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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 $\leq$ 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

for gestational age analysis and 297,043 infants (6398 term low birthweight and 290,645 full-term normal birthweight) were included in the term low birthweight analysis. Infants that were small for gestational age or term low birthweight were more likely to be born to mothers who had less education, younger age, smoked during pregnancy, and who were single (Table 1). Infants born term low birthweight were also more likely to be female, first born, and of non-Hispanic black maternal race/ethnicity (these variables were used in construction of small for gestational age variables and therefore similar across small for gestational age and non-small for gestational age status). $PM_{2.5}$ and O_3 concentrations were similar across categories of small for gestational age and term low birthweight for all three trimesters (Table 2). The correlations between $PM_{2.5}$ and O_3 concentrations, weighted by the distribution of the study population, were 0.43 for the first trimester, 0.41 for the second trimester, and 0.44 for the third trimester.

In adjusted single-pollutant models, O_3 concentrations during the third trimester were positively associated with small for gestational age (RR 1.16 [95% CI 1.11, 1.22], respectively) and with term low birthweight (RR 2.13 [95% CI 1.87, 2.42]) (Table 3). However, O_3 concentrations in the first and second trimesters were inversely associated with term low birthweight. $PM_{2.5}$ concentrations in these models resulted in null or slightly inverse associations. The associations were similar in the co-pollutant models and when examining the relationships by quartiles of pollutants instead of linearly (Table 3).

When birthweight was evaluated as a continuous variable among term births, increased $PM_{2.5}$ during the second trimester was associated with a decrease in birthweight in crude but not adjusted models (Table 4). The association was positive between $PM_{2.5}$ during the first trimester and birthweight. Increases in O_3 concentration during the second and third trimesters were associated with decreases in birthweight among term births in adjusted models.

Table 1
Maternal and fetal characteristics across categories of Small for Gestational Age and Term Low Birthweight for a study of women in North Carolina, 2003–2005.

	Small for gestational age (N=33,118)	Not small for gestational age (N=279,520)	Term low birthweight (N=6398)	Not term low birthweight (N=290,645)
	N (%)			
Maternal educational attainment				
Less than a high school degree	9740 (29.47)	59,545 (21.35)	2015 (31.60)	63,246 (21.81)
High school degree	10,612 (32.11)	78,569 (28.17)	2151 (33.74)	82,388 (28.41)
More than a high school degree	12,693 (38.41)	140,777 (50.48)	2210 (34.66)	144,352 (49.78)
Parity				
First birth	13,607 (41.09)	114,583 (40.99)	3284 (51.34)	118,874 (40.92)
Second birth	11,195 (33.81)	94,575 (33.84)	1659 (25.93)	99,127 (34.12)
Third birth	5280 (15,94)	45,566 (16.30)	881 (13.77)	47,204 (16.25)
Fourth or more births	3034 (9.16)	24,786 (8.87)	573 (8.96)	25,317 (8.71)
Maternal race/ethnicity				
Non-hispanic white	19,884 (60.04)	169,262 (60.55)	3052 (47.75)	174,500 (60.09)
Non-hispanic black	7468 (22.55)	62,092 (22.21)	2327 (36.41)	60,843 (20.95)
Hispanic	4938 (14.91)	41,371 (14.80)	697 (10.91)	43,324 (14.92)
American Indian	828 (2.50)	6795 (2.43)	191 (2.99)	8104 (2.79)
Other	N/A	N/A	124 (1.94)	3608 (1.24)
Maternal age				
15–19 years	4514 (13.63)	29,760 (10.65)	1108 (17.32)	31,302 (10.77)
20–24 years	10,362 (31.29)	72,792 (26.04)	2118 (33.10)	77,196 (26.56)
25–29 years	8385 (25.32)	76,703 (27.44)	1500 (23.44)	79,568 (27.38)
30–34 years	6359 (19.20)	65,847 (23.56)	1049 (16.40)	67,725 (23.30)
35–39 years	2918 (8.81)	28,833 (10.32)	513 (8.02)	29,305 (10.08)
40–50 years	580 (1.75)	5585 (2.00)	110 (1.72)	5549 (1.91)
Infant sex				
Male	16,968 (51.23)	143,326 (51.28)	2575 (40.25)	149,199 (51.33)
Female	16,150 (48.77)	136,194 (48.72)	3823 (59.75)	141,446 (48.67)
Prenatal care in first trimester				
Yes	26,525 (80.80)	235,142 (84.75)	5009 (79.14)	244,482 (84.73)
No	6303 (19.20)	42,314 (15.25)	1320 (20.86)	44,053 (15.27)
Smoking during pregnancy				
No	25,010 (75.57)	219,807 (89.44)	4691 (73.42)	257,076 (88.52)
Yes	8083 (24.43)	29,489 (10.56)	1698 (26.58)	33,345 (11.48)
Marital status				
Married	18,545 (56.00)	182,514 (65.31)	2962 (46.30)	189,031 (65.05)
Single	14,571 (44.00)	96,962 (34.69)	3436 (53.70)	101,568 (34.95)
Rural–urban continuum codes category				
Metropolitan urbanized counties with populations $\geq$1 million	5669 (17.19)	50,001 (17.97)	1016 (15.94)	51,912 (17.94)
Metropolitan urbanized counties with populations of 250,000–1 million	14,568 (44.17)	129,383 (46.50)	2763 (43.35)	133,415 (46.11)
Metropolitan urbanized counties with populations $<$250,000	2893 (8.77)	25,586 (9.20)	605 (9.49)	26,112 (9.03)
Nonmetropolitan urbanized counties	6025 (18.27)	45,226 (16.25)	1218 (19.11)	48,545 (16.77)
Less urbanized counties	2857 (8.66)	21,332 (7.67)	569 (8.93)	22,197 (7.67)
Thinly populated counties	966 (2.93)	6728 (2.42)	203 (3.18)	7138 (2.47)

