionally, in our sample, there was possibly live birth selection bias as infant mortality does not include loss of pregnancy due to fetal death or stillbirth. Some literature shows that increased in-utero air pollution exposure might increase the risk of loss of pregnancy (Ha, Ghimire, and Martinez 2022). This effect would possibly attenuate a potential association as more resilient infants might be carried to term.

The diversity of race and ethnicity, urbanicity of housing, and socioeconomic status in North Carolina make this a strong study population to study the effect of $PM_{2.5}$ and increase the generalizability. However, relative to the entire U.S., North Carolina has a lower and narrower range of $PM_{2.5}$ values, and experiences relatively few extreme $PM_{2.5}$ concentrations due to wildfires or other events. Given the decreasing $PM_{2.5}$ values nationally and in NC and increasing extreme wildfire events, future work should replicate this study in locations which experience more extreme values of $PM_{2.5}$.

In this study, we use birth certificates which restrict participants to choose from six race/ethnicity categories. This affects our ability to use race as a proxy for exposure to racism because individuals might not identify as just one of the categories, or any of them at all, and therefore true identities might not be adequately captured. The small counts in the Other/Unknown group in this analysis did not allow us to evaluate several minoritized races/ethnicities grouped together who might not have a common experience. Additionally, these categories are a poor proxy for racism. Future data collection that involves strategies to understand exposure to different aspects of racism directly such as structural, institutional, interpersonal and internalized racism would be beneficial in subsequent analyses. By evaluating the types of racism, we can better identify what is driving the health inequity and design interventions (Lett et al. 2022). There is, however, no missingness in race/ethnicity data allowing the study to assess effect modification of the complete sample. Future work would aim to explore how $PM_{2.5}$ and infant mortality are influenced by intersectional issues including sexism, ableism, and/or xenophobia to better describe lived experiences (Lett et al. 2022).

$PM_{2.5}$ exposure and infant mortality both decreased over the study period leading to year of birth acting as a confounder. Adjusting for year of birth as an indicator variable seemed to be the main driver of the effect estimate attenuation between the unadjusted and adjusted models. While the model was robust to categorizing year of birth as an indicator variable or a spline, stratifying by year of birth resulted in highly varied effect estimates by year. Over the study period, $PM_{2.5}$ levels declined dramatically statewide and sensitivity analyses revealed a significantly positive association between exposure over the entire pregnancy under the earlier years of the study (2003-2008) and infant mortality whereas exposure during the later years of the study (2012-2015), which had on average lower levels, resulted in a null association. Our sensitivity threshold analysis revealed, among lower levels of $PM_{2.5}$, there was a negative association between $PM_{2.5}$ and infant mortality. The association between $PM_{2.5}$ and infant mortality might change based on $PM_{2.5}$ average levels which decreased over the course of the

study. Additionally, we chose not to adjust for seasonality to reduce the number of variables and because there was no seasonality apparent in $PM_{2.5}$ concentration in the later years of the study. However, in the earlier years there appeared to be a seasonal trend which might have benefited from adjustment.

Some previous studies with shorter study periods chose not to match or adjust for year of birth and instead adjusted for other spatial or temporal variables. A study in Massachusetts from 2001-2007 adjusted for season of birth, temperature, and relative humidity (Son et al. 2017). A matched case-control study from 2010-2015 in South Korea matched the season of birth but did not have any year adjustment (Jung et al. 2020). Another study a North Carolina birth cohort from 2003-2005 studied prenatal $PM_{2.5}$ exposure and small for gestational age and low birth weight and did not adjust for any time or seasonality (Vinikoor-Imler et al. 2013). One of the larger cohort studies on postnatal exposure to $PM_{2.5}$ and postneonatal mortality from 1999-2002 across the United States adjusted for birth year, birth month, and 6 US regions and did not find an association (Tracey J. Woodruff, Darrow, and Parker 2008).

We are concerned about a violation of positivity, or the assumption that there are exposed and unexposed participants for every combination of covariates included in the model (Westreich and Cole 2010). We plan to evaluate this assumption for the final manuscript publication. When adding indicators for year of birth, there may no longer be combinations of different confounders present in the study. Decisions about spatiotemporal factors appear to have a profound influence on model outcomes and warrant further discussion of best practices in this field.

