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Associations between prenatal exposure to air pollution, small for gestational age, and term low birthweight in a state-wide birth cohort

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ABSTRACT

A range of health effects, including adverse pregnancy outcomes, have been associated with exposure to ambient concentrations of particulate matter (PM) and ozone (O_3). The objective of this study was to determine whether maternal exposure to fine particulate matter ($PM_{2.5}$) and O_3 during pregnancy is associated with the risk of term low birthweight and small for gestational age infants in both single and co-pollutant models. Term low birthweight and small for gestational age were determined using all birth certificates from North Carolina from 2003 to 2005. Ambient air concentrations of $PM_{2.5}$ and O_3 were predicted using a hierarchical Bayesian model of air pollution that combined modeled air pollution estimates from the EPA's Community Multi-Scale Air Quality (CMAQ) model with air monitor data measured by the EPA's Air Quality System. Binomial regression, adjusted for multiple potential confounders, was performed. In adjusted single-pollutant models for the third trimester, O_3 concentration was positively associated with small for gestational age and term low birthweight births [risk ratios for an interquartile range increase in O_3: 1.16 (95% CI 1.11, 1.22) for small for gestational age and 2.03 (95% CI 1.80, 2.30) for term low birthweight]; however, inverse or null associations were observed for $PM_{2.5}$ [risk ratios for an interquartile range increase in $PM_{2.5}$: 0.97 (95% CI 0.95, 0.99) for small for gestational age and 1.01 (95% CI 0.97, 1.06) for term low birthweight]. Findings were similar in co-pollutant models and linear models of birthweight. These results suggest that O_3 concentrations in both urban and rural areas may be associated with an increased risk of term low birthweight and small for gestational age births.

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1. Introduction

Particulate matter (PM) and ozone (O_3) are among the air pollutants regulated under the Clean Air Act. They are associated with a variety of health outcomes, such as respiratory effects, cardiovascular effects, and mortality (EPA, 2009; EPA, 2013). Studies have also investigated if maternal exposure to these air pollutants during pregnancy could affect fetal growth and development.

Infants who are born low birthweight or small for their gestational age have a higher incidence of death and disabilities that continue into adulthood and include conditions such as metabolic syndromes and other adverse health effects (Barker et al., 1993; Valsamakis et al., 2006; Hack and Fanaroff, 1999; McCormick, 1985). Multiple studies have reported the association of fine particulate matter ($PM_{2.5}$) with low birthweight and growth restriction. The results of these studies generally demonstrate positive associations with $PM_{2.5}$ either averaged over the full pregnancy period or averaged over specific trimesters or periods of pregnancy (Basu et al., 2004; Bell et al., 2007; Wilhelm and Ritz, 2005; Liu et al., 2007; Morello-Frosch et al., 2010; Parker et al., 2005; Rich et al., 2009). However, some studies have also reported null results (Brauer et al., 2008; Mannes et al., 2005; Darrow et al., 2011). Findings for the relationship between O_3 and low birthweight and fetal growth have been inconsistent (Wilhelm and Ritz, 2005; Morello-Frosch et al., 2010; Brauer et al., 2008; Mannes et al., 2005; Darrow et al., 2011; Hansen et al., 2007, 2008; Salam et al., 2005; Ha et al., 2001; Lin et al., 2004; Gouveia et al., 2004; Chen et al., 2002; Dugandzic et al., 2006).

One reason why findings might be inconsistent is that $PM_{2.5}$ and O_3 do not occur in isolation and vary by urban-rural status. Few studies have examined the co-pollutant effects of both $PM_{2.5}$ and O_3 on birthweight and reduced fetal growth. In this study,

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we examine the associations between fetal growth and $PM_{2.5}$ and O_3, both individually and in co-pollutant models, for all births in North Carolina occurring between 2003 and 2005. A common limitation of prior studies is the reliance on proximity of maternal residence to an air pollution monitor in order to assign exposure, which restricts analyses to those residing near the monitors. In this study, we improve upon previous work by utilizing EPA's Community Multiscale Air Quality (CMAQ) model, which allows assignment of model-predicted concentrations during critical periods of gestation for all births regardless of proximity to a monitor. In addition, we examine how socioeconomic status (measured by maternal educational attainment) and urban or rural residency (i.e., urbanicity) affect the association between fetal growth and O_3 or $PM_{2.5}$, respectively.