Table 2
Descriptive statistics of average predicted concentrations of $PM_{2.5}$ ($\mu g/m^3$) and O_3 (ppb) across categories of Small for Gestational Age and Term Low Birthweight (2003–2005).

	Small for gestational age	Not small for gestational age	Term low birthweight	Not term low birthweight
$PM_{2.5}$ trimester 1				
Mean (Standard deviation)	13.90 (2.81)	14.04 (2.75)	13.89 (2.75)	14.05 (2.75)
Median	14.12	14.25	14.05	14.27
Interquartile range	12.30–15.72	12.46–15.81	12.33–15.64	12.46–15.83
Range	4.03–21.95	3.95–21.86	4.48–21.86	3.95–21.86
$PM_{2.5}$ trimester 2				
Mean (Standard deviation)	14.05 (2.91)	14.11 (2.82)	14.04 (2.83)	14.11 (2.83)
Median	14.25	14.28	14.18	14.30
Interquartile range	12.35–15.88	12.48–15.85	12.40–15.79	12.49–15.87
Range	4.16–24.87	3.94–24.83	4.76–24.87	3.94–24.77
$PM_{2.5}$ trimester 3				
Mean (Standard deviation)	14.10 (3.01)	14.20 (2.95)	14.16 (3.00)	14.21 (2.95)
Median	14.22	14.31	14.28	14.33
Interquartile range	12.29–15.95	12.44–16.03	12.38–15.93	12.46–16.03
Range	4.23–26.35	3.88–27.18	4.35–26.35	3.88–26.58
O_3 Trimester 1				
Mean (Standard deviation)	40.85 (10.13)	40.69 (10.05)	40.55 (10.48)	40.72 (10.04)
Median	41.86	41.50	41.26	41.54
Interquartile range	31.60–48.86	31.59–48.68	30.87–48.84	31.63–48.69
Range	20.47–70.35	18.35–70.50	21.94–68.58	18.35–70.50
O_3 Trimester 2				
Mean (Standard deviation)	40.76 (9.12)	40.46 (9.16)	40.51 (9.41)	40.50 (9.13)
Median	42.57	42.12	42.09	42.18
Interquartile range	32.56–48.73	32.01–48.58	31.92–48.82	32.10–48.59
Range	21.94–67.18	17.39–66.67	21.94–61.50	17.39–67.18
O_3 Trimester 3				
Mean (Standard deviation)	40.69 (9.12)	40.69 (9.11)	40.98 (9.35)	40.68 (9.06)
Median	42.39	42.46	42.92	42.43
Interquartile range	32.50–48.62	32.39–48.67	32.86–48.90	32.46–48.62
Range	21.05–60.17	17.92–61.54	21.49–60.17	20.88–60.64

Analyses stratified by educational attainment of women examined whether associations varied for both $PM_{2.5}$ and O_3 and fetal growth (Supplement Table 1). No substantial differences were observed. When examining the associations between $PM_{2.5}$ and O_3 and small for gestational age, no differences were observed based on urbanicity (Supplement Table 2). For term low birthweight, the associations with $PM_{2.5}$ were slightly less than the null among those living in urban environments and null among those living in less urban areas. However, the opposite was observed for O_3 concentrations and term low birthweight. Associations between third trimester O_3 concentration and term low birthweight were observed among those living in urban environments, whereas the associations was smaller among those living in less urban environments.