Conclusion

This study builds upon previous work on infant mortality and $PM_{2.5}$ exposure by modeling exposure to census block locations and completing threshold and effect modification analyses. Our study points to a possible association between infant and postneonatal mortality and $PM_{2.5}$

exposure with suggestive positive effects in critical prenatal exposure periods of trimester 1, 2, and entire pregnancy, although confidence intervals included null values. Exposure to lower levels of $PM_{2.5}$ may attenuate the association more completely. In stratified analyses, point estimates for Black Non-Hispanic individuals were consistently higher or the same as odds ratios for infant mortality in the unstratified model which suggests a need to place environmental justice issues at the forefront of analyses. Further discussion must carefully consider best practices for spatiotemporal adjustment in the models. Our findings will be important to inform policies that aim to protect infant's environmental health with respect to air pollution.

Tables and Figures

Table 1: Descriptive statistics of characteristics of analytical dataset and sample

This table displays birthing parent, infant, and community level characteristics of the analytical dataset (N = 1315691), sampled non-cases (controls) (n = 6000), postneonatal mortality (n = 52460) and all infant mortality (n = 5992). [1] High school (HS). [2] Race/ethnicity self-reported by birthing parent on birth certificate with ability to choose one of the categories. [3] Non-hispanic (NH). [4] Smoking any number of cigarettes during any time period of pregnancy. [5] Diabetes includes pre-pregnancy or gestational diabetes. [5] Urbanicity is based on 2010 Rural-Urban Commuting Area (RUCA) codes from the US Department of Agriculture ("USDA ERS - Rural-Urban Commuting Area Codes" 2010). [6] Neighborhood Deprivation Index (NDI) uses eight previously identified socio-demographic variables representing five domains - poverty, housing, employment, occupation, and education from the 2013-2017 American Community Survey (ACS) at the census tract (Messer et al. 2006).

	Total Analytical Dataset (N=1315691)	Sampled Non-Cases (Controls) (n=60000)	Cases	
			Postneonatal Mortality (n=2460)	All (n=5992)
Birthing Parent Characteristics				
Age (years)				
15-19	126744 (9.6%)	5751 (9.6%)	366 (14.9%)	868 (14.5%)
20-24	339608 (25.8%)	15491 (25.8%)	859 (34.9%)	1841 (30.7%)
25-34	676619 (51.4%)	30804 (51.3%)	988 (40.2%)	2535 (42.3%)
35-39	143052 (10.9%)	6673 (11.1%)	179 (7.3%)	549 (9.2%)
40-50	29668 (2.3%)	1281 (2.1%)	68 (2.8%)	199 (3.3%)
Education				
>HS[1]	714540 (54.3%)	32539 (54.2%)	898 (36.5%)	2386 (39.8%)
HS[1]	338576 (25.7%)	15444 (25.7%)	814 (33.1%)	1919 (32.0%)
<HS[1]	258534 (19.7%)	11816 (19.7%)	738 (30.0%)	1637 (27.3%)
Missing	4041 (0.3%)	201 (0.3%)	10 (0.4%)	50 (0.8%)
Race/Ethnicity[2]				
White NH[3]	749980 (57.0%)	34144 (56.9%)	1143 (46.5%)	2749 (45.9%)
Black NH[3]	301369 (22.9%)	13732 (22.9%)	964 (39.2%)	2244 (37.5%)

Hispanic	201019 (15.3%)	9260 (15.4%)	245 (10.0%)	733 (12.2%)
Asian/Pacific Islander NH[3]	45501 (3.5%)	2058 (3.4%)	52 (2.1%)	143 (2.4%)
American Indian NH[3]	15525 (1.2%)	715 (1.2%)	51 (2.1%)	110 (1.8%)
Other/Unknown	2297 (0.2%)	91 (0.2%)	5 (0.2%)	13 (0.2%)
Smoke[4]				
No	1172626 (89.1%)	53461 (89.1%)	1863 (75.7%)	4835 (80.7%)
Yes	139061 (10.6%)	6350 (10.6%)	583 (23.7%)	1097 (18.3%)
Missing	4004 (0.3%)	189 (0.3%)	14 (0.6%)	60 (1.0%)
Diabetes[5]				
No	1256771 (95.5%)	57252 (95.4%)	2340 (95.1%)	5707 (95.2%)
Yes	56946 (4.3%)	2647 (4.4%)	115 (4.7%)	269 (4.5%)
Missing	1974 (0.2%)	101 (0.2%)	5 (0.2%)	16 (0.3%)
Prenatal Care in First Trimester				
No	282788 (21.5%)	12952 (21.6%)	755 (30.7%)	1630 (27.2%)
Yes	1018654 (77.4%)	46416 (77.4%)	1650 (67.1%)	4198 (70.1%)
Missing	14249 (1.1%)	632 (1.1%)	55 (2.2%)	164 (2.7%)
Medicaid				
No	659864 (50.2%)	30002 (50.0%)	746 (30.3%)	2189 (36.5%)
Yes	655827 (49.8%)	29998 (50.0%)	1714 (69.7%)	3803 (63.5%)
Marital Status				
Married	798703 (60.7%)	36427 (60.7%)	1048 (42.6%)	2695 (45.0%)
Unmarried	516502 (39.3%)	23544 (39.2%)	1410 (57.3%)	3288 (54.9%)
Missing	486 (0.0%)	29 (0.0%)	2 (0.1%)	9 (0.2%)
Parity Levels				