2. Methods

We utilized North Carolina birth records for all infants born between 2003 and 2005 from the North Carolina State Center for Health Statistics and extracted relevant maternal and infant data. Term low birthweight was defined as an infant delivered at term and weighing less than 2500 g (term births were defined as: births with gestational ages of at least 37 weeks or a birthweight of at least 3888 g (Alexander et al., 1996)). The referent population in term low birthweight analyses was term births weighing at least 2500 g. As a measure of reduced fetal growth, we used a metric for small for gestational age, which was defined using the 10th percentile cutpoint for infants of similar sex, race, parity, and gestational age based on the 2003–2005 North Carolina birth cohort as the reference population. Non-small for gestational age births were those in the 10–100th percentiles. Any sex-race-parity-gestational age combination with less than 100 births was not used in the small for gestational age analyses. Non-race specific small for gestational age cut-points were also examined but produced similar findings and are not reported here. Cut-points for the small for gestational age analyses were similar to those observed in other studies (Alexander et al., 1996; Oken et al., 2003; Zhang and Bowes, 1995). Other variables of interest from the birth records were maternal age, maternal educational attainment, parity, maternal race/ethnicity, maternal smoking during pregnancy, maternal marital status, month prenatal care began, and infant sex.

Data on $PM_{2.5}$ and O_3 concentrations in ambient air were obtained from a hierarchical Bayesian model that combined data from air monitors (provided by the US EPA Air Quality System) with modeled air pollution estimates from the US EPA's CMAQ model (which bases its estimates on data from EPA's National Emissions Inventory and meteorological and geographical factors) (McMillan et al., 2010). This approach uses a space-time hierarchical Bayesian model to fuse daily O_3 monitoring data from the National Air Monitoring Stations/State and Local Air Monitoring Stations with gridded output from the CMAQ model. Similarly, fused discrete surfaces are produced for $PM_{2.5}$. These predictions represent average pollutant concentrations for CMAQ cells, not point predictions. Predictions are provided at the centroid locations (latitude, longitude) of all CMAQ cells. These air pollution estimates are predicted for 12 × 12 km grids across the entire spatial extent of North Carolina (More details and data available for download here: http://www.epa.gov/esd/land-sci/lcb/lcb_fdaqs_archive.html). Maternal residence at birth as reported on the birth record were geocoded and then matched to the appropriate 12 × 12 km grid using ARCGIS (version 9.3). The CMAQ model generates hourly predictions for $PM_{2.5}$ and O_3 and these were averaged to generate trimester-specific mean concentrations. Days included in each trimester were calculated starting with a woman's last menstrual period, if this information was available. Otherwise, the birthdate and estimated gestational age were used to estimate exposure days. Trimester specific averages were excluded if more than 45 days of the trimester were missing concentration data for trimesters 1 and 2. For trimester 3, averages were excluded if there were less than 8 days of air pollution information available. The number of days required for trimester 3 was less than those required for trimesters 1 and 2 due to the variable length of the third trimester. The number of days in the third trimester was not correlated with pollutant concentration.

A total of 361,105 birth records were obtained for this study. We excluded non-singleton births ($n=12{,}083$), infants whose gestational age was unknown, less than 20 weeks, or greater than 45 weeks ($n=237$), infants whose gestational age was implausible for their birthweight (Alexander et al., 1996) ($n=1439$), and infants with a chromosomal anomaly as ascertained by the North Carolina Birth Defects Monitoring Program ($n=745$). Births were also excluded if maternal age was less than 15 years, greater than 50 years, or unknown ($n=821$) or if the maternal residence at birth was outside of North Carolina or missing ($n=524$). It was possible for a birth to have been excluded for more than one factor. Among the remaining individuals in the dataset, 22,485 (6.5%) were excluded because maternal addresses were not geocodable to the 12 × 12 km CMAQ grid covering North Carolina. The final study population was 322,981 (89% of all birth records obtained for the study).