4. Discussion

We observed a positive association between O_3 concentration and decreased fetal growth among all singleton births in North Carolina from 2003–2005. To our knowledge, this is the first study of air pollution and fetal growth that has utilized a state-wide birth cohort, including mothers who resided in both urban and rural locations during their pregnancy. The use of the state-wide birth cohort (and thus inclusion of mothers residing in both urban and non-urban locations) was facilitated by the availability of predicted O_3 and $PM_{2.5}$ estimates across the spatial extent of North Carolina from the fused CMAQ model, as we were not restricted to including subjects who lived within a predefined distance from an air pollution monitor. Typical air pollution studies that rely on ambient monitoring data for exposure assignment can suffer from low spatial and temporal resolution. Air pollution monitors are typically located in urban areas, thus limiting the population that can be included in a study and precluding the investigation of the differential effects air pollution may elicit in rural populations. Additionally, air pollution monitors may only collect data during a specific season (e.g. O_3) or subset of days (e.g., every 3 days, PM). Recently, in an analysis covering the Eastern United States, Bravo et al. (2012) demonstrated that use of the CMAQ model provided increased spatial and temporal resolution compared to the use of monitoring data. Additionally, Bravo et al. (2012) observed that a number of demographic characteristics (self-identification as Black, median income, poverty, age, and educational attainment) differed between counties with and without AQS monitors. Bell and Dominici (2008) previously reported that some community-level characteristics (including percent Black population and unemployment) can act as effect measure modifiers in epidemiologic studies of air pollution. In the present study, if these populations respond differently to air pollution, exclusion of these populations from the study would hinder the full characterization of air pollution-related effects in the general population as a whole. However, the CMAQ model was used in the present study, and all births with an address in North Carolina that could be successfully geocoded were included, allowing for analysis of any differential effects of air pollution exposure in urban and rural populations.

We examined co-pollutant models because both O_3 and $PM_{2.5}$ are regional pollutants and we wanted to distinguish the associations of each pollutant, without worrying about confounding by the other. The results were similar to the single pollutant models, making it unlikely that air pollution concentrations of $PM_{2.5}$ or O_3 affect the others' relationship with fetal growth in North Carolina. We also conducted several sensitivity analyses to evaluate the robustness of observed findings from the fused CMAQ model to assign exposure in the state-wide birth cohort. First, we applied

Table 3
Risk Ratios (95% Confidence Intervals) for the association between air pollution concentrations and Small for Gestational Age and Term Low Birthweight in single and co-pollutant models.