0	543984 (41.3%)	24777 (41.3%)	863 (35.1%)	2454 (41.0%)
1	427573 (32.5%)	19587 (32.6%)	766 (31.1%)	1685 (28.1%)
2	212265 (16.1%)	9656 (16.1%)	452 (18.4%)	996 (16.6%)
3+	131284 (10.0%)	5952 (9.9%)	379 (15.4%)	847 (14.1%)
Missing	585 (0.0%)	28 (0.0%)	0 (0%)	10 (0.2%)
Infant Characteristics				
Infant Sex				
Female	642306 (48.8%)	29148 (48.6%)	1056 (42.9%)	2477 (41.3%)
Male	673378 (51.2%)	30852 (51.4%)	1404 (57.1%)	3511 (58.6%)
Missing	7 (0.0%)	0 (0%)	0 (0%)	4 (0.1%)
Birthweight (g)				
Mean (SD)	3300 (576)	3310 (565)	2540 (1010)	2010 (1150)
Median [Min, Max]	3340 [500, 6290]	3350 [510, 5900]	2810 [500, 5100]	2100 [500, 5610]
Low Birthweight (<2500 g)				
No	1223854 (93.0%)	55956 (93.3%)	1523 (61.9%)	2449 (40.9%)
Yes	91837 (7.0%)	4044 (6.7%)	937 (38.1%)	3543 (59.1%)
Preterm Birth (<37 weeks)				
No	1202927 (91.4%)	55015 (91.7%)	1542 (62.7%)	2537 (42.3%)
Yes	112764 (8.6%)	4985 (8.3%)	918 (37.3%)	3455 (57.7%)
Chromosomal Defects				
No	1312775 (99.8%)	59918 (99.9%)	2231 (90.7%)	5442 (90.8%)
Yes	2916 (0.2%)	82 (0.1%)	229 (9.3%)	550 (9.2%)
Month of birth				
1	108621 (8.3%)	4946 (8.2%)	220 (8.9%)	489 (8.2%)

2	100164 (7.6%)	4581 (7.6%)	190 (7.7%)	447 (7.5%)
3	108488 (8.2%)	4867 (8.1%)	226 (9.2%)	517 (8.6%)
4	104231 (7.9%)	4811 (8.0%)	196 (8.0%)	467 (7.8%)
5	107787 (8.2%)	4961 (8.3%)	188 (7.6%)	494 (8.2%)
6	107989 (8.2%)	4945 (8.2%)	203 (8.3%)	500 (8.3%)
7	114826 (8.7%)	5175 (8.6%)	205 (8.3%)	507 (8.5%)
8	117509 (8.9%)	5501 (9.2%)	208 (8.5%)	532 (8.9%)
9	115299 (8.8%)	5310 (8.9%)	196 (8.0%)	476 (7.9%)
10	112588 (8.6%)	5046 (8.4%)	230 (9.3%)	562 (9.4%)
11	107054 (8.1%)	4759 (7.9%)	206 (8.4%)	514 (8.6%)
12	111135 (8.4%)	5098 (8.5%)	192 (7.8%)	487 (8.1%)
Season of birth				
Winter	319920 (24.3%)	14625 (24.4%)	602 (24.5%)	1423 (23.7%)
Fall	334941 (25.5%)	15115 (25.2%)	632 (25.7%)	1552 (25.9%)
Spring	320506 (24.4%)	14639 (24.4%)	610 (24.8%)	1478 (24.7%)
Summer	340324 (25.9%)	15621 (26.0%)	616 (25.0%)	1539 (25.7%)
Year of birth				
2003	100081 (7.6%)	4638 (7.7%)	181 (7.4%)	488 (8.1%)
2004	102283 (7.8%)	4729 (7.9%)	196 (8.0%)	497 (8.3%)
2005	105535 (8.0%)	4825 (8.0%)	200 (8.1%)	525 (8.8%)
2006	109859 (8.4%)	5031 (8.4%)	205 (8.3%)	512 (8.5%)
2007	113274 (8.6%)	5055 (8.4%)	239 (9.7%)	559 (9.3%)
2008	113720 (8.6%)	5280 (8.8%)	246 (10.0%)	547 (9.1%)
2009	110993 (8.4%)	5099 (8.5%)	217 (8.8%)	513 (8.6%)

