Modification of the Effect of Ambient Air Pollution on Pediatric Asthma Emergency Visits

Susceptible Subpopulations

Matthew J. Strickland,[a] *Mitchel Klein,*[a] *W. Dana Flanders,*[b] *Howard H. Chang,*[c] *James A. Mulholland,*[d] *Paige E. Tolbert,*[a] *and Lyndsey A. Darrow*[b]

Background: Children may have differing susceptibility to ambient air pollution concentrations depending on various background characteristics of the children.

Methods: Using emergency department (ED) data linked with birth records from Atlanta, Georgia, we identified ED visits for asthma or wheeze among children 2 to 16 years of age from 1 January 2002 through 30 June 2010 (n = 109,758). We stratified by preterm delivery, term low birth weight, maternal race, Medicaid status, maternal education, maternal smoking, delivery method, and history of a bronchiolitis ED visit. Population-weighted daily average concentrations were calculated for 1-hour maximum carbon monoxide and nitrogen dioxide; 8-hour maximum ozone; and 24-hour average particulate matter less than 10 microns in diameter, particulate matter less than 2.5 microns in diameter ($PM_{2.5}$), and the $PM_{2.5}$ components sulfate, nitrate, ammonium, elemental carbon, and organic carbon, using measurements from stationary monitors. Poisson time-series models were used to estimate rate ratios for associations between 3-day moving average pollutant concentrations and daily ED visit counts and to investigate effect-measure modification by the stratification factors.

Results: Associations between pollutant concentrations and asthma exacerbations were larger among children born preterm and among children born to African American mothers. Stratification by race and preterm status together suggested that both factors affected susceptibility. The largest estimated effect size (for an interquartile range increase in pollution) was observed for ozone among preterm births to African American mothers: rate ratio = 1.138 (95% confidence interval = 1.077–1.203). In contrast, the rate ratio for the ozone association among full-term births to mothers of other races was 1.025 (0.970–1.083).

Conclusions: Results support the hypothesis that children vary in their susceptibility to ambient air pollutants.

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Epidemiologic and experimental research supports the conclusion that certain outdoor air pollutants cause exacerbations of asthmatic symptoms among children with asthma.[1,2] Similarly, there is a growing body of literature describing how in utero and early-life experiences affect physiological development and influence sensitivity to environmental factors throughout life.[3] Unfortunately, most large population-based studies of associations between short-term changes in ambient air pollutant concentrations and asthma exacerbations have lacked data on early-life risk factors, whereas the cohort studies that include such information are often too small to support investigation of effect-measure modification among potentially susceptible subgroups.

In the U.S. state of Georgia, data on live birth records have been linked with pediatric emergency department visits by staff at the Office of Health Indicators for Planning at the Georgia Department of Public Health. In addition, in metropolitan Atlanta there are several long-running air quality measurement campaigns that include, among other more commonly measured pollutants, daily measurements from 4 monitoring stations of speciated particulate matter less than 2.5 microns in diameter ($PM_{2.5}$). We used these 2 data resources to estimate the rate ratio (RR) relating short-term changes in air pollutant concentrations to emergency department (ED) visits for asthma or wheeze and to investigate whether there was evidence for effect-measure modification of the RR by various risk factors available from the linked data set. Although we examined effect-measure modification for 8 different factors,

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From the [a]Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA; [b]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA; [c]Department of Biostatistics, Rollins School of Public Health, Emory University, Atlanta, GA; and [d]Department of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA.

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Correspondence: Matthew J. Strickland, Department of Environmental Health, Rollins School of Public Health, Emory University, 1518 Clifton Rd NE, Atlanta, GA 30322. E-mail: mjstric@sph.emory.edu.

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we had particular a priori interest in investigating whether susceptibility might have varied by gestational age, as accumulating evidence suggests that children born preterm have long-term decrements in lung function.[4,5]

METHODS

Air Quality Data

From various networks throughout Atlanta during 2002 to 2010, we obtained daily measurements of outdoor concentrations of 1-hour maximum carbon monoxide (CO) (5 monitors) and nitrogen dioxide (NO_2) (6 monitors); 8-hour maximum ozone (O_3) (5 monitors); and 24-hour average particulate matter less than 10 microns in diameter (PM_{10}) (9 monitors), $PM_{2.5}$ (11 monitors), and the $PM_{2.5}$ components sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), elemental carbon (EC), and organic carbon (OC) (6 monitors each). We selected these averaging times to correspond with those used in the U.S. National Ambient Air Quality Standards.[6] Population weighting was used to generate citywide daily average concentrations for each pollutant using a previously described interpolation method.[7,8] Briefly, we estimated the citywide average using a model that adjusts the inverse distance-weighted scaled concentration at each census tract (calculated from the monitoring data) by the population density at that tract centroid averaged over a 10-km radius. We then averaged the tract-specific estimates, weighting each one by its population, to create the citywide daily average.