	Small for gestational age			Term low birthweight		
	Single pollutant models		Co-pollutant models [b]	Single pollutant models		Co-pollutant models [b]
	Crude	Adjusted [a]	Adjusted [a]	Crude	Adjusted [a]	Adjusted [a]
$PM_{2.5}$						
Trimester 1						
Linear [c]	0.94 (0.93, 0.96)	0.96 (0.94, 0.98)	0.96 (0.94, 0.97)	0.93 (0.91, 0.96)	0.94 (0.91, 0.98)	0.96 (0.92, 1.00)
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	0.96 (0.93, 0.99)	0.99 (0.96, 1.01)	0.98 (0.95, 1.01)	0.99 (0.92, 1.05)	0.99 (0.93, 1.06)	0.98 (0.91, 1.05)
Quartile 3	0.92 (0.89, 0.94)	0.93 (0.90, 0.96)	0.93 (0.90, 0.96)	0.93 (0.87, 0.99)	0.92 (0.86, 1.00)	0.92 (0.85, 0.99)
Quartile 4	0.91 (0.88, 0.93)	0.94 (0.91, 0.98)	0.93 (0.89, 0.89)	0.85 (0.79, 0.91)	0.89 (0.81, 0.97)	0.90 (0.82, 0.98)
Trimester 2						
Linear [c]	0.98 (0.97, 0.99)	0.97 (0.95, 0.98)	0.97 (0.95, 0.98)	0.97 (0.94, 1.00)	0.95 (0.92, 0.99)	0.97 (0.93, 1.01)
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	0.93 (0.90, 0.96)	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)	1.01 (0.94, 1.08)	1.01 (0.94, 1.08)	0.99 (0.93, 1.07)
Quartile 3	0.93 (0.90, 0.95)	0.93 (0.91, 0.96)	0.93 (0.90, 0.96)	0.92 (0.86, 0.99)	0.90 (0.83, 0.97)	0.89 (0.82, 0.96)
Quartile 4	0.96 (0.94, 0.99)	0.95 (0.92, 0.99)	0.94 (0.91, 0.98)	0.93 (0.87, 1.00)	0.92 (0.84, 1.00)	0.89 (0.81, 0.97)
Trimester 3						
Linear [c]	0.96 (0.95, 0.97)	0.97 (0.95, 0.99)	0.95 (0.94, 0.97)	0.98 (0.95, 1.01)	1.01 (0.97, 1.06)	0.95 (0.91, 0.99)
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	0.95 (0.92, 0.98)	0.99 (0.96, 1.01)	0.98 (0.96, 1.01)	0.96 (0.89, 1.02)	0.96 (0.90, 1.04)	0.95 (0.89, 1.03)
Quartile 3	0.93 (0.90, 0.95)	0.96 (0.93, 0.99)	0.94 (0.91, 0.97)	0.98 (0.92, 1.05)	1.00 (0.92, 1.07)	0.94 (0.87, 1.01)
Quartile 4	0.92 (0.89, 0.94)	0.93 (0.90, 0.97)	0.90 (0.87, 0.94)	0.91 (0.85, 0.98)	0.96 (0.88, 1.05)	0.82 (0.74, 0.90)
O_3						
Trimester 1						
Linear [c]	1.03 (1.01, 1.04)	1.03 (0.98, 1.07)	1.05 (1.01, 1.10)	0.97 (0.94, 1.01)	0.84 (0.76, 0.93)	0.87 (0.78, 0.96)
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	0.97 (0.94, 1.00)	0.93 (0.89, 0.98)	0.93 (0.89, 0.98)	0.86 (0.80, 0.92)	0.60 (0.54, 0.67)	0.60 (0.54, 0.68)
Quartile 3	1.01 (0.98, 1.04)	0.93 (0.86, 0.99)	0.94 (0.88, 1.00)	0.86 (0.80, 0.92)	0.47 (0.40, 0.55)	0.48 (0.41, 0.56)
Quartile 4	1.03 (1.00, 1.06)	0.95 (0.89, 1.02)	0.98 (0.92, 1.06)	0.93 (0.87, 1.00)	0.51 (0.43, 0.60)	0.54 (0.46, 0.64)
Trimester 2						
Linear [c]	1.06 (1.04, 1.07)	0.99 (0.94, 1.04)	1.01 (0.96, 1.07)	1.00 (0.96, 1.05)	0.79 (0.70, 0.90)	0.81 (0.71, 0.92)
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	1.05 (1.02, 1.08)	0.97 (0.92, 1.02)	0.97 (0.92, 1.02)	0.97 (0.91, 1.04)	0.72 (0.64, 0.81)	0.73 (0.65, 0.81)
Quartile 3	1.07 (1.04, 1.11)	0.95 (0.89, 1.01)	0.95 (0.90, 1.02)	0.92 (0.86, 0.98)	0.58 (0.50, 0.67)	0.60 (0.52, 0.70)
Quartile 4	1.08 (1.05, 1.11)	0.98 (0.92, 1.05)	1.00 (0.93, 1.07)	1.04 (0.97, 1.11)	0.70 (0.60, 0.82)	0.75 (0.64, 0.89)
Trimester 3						
Linear [c]	1.00 (0.98, 1.02)	1.16 (1.11, 1.22)	1.21 (1.15, 1.28)	1.06 (1.01, 1.11)	2.03 (1.80, 2.30)	2.13 (1.87, 2.42)
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	1.03 (1.00, 1.06)	1.12 (1.07, 1.17)	1.13 (1.08, 1.18)	1.01 (0.95, 1.09)	1.31 (1.18, 1.46)	1.33 (1.19, 1.48)
Quartile 3	1.01 (0.98, 1.04)	1.17 (1.11, 1.25)	1.21 (1.14, 1.29)	1.01 (0.94, 1.08)	1.70 (1.47, 1.97)	1.80 (1.55, 2.09)
Quartile 4	1.00 (0.97, 1.03)	1.19 (1.12, 1.27)	1.26 (1.18, 1.35)	1.11 (1.04, 1.19)	2.13 (1.82, 2.50)	2.35 (2.00, 2.77)