2011	112057 (8.5%)	5153 (8.6%)	194 (7.9%)	447 (7.5%)
2012	111762 (8.5%)	4958 (8.3%)	191 (7.8%)	467 (7.8%)
2013	110794 (8.4%)	5081 (8.5%)	180 (7.3%)	472 (7.9%)
2014	112717 (8.6%)	5112 (8.5%)	198 (8.0%)	474 (7.9%)
2015	112616 (8.6%)	5039 (8.4%)	213 (8.7%)	491 (8.2%)
Community Level Characteristics				
Urbanicity[5]				
Metropolitan	1052913 (80.0%)	47966 (79.9%)	1868 (75.9%)	4570 (76.3%)
Micropolitan	182309 (13.9%)	8393 (14.0%)	415 (16.9%)	995 (16.6%)
Small Town	54395 (4.1%)	2433 (4.1%)	120 (4.9%)	302 (5.0%)
Rural	26047 (2.0%)	1205 (2.0%)	57 (2.3%)	125 (2.1%)
Missing	27 (0.0%)	3 (0.0%)	0 (0%)	0 (0%)
NDI[6]				
Mean (SD)	0.07 (1.00)	0.08 (1.00)	0.40 (1.00)	0.33 (0.99)
Median [Min, Max]	-0.01 [-2.00, 4.39]	-0.00 [-2.00, 4.39]	0.28 [-1.94, 3.56]	0.22 [-1.94, 4.39]
Missing	24 (0.0%)	2 (0.0%)	0 (0%)	0 (0%)
Number of Census Blocks				
Count	137865	36141	2340	5394
Missing	24 (0.0%)	2 (0.0%)	0 (0%)	0 (0%)

Table 2: Descriptive statistics of $PM_{2.5}$ exposure by exposure window and infant mortality
This table describes the $PM_{2.5}$ exposure for the analytical sample, cases, neonatal mortality, postneonatal mortality, and the total analytical dataset. [1] Non-NA counts include individuals who had a census block assignment and therefore could have a $PM_{2.5}$ estimate. Trimester 3 and Month 1 have smaller non-NA counts than Trimester 1, 2, and pregnancy because only individuals with greater than or equal to 11 days in the exposure time period were included. The denominator is the total in the category before census block assignment. [2] Standard deviation (SD). [3] Interquartile range (IQR).

Period	Non-NA Count / Total[1]	Mean (SD)[2]	Median	IQR[3]	Range	Proportion < 8 µg/m^3	Proportion < 10 µg/m^3	Proportion < 12 µg/m^3
Analytical Sample								
Trimester 1	65990 / 65992	10.7 (3.0)	10.0	8.4 - 12.4	4.5 - 22.1	0.2	0.5	0.7
Trimester 2	65990 / 65992	10.6 (3.0)	9.8	8.3 - 12.2	4.6 - 22.0	0.2	0.5	0.7
Trimester 3	63856 / 65992	10.4 (3.1)	9.7	8.2 - 12.1	3.9 - 23.2	0.2	0.5	0.7
Pregnancy	65990 / 65992	10.6 (2.4)	10.3	8.5 - 12.5	5.2 - 18.6	0.2	0.5	0.7
Month 1	63334 / 65992	10.3 (3.4)	9.5	7.9 - 12.1	3.0 - 24.6	0.3	0.6	0.7
Controls								
Trimester 1	59998 / 60000	10.7 (3.0)	10.0	8.3 - 12.4	4.5 - 22.1	0.2	0.5	0.7
Trimester 2	59998 / 60000	10.5 (2.9)	9.8	8.3 - 12.1	4.6 - 22.0	0.2	0.5	0.7
Trimester 3	59777 / 60000	10.4 (3.0)	9.7	8.2 - 12.1	3.9 - 23.2	0.2	0.5	0.7
Pregnancy	59998 / 60000	10.6 (2.4)	10.3	8.5 - 12.5	5.2 - 17.7	0.2	0.5	0.7
Month 1	59998 / 60000	10.3 (3.4)	9.5	7.9 - 12.1	3.0 - 24.6	0.3	0.6	0.7
Cases								
Trimester 1	5992 / 5992	10.8 (3.1)	10.1	8.5 - 12.5	4.9 - 21.2	0.2	0.5	0.7
Trimester 2	5992 / 5992	10.7 (3.1)	10.0	8.4 - 12.5	4.7 - 21.3	0.2	0.5	0.7
Trimester 3	4079 / 5992	10.5 (3.2)	9.7	8.2 - 12.2	4.5 - 23.1	0.2	0.5	0.7
Pregnancy	5992 / 5992	10.7 (2.5)	10.4	8.6 - 12.6	5.2 - 18.6	0.1	0.5	0.7
Month 1	3336 / 5992	10.5 (3.4)	9.7	7.9 - 12.2	3.3 - 23.1	0.3	0.5	0.7