Binomial regression was performed to determine the association between air pollution and infant growth. This model was chosen because our sample includes the entire state of North Carolina and it is preferable to estimate risk ratios as opposed to approximating these with odds ratios. None of the binomial regression models had issues with convergence. Confounders considered in the analyses were maternal age (15–19 yr, 20–24 yrs, 25–29 yr, 30–34 yr, 35–39 yr, 40–50 yr), maternal educational attainment (less than high school degree, high school degree, more than a high school degree), parity (first birth, second birth, third birth, fourth or more births), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, American Indian, other), maternal smoking during pregnancy (yes, no), maternal marital status (married, not married), prenatal care began in first trimester (yes, no), rural–urban continuum codes assigned based on county (metropolitan urbanized counties with populations of 1 million or more [rural-urban continuum code: 1], metropolitan urbanized counties with populations of 250,000 to 1 million [rural-urban continuum code: 2], metropolitan urbanized counties with populations less than 250,000 [rural-urban continuum code: 3], nonmetropolitan urbanized [rural-urban continuum codes: 4, 5], less urbanized [rural-urban continuum codes: 6, 7], thinly populated [rural-urban continuum codes: 8, 9]) (USDA, 2008), and month of conception. These confounders were chosen a priori for inclusion based on knowledge of their relationships with the exposure and outcomes. After examining the linearity assumptions, those with multiple categories were included as indicator variables. Single-pollutant models were run individually for $PM_{2.5}$ and O_3. Then, a combined analysis was performed with both pollutants included in the same binomial regression model. Associations between air pollution and term low birthweight and small for gestational age were stratified by maternal educational attainment (categorized as ≤ high school degree and > high school degree), as a proxy for socioeconomic status, and associations were also stratified by urbanicity, using rural–urban continuum codes (categorized as urban [rural–urban continuum codes [1–5] and non-urban [rural–urban continuum codes [6–9]).

In addition to the binomial regression models, the relationship between air pollution and birthweight among term births was investigated utilizing a linear model with the same covariates in the adjusted model. Additionally, a linear model was run that included a term for gestational age. This variable did not affect the results and was not retained for the final models.

Two sensitivity analyses were also performed. The first sensitivity analysis used weights equal to 1 minus the quantity of the standard deviation associated with the mean trimester-specific O_3 or $PM_{2.5}$ exposure estimate divided by that mean to account for exposure measurement variability (Waller et al., 2001). If the standard deviation was greater than the mean, the weight was set to 0. Briefly, we explored the effect of using a weighting factor upon the risk estimates using the uncertainty associated with the CMAQ predictions to weight the exposures, such that subjects linked to CMAQ predictions with smaller associated uncertainty would be weighted more than subjects linked to CMAQ predictions with greater associated uncertainty when calculating the relative risks. In unweighted analyses, each observation contributes a value of 1 to the frequency count. In the weighted analysis, each observation contributes the value of the weighting variable to the frequency count. The weighting variables may range from 0 to 1, such that a subject assigned a weighting variable of 0 is essentially excluded from the analysis, and subjects with a weighting variable of 1 are included in the analysis. If, for example, a subject has a weighting variable of 0.5, she would contribute an n of 0.5 to the analysis. This allows us to emphasize the contribution of the subjects in which we have greater confidence in the exposure assessment and minimize the influence of the subjects in which our confidence in the exposure assessment is less certain. The second sensitivity analysis restricted the models to those women residing within a certain distance of an air monitor (20 km [44% of the study population for $PM_{2.5}$; 52% of the study population for O_3;] or 10 km [26% of the study population for $PM_{2.5}$; 19% of the study population for O_3]) in order to compare the results of the population that would have likely been included in a study that relied on residential proximity to stationary monitors to assign exposure with the results for the population that includes subjects across the entire state, regardless of their proximity to a stationary monitor. If the results of this sensitivity analysis are similar across the two populations, we will have greater confidence that the state-wide results that use CMAQ predictions to assign exposures could be compared to the results of other studies that assigned exposure using proximity to a stationary monitor. If the results of this sensitivity analysis are different across the two populations, the results from the state-wide analysis might be less generalizable, and it may be difficult to interpret the results for the state-wide analysis in the context of other studies that have relied on proximity to stationary monitors for exposure assessment. The results for both sensitivity analyses were similar, and in a few instances, further from the null, compared to those reported in the results below and are presented in the Supplementary material.

This research was approved by the EPA/University of North Carolina Institutional Review Boards.

3. Results

A total of 312,638 infants (33,118 small for gestational age and 279,520 non-small for gestational age) were included in the small