[a] Adjusted for: marital status (married, single), maternal education (less than high school degree, high school degree, more than a high school degree), maternal race (Non-Hispanic white, Non-Hispanic black, Hispanic, American Indian, Other), maternal age (15–19 yr, 20–14 yr, 25–29 yr, 30–34 yr, 35–39 yr, 40–50 yr), maternal smoking (yes, no), parity (first birth, second birth, third birth, fourth or higher birth), prenatal care in first trimesters (yes, no), rural–urban continuum codes category (metropolitan urbanized counties with populations of 1 million or more, metropolitan urbanized counties with populations of 250,000–1 million, metropolitan urbanized counties with populations less than 250,000, nonmetropolitan urbanized, less urbanized, thinly populated), month of conception.

[b] Co-pollutant models include the same covariates but also includes both $PM_{2.5}$ and O_3 of the same trimester.

[c] Linear models are per Interquartile Range (3.5 $\mu g/m^3$ for $PM_{2.5}$ and 16.5 ppb for O_3).

a weighting factor derived from the standard deviations in order to account for uncertainty associated with exposure estimates. Second, we restricted our analyses to subjects who lived within 10 km or 20 km of an air pollution monitor to approximate the study population that would have been included in the analyses if we had not used the fused CMAQ model predictions and instead only included subjects living in close proximity to an air pollution monitor. The results of both of these sensitivity analyses were similar to the results of the main analyses.

Our findings for O_3 and term low birthweight and small for gestational age are supported by other studies conducted in the U.S. that have investigated these associations (Wilhelm and Ritz, 2005; Morello-Frosch et al., 2010; Darrow et al., 2011; Salam et al., 2005). Three of these studies were performed in California and had lower O_3 concentrations than those estimated in North Carolina for our study period. The inverse association between O_3 concentrations and birthweight was observed in all three trimesters of pregnancy in the study by Morello-Frosch et al. (2010), but similar to our results, the other two studies in California only observed associations with O_3 exposure estimates later in the pregnancy (Wilhelm and Ritz, 2005; Salam et al., 2005). The associations for O_3 in the third trimester were robust to adjustment for other pollutants (PM_{10}) in the study by Salam et al. (2005) but became null after adjustment for PM_{10} and/or CO in the study by Wilhelm and Ritz (2005). A study in Georgia with O_3 concentrations similar to those in North Carolina reported inverse associations between birthweight and O_3 concentration averaged during the second through eighth months of pregnancy (Darrow et al., 2011). Most studies that reported no association between O_3 concentrations and fetal growth were conducted outside of the U.S. (Mannes et al., 2005; Hansen et al., 2007; Ha et al., 2001; Lin et al., 2004; Gouveia et al., 2004; Dugandzic et al., 2006) with the exception of Chen et al. (2002) in Nevada. Chen et al. (2002) reported no association between birthweight and O_3 concentrations, which were lower than the concentrations observed in North Carolina and may have been too low to observe associations.

Table 4
Change in birthweight (grams) (95% Confidence Intervals) for linear regression models of air pollution concentrations and birthweight among term births.

	Crude	Adjusted[a]
$PM_{2.5}$ per interquartile range (3.5 μg/m^3)		
Trimester 1	4.04 (1.88, 6.19)	4.43 (1.60, 7.25)
Trimester 2	−5.02 (−7.11, −2.92)	0.33 (−2.45, 3.11)
Trimester 3	−0.21 (−2.24, 1.81)	2.14 (−0.58, 4.85)
O_3 per interquartile range (16.5 ppb)		
Trimester 1	−2.66 (−5.45, 0.12)	2.58 (−4.15, 9.31)
Trimester 2	−12.83 (−15.89, −9.77)	−11.95 (−20.38, −3.52)
Trimester 3	2.26 (−0.85, 5.37)	−37.95 (−46.29, −29.61)