Neonatal mortality								
Trimester 1	3532 / 3532	10.8 (3.1)	10.1	8.5 - 12.5	5.2 - 21.2	0.2	0.5	0.7
Trimester 2	3532 / 3532	10.7 (3.1)	10.0	8.4 - 12.5	5.2 - 21.1	0.2	0.5	0.7
Trimester 3	1961 / 3532	10.5 (3.2)	9.7	8.2 - 12.2	4.5 - 22.7	0.2	0.5	0.7
Pregnancy	3532 / 3532	10.7 (2.6)	10.3	8.6 - 12.6	5.2 - 18.6	0.1	0.5	0.7
Month 1	876 / 3532	10.5 (3.5)	9.8	8.1 - 12.2	3.3 - 23.1	0.2	0.5	0.7
Postneonatal mortality								
Trimester 1	2460 / 2460	10.8 (3.1)	10.2	8.4 - 12.6	4.9 - 20.9	0.2	0.5	0.7
Trimester 2	2460 / 2460	10.7 (3.0)	10.0	8.4 - 12.4	4.7 - 21.3	0.2	0.5	0.7
Trimester 3	2118 / 2460	10.4 (3.1)	9.6	8.1 - 12.0	4.6 - 23.1	0.2	0.5	0.7
Pregnancy	2460 / 2460	10.7 (2.5)	10.4	8.6 - 12.6	5.5 - 17.6	0.1	0.5	0.7
Month 1	2460 / 2460	10.4 (3.4)	9.7	7.9 - 12.2	3.3 - 23.1	0.3	0.5	0.7
Total Analytical Dataset								
Trimester 1	1315667 / 1315691	10.7 (3.0)	10.0	8.4 - 12.4	4.2 - 22.7	0.2	0.5	0.7
Trimester 2	1315667 / 1315691	10.5 (3.0)	9.8	8.3 - 12.2	4.4 - 22.9	0.2	0.5	0.7
Trimester 3	1310274 / 1315691	10.4 (3.0)	9.7	8.2 - 12.1	3.3 - 26.8	0.2	0.5	0.7
Pregnancy	1315667 / 1315691	10.6 (2.4)	10.3	8.5 - 12.5	4.7 - 19.0	0.2	0.5	0.7
Month 1	1315667 / 1315691	10.3 (3.4)	9.5	7.9 - 12.0	2.7 - 27.0	0.3	0.6	0.8

Table 3: Main results from logistic regression on analytical sample per 4.0 μg/m^3 increase in $PM_{2.5}$

This table presents adjusted and unadjusted results from the logistic regression of critical exposure periods of pregnancy and first month of life for all infant mortality and postneonatal infant mortality. Results for all exposure periods and neonatal mortality can be found in the Supplemental material. There are fewer cases for all infant mortality in the month 1 exposure period compared to the pregnancy because only infants who lived for 11 days or more were included in the analysis. [1]Fully adjusted model includes adjustment for all birthing parent, infant, and community level characteristics. A partially adjusted model with only individual level confounders can be found in the supplementary figures. [2]Confidence Interval (CI).

		Unadjusted Model			Fully Adjusted Model[1]		
Period	Infant Mortality	Estimate (95% CI[2])	P-value	Cases / Observations	Estimate (95% CI[2])	P-value	Cases / Observations
Pregnancy	All	1.12 (1.06, 1.17)	0.00	5992 / 65990	1.05 (0.95, 1.17)	0.30	5741 / 64787
Pregnancy	Postneonatal	1.10 (1.06, 1.20)	0.01	2460 / 62458	1.09 (0.94, 1.27)	0.24	2373 / 61419
Month 1	All	1.04 (1.00, 1.08)	0.06	3336 / 63334	0.99 (0.94, 1.04)	0.68	3221 / 62267
Month 1	Postneonatal	1.03 (0.98, 1.08)	0.23	2460 / 62458	1.00 (0.94, 1.07)	0.90	2373 / 61419