[a] Adjusted for: marital status (married, single), maternal education (less than high school degree, high school degree, more than a high school degree, maternal race (-Hispanic white, Non-Hispanic black, Hispanic, American Indian, Other), maternal age (15–19 yr, 20–14 yr, 25–29 yr, 30–34 yr, 35–39 yr, 40–50 yr), maternal smoking (yes, no), parity (first birth, second birth, third birth, fourth or higher birth), prenatal care in first trimesters (yes, no), rural–urban continuum codes category (metropolitan urbanized counties with populations of 1 million or more, metropolitan urbanized counties with populations of 250,000–1 million, metropolitan urbanized counties with populations less than 250,000, nonmetropolitan urbanized, less urbanized, thinly populated), month of conception.

Our study, as well as others mentioned above (Wilhelm and Ritz, 2005; Salam et al., 2005), identified associations only during the later part of pregnancy, which is consistent with known fetal development processes. The third trimester of pregnancy is the most prolific period of fetal growth and therefore insults during this pregnancy period may have more of an effect on gestational development and birthweight than insults during the first trimester of pregnancy. Earlier insults may be associated with other developmental effects, such as birth defects, which occur during the first trimester. Our study detected no association, and sometimes a slightly protective association, between $PM_{2.5}$ and small for gestational age or term low birthweight. This finding is similar to another study performed in the southeastern U.S. Darrow et al. (2011) reported no association between $PM_{2.5}$ during the first month of gestation or during the third trimester of pregnancy and birthweight, although some associations were observed for specific $PM_{2.5}$ components. The $PM_{2.5}$ concentrations in the study were similar to those observed in North Carolina. Another study conducted in North Carolina examining PM concentrations and birthweight reported a positive association between third trimester $PM_{2.5}$ concentrations and decreased birthweight (Gray et al., 2010). The reported PM concentrations were similar between our studies. However, this study included preterm births and therefore is not directly comparable to our study. Other studies in the U.S. also reported positive associations between $PM_{2.5}$ and fetal growth restriction (Basu et al., 2004; Bell et al., 2007; Wilhelm and Ritz, 2005; Morello-Frosch et al., 2010; Parker et al., 2005; Rich et al., 2009). As previously noted, these studies took place in California (Basu et al., 2004; Wilhelm and Ritz, 2005; Morello-Frosch et al., 2010; Parker et al., 2005) and the northeastern U.S. (Bell et al., 2007; Rich et al., 2009). The studies in California had slightly higher mean $PM_{2.5}$ concentrations, and when reported, the 75th percentile or maximum concentrations detected were also higher than those in our study (e.g., mean $PM_{2.5}$ in Wilhelm and Ritz (2005) was 21.0 μg/m^3 for third trimester exposures, and 14.2 μg/m^3 in our analyses). Similar $PM_{2.5}$ concentrations to those estimated in our study were observed in a study conducted in New Jersey in which an association was observed between $PM_{2.5}$ concentrations in the first and third trimesters (not second trimester) and small for gestational age (Rich et al., 2009). The results were consistent when the authors controlled for NO_2 in the model as well. Lower mean $PM_{2.5}$ concentrations were reported in a study taking place in Massachusetts and Connecticut (Bell et al., 2007). $PM_{2.5}$ concentrations were associated with decreased birthweight in this study. The associations were robust to co-pollutant adjustment for CO and SO_2.

Fetal growth is influenced by maternal, placental, and fetal factors. The biological mechanisms by which air pollutants may influence the developing fetus remain largely unknown. Fetal growth restriction may result from stressors that impact transplacental oxygen and nutrient transport by a variety of mechanisms including oxidative stress, placental inflammation and placental vascular dysfunction (Kannan et al., 2006). These mechanisms may be linked since oxidative/nitrosative stress is reported to cause vascular dysfunction in the placenta (Myatt et al., 2000). Direct effects on maternal health, such as susceptibility to infection, and on fetal health, such as DNA damage, have also been proposed as mechanisms underlying adverse birth outcomes (Ritz et al., 2000).