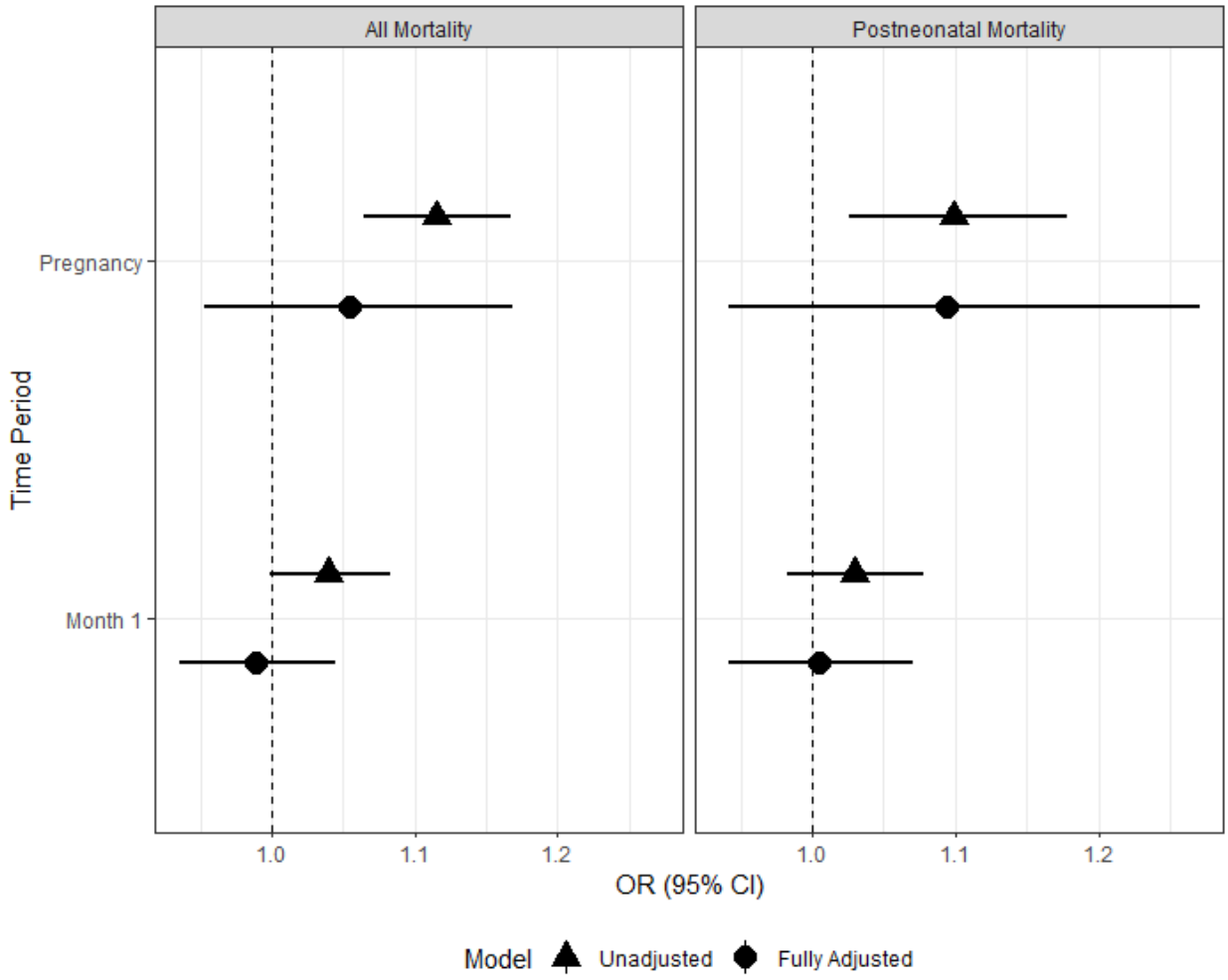
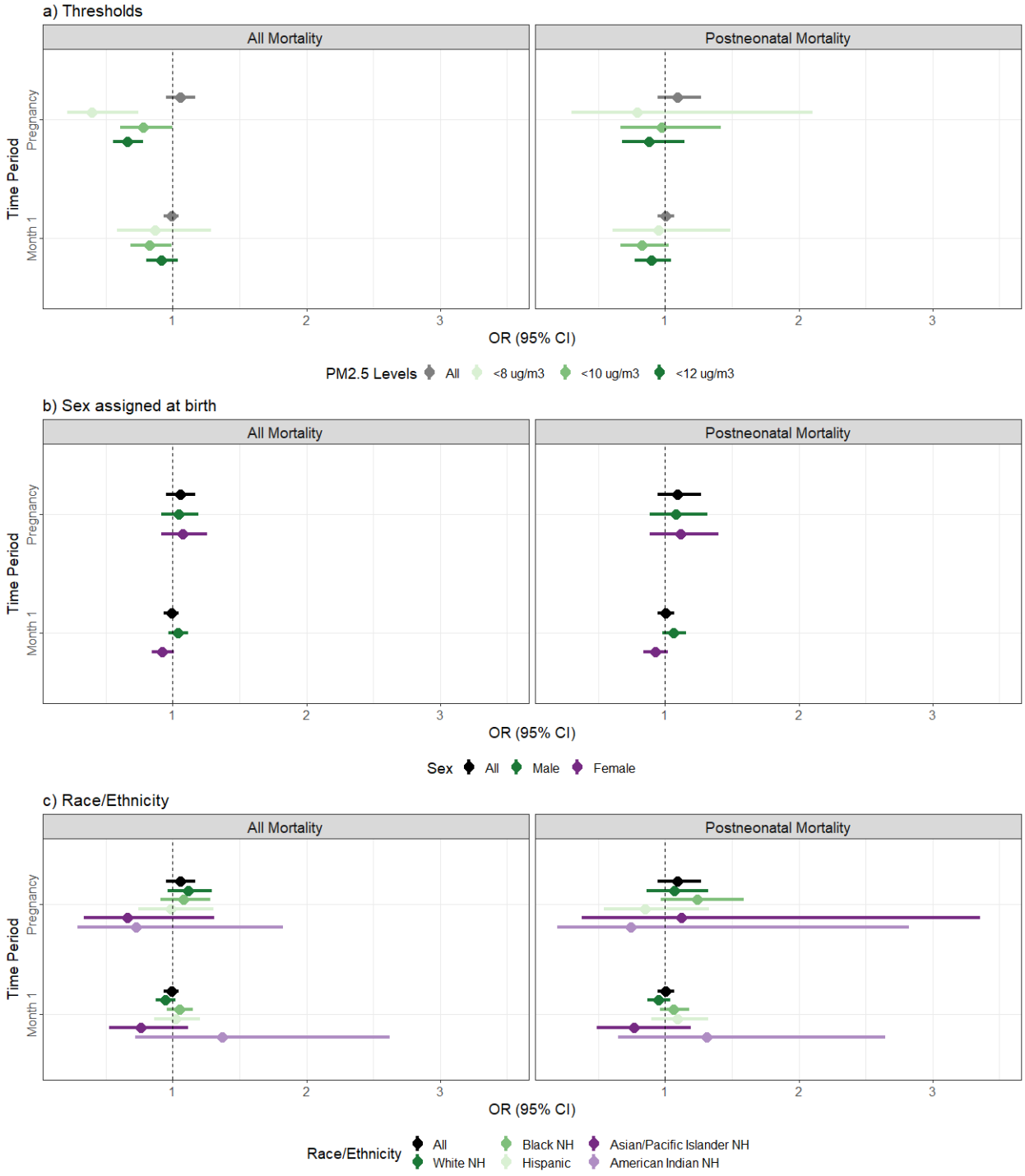