This study has multiple strengths. First, fused CMAQ model predictions were used to estimate concentrations of air pollutants that were based on both model estimates and air monitor measurements. The method was validated and found to provide reliable information on $PM_{2.5}$ (McMillan et al., 2010). Second, utilizing the fused CMAQ data allowed inclusion of all births in North Carolina with a successfully geocoded residential address, regardless of their proximity to an air monitor. Sensitivity analysis demonstrated that the model results were similar when restricted to births near air monitors, providing greater certainty to the statewide estimates. Infant characteristics and outcomes, such as term low birthweight, were determined using birth records, which are a reliable source of such data. The number of births included in the study was large which allowed for inclusion of multiple races/ethnicities often excluded from studies. Finally, stratification by rural–urban continuum codes allowed estimates to vary by urban and rural status, whereas many studies are not able to include or examine rural areas because of the lack of data on women residing in rural areas where air monitoring is not present.

Additionally, this study has some limitations. First, no information is available regarding time at residence during pregnancy. The assumption had to be made that the address at birth was the same as the residence during the entire pregnancy. If a woman moved during pregnancy, she may have experienced different air pollution concentrations than those assigned to her based on her residence at time of delivery resulting in exposure misclassification. It is possible that such misclassification may have contributed to the lack of association found for the first trimester exposures in this study. Also, although the CMAQ estimates are an excellent source of information on ambient air conditions, they do not measure personal exposure. An individual's exposure may vary based on time spent outdoors, time spent commuting, proximity to roadways, etc. Thus, there will be variability of personal exposures among women living in similar areas. We were also unable to geocode 6.5% of the addresses, which was often due to the lack of street address, and only a rural route or PO box being listed on the birth certificate. This probably had a greater effect on our ability to successfully geocode subjects in rural areas. The women who were excluded due to inability to geocode their address were slightly different than the women included in the study with a lower proportion of women with more than a high school degree, older age, and non-Hispanic white race/ethnicity. As with any study utilizing addresses, there will always be some degree of spatial dependence, as individuals living near each other will likely be more similar than those living far from each other. The use of 12 × 12 km grids for air pollutant concentrations, as well as multiple categories for urbanicity, should create some independence between individuals; however, residual spatial dependence cannot be ruled out. Additionally, the use of monitoring data to improve CMAQ estimates in the fused CMAQ data we

utilized is not an option in more rural areas where there are no monitors. Therefore, the possibility of exposure error is greater in these rural areas. Finally, using categorical variables created from continuous variables, such as low birth weight as an outcome, impose a cut-off point that states those above and below the cut-point are different. However, there is actually a range of values and a birth at 2510 g may not be as different from a birth with a weight of 2490 g when compared to a birthweight of 1000 g.

The pregnancy outcome small for gestational age, which is defined as a birthweight $<$ 10th percentile for gestational age, sex, race, and parity, is sometimes used as a proxy for intrauterine growth retardation or fetal growth restriction. However, this use of small for gestational age does have limitations. For example, using it for intrauterine growth retardation may overestimate the percentage of "growth-restricted" neonates as it is unlikely that 10% of neonates have growth restriction (Wollmann, 1998). On the other hand, when the 10th percentile is based on the distribution of live births at a population level, the percentage of small for gestational age among preterm births is most likely underestimated (Hutcheon and Platt, 2008). Nevertheless, small for gestational age represents a statistical description of a small neonate, whereas the term intrauterine growth retardation is reserved for those with clinical evidence of abnormal growth. Thus all intrauterine growth retarded neonates will be small for gestational age, but not all small for gestational age neonates will have intrauterine growth retardation (Wollmann, 1998).

In summary, this study found that O_3 concentrations during the third trimester was associated with small for gestational age and with term low birthweight in a large, statewide cohort of live-born infants. These associations were robust to inclusion of $PM_{2.5}$ in the model. When stratified by urbanicity, the associations were stronger between third trimester O_3 concentration and term low birthweight among those living in urban environments compared to those in rural areas. $PM_{2.5}$ concentrations had null or slightly inverse associations with small for gestational age and term low birthweight. Neither pollutant's associations with fetal growth varied by socioeconomic status, as measured by maternal educational attainment. In conclusion, this study suggests that maternal exposure to air pollution, specifically O_3, during the third trimester of pregnancy may affect the risk of small for gestational age and term low birthweight.

Competing financial interests

The authors have no competing financial interests to declare.

Human subjects research approval

The study was conducted using information collected on birth records and informed consent was not sought. The study was approved by the EPA/UNC Institutional Review Board.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2014.03.040.

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