Figure 1: Main results from logistic regression on analytical sample per 4.0 μg/m^3 increase in $PM_{2.5}$
This figure presents adjusted (circle) and unadjusted (triangle) results in a forest plot from the logistic regression of critical exposure periods of pregnancy and first month of life for all infant mortality and postneonatal infant mortality. Results for all exposure periods and neonatal mortality can be found in the Supplementary material. Fully adjusted model includes adjustment for all birthing parent, infant, and community level characteristics. A partially adjusted model with only individual level confounders can be found in the Supplementary material. Confidence Interval (CI). Odds Ratio (OR).


a) Thresholds
All Mortality
Postneonatal Mortality
Time Period
Pregnancy
Month 1
1
2
3
OR (95% CI)
PM2.5 Levels All <8 ug/m3 <10 ug/m3 <12 ug/m3
b) Sex assigned at birth
All Mortality
Postneonatal Mortality
Time Period
Pregnancy
Month 1
1
2
3
OR (95% CI)
Sex All Male Female
c) Race/Ethnicity
All Mortality
Postneonatal Mortality
Time Period
Pregnancy
Month 1
1
2
3
OR (95% CI)
Race/Ethnicity All White NH Black NH Hispanic Asian/Pacific Islander NH American Indian NH

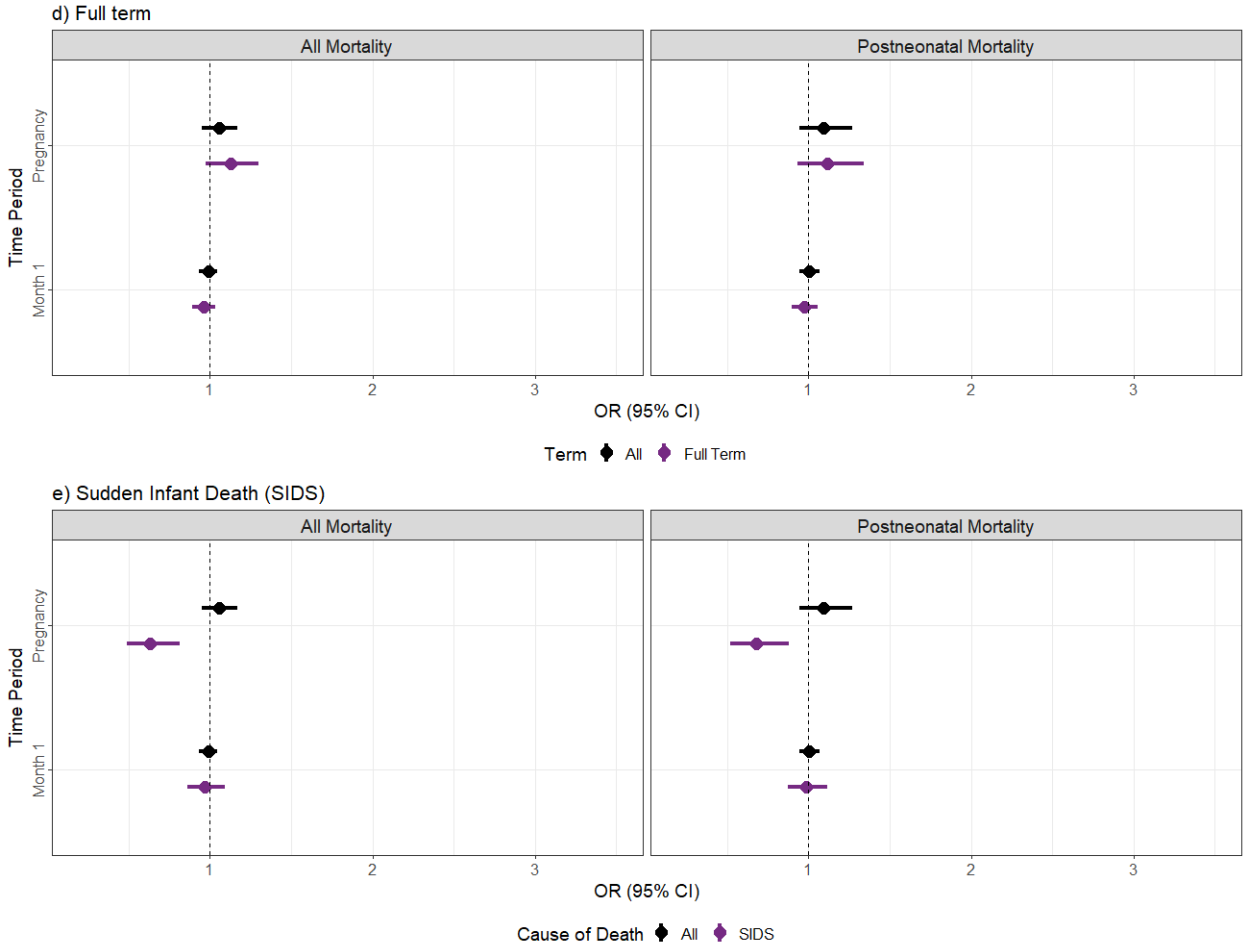


Figure 2: Additional analyses of increases in mortality per 4.0 μg/m^3 increase in $PM_{2.5}$ on analytical sample

This figure presents forest plots after full adjustment for birthing parent, infant, and community level characteristics for additional analyses compared to the unrestricted model (black or grey). We present forest plots for critical exposure periods of pregnancy and first month of life for all infant mortality and postneonatal infant mortality. Results for all exposure periods and neonatal mortality can be found in the Supplementary material. Odds Ratio (OR). Confidence Interval (CI). a) This model subset the data to only exposures less than the thresholds (<8 μg/m^3, <10 μg/m^3, <12 μg/m^3) and then ran a continuous logistic regression on this subset. b) Results are stratified by sex assigned at birth. c) Results are stratified by race self-reported on the birth certificate with six choices but results from Other/Unknown are not included. Non-Hispanic (NH). d) Results are restricted to only full term births defined as greater than or equal to 37 weeks. e) Results are restricted to infants whose cause of death was attributed to Sudden Infant Death Syndrome (SIDS) (ICD10 code: R95). Results for respiratory disease as cause of death can be found in the Supplementary material.

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