Health Data

From the Georgia Hospital Association, we obtained individual-level data on ED visits from 1 January 2002 through 30 June 2010. From the Office of Health Indicators for Planning at the Georgia Department of Public Health, we obtained individual-level data on live births from 1 January 1994 through 31 December 2006. A longitudinal identifier composed of components of first and last name, date of birth, and child sex enabled linkage of records from the 2 data sets. Although longitudinal identifiers are meant to be unique, 18,921 of the 1,705,130 (1.1%) birth records had an identifier that was not unique. Of these, 6,880 (36%) were multiple births, and 12,041 (64%) were children born to different mothers (typically from different zip codes). Whenever an ED visit contained a longitudinal identifier that was not unique, we used zip code (which was present in both the birth record and ED data set) to determine the appropriate match. If no zip code was concordant, then we excluded that ED visit. When the longitudinal identifier on the ED record was not unique because of multiple births, we randomly selected 1 of the multiple births to associate with the ED visit.

There were 2,369,760 ED visits among children 2 to 16 years of age whose zip code was in 20-county Atlanta and who were born during the eligible time period. Of these, 1,639,039 ED visits (69.1%) were successfully linked to a birth record. This linked data set contained information from 493,548 children. From these linked records, we identified all ED visits with an *International Classification of Diseases*, *9th revision* (*ICD-9*) code for asthma (codes beginning with 493) or wheeze (code 786.07) present in any diagnosis field (n = 111,929). Analyses were performed on records with complete information on the stratification variables listed below (n = 109,758).

To investigate potential differences in susceptibility to outdoor pollutant concentrations, we stratified the data set according to information contained on either the birth record or the ED visit record: preterm birth (gestational age <37 weeks) versus full-term birth; term low birth weight (<2,500 g among full-term births) versus normal birth weight; Medicaid versus other sources of payment for childbirth; African American versus all other self-reported maternal races; maternal smoking versus nonsmoking; low maternal education (less than high school education) versus higher maternal education; Cesarean versus vaginal delivery; and history of an ED visit for bronchiolitis during infancy (an *ICD-9* code of 466.1, 466.11, or 466.19 in any diagnosis field). Daily counts of ED visits for asthma or wheeze for each unique combination of these stratification factors were calculated on each day.

Statistical Analysis

Associations between 3-day moving average pollutant concentrations (lags 0-1-2) and the stratum-specific daily count of ED visits were estimated using Poisson time-series models with scaled variance to allow for over-dispersion. The models for the overall effects of air pollution contained indicators for the 8 factors described above, as well as a cubic spline on day of study with 8 degrees of freedom per year; indicator variables for season (4 seasons), day of week, holiday, and lag holiday (indicating whether 1 of the previous 2 days was a holiday); and cubic polynomials for 3-day moving average maximum temperature (lags 0-1-2) and 3-day moving average dew point (lags 0-1-2). In addition, models included product terms between the season indicator variables and day of week, holiday, lag holiday, and the maximum temperature polynomial to allow the effects of these covariates to vary by season. Models also included indicator variables whenever a hospital had a gap in data reporting. Pollutant concentrations were modeled as linear effects and are reported per interquartile range (IQR) increase. To estimate effect-measure modification, we stratified the data according to the factor of interest (eg, preterm births vs. full-term births) and created separate models for each stratum. These stratum-specific models contained indicators for the 7 other factors not stratified upon, as well as the meteorological and time variables described above. By stratifying we allowed all covariates to be estimated separately within each stratum. For the investigation of effect-measure modification by term low birth weight, we excluded all preterm births from the analysis. Rate ratios and 95% confidence intervals (CIs) are presented for the overall associations and for each subgroup; *P* values for the null hypothesis that

the 2 stratum-specific rate ratios are equal are presented when *P* is less than 0.15. Analyses were performed using R 2.15.2.

We assessed model misspecification by varying the number of knots in the cubic spline and by examining associations between the daily count of ED visits with pollution levels occurring 1 day in the future (controlling for the lag 0-1-2 pollutant concentration, the hypothesized causal window, as well as all other covariates) using the approach described by Flanders et al.[9] Because future pollution levels cannot cause past health events, an association of ED visits with future pollutant concentrations suggests model misspecification. Thus, examination of these associations can provide an indication of whether the association observed with the lag 0-1-2 pollutant concentrations might be confounded.

Because of our a priori interest in effect-measure modification by preterm birth, we conducted analyses to investigate whether any observed effect-measure modification was explained by the effect-measure modification for other factors, that is, we attempted to determine whether preterm birth was itself causing the heterogeneity observed in the RRs or whether preterm birth was associated with other factors that were responsible for the observed heterogeneity. After examining our main results, we performed an analysis to estimate effect modification by both preterm birth and maternal race (jointly) on the RR for the associations between air pollutant concentrations and ED visits for asthma or wheeze. We chose to explore maternal race in this way because it was the strongest modifier of the pollutant effects and because of the strong association between maternal race and preterm birth in the United States.[10] *P* values are presented for the null hypothesis that the RR (for the association between air pollution and asthma) among children born full-term to mothers of non-African American race is equal to the RR among children born preterm to African American mothers.

RESULTS

The distribution of ED visits for asthma or wheeze is presented in Table 1. Descriptive statistics for the lag 0-1-2 population-weighted average pollutant concentrations are presented in Table 2. Although long-term trends in air quality are not conveyed in Table 2, in general the pollutant concentrations decreased during the study period. Spearman correlation coefficients for the between-pollutant correlations are presented in eTable 1 (http://links.lww.com/EDE/A828).

Associations between the 3-day moving average pollutant concentrations and the rate of ED visits for asthma or wheeze are presented in Table 3. With the exception of NO_3^-, all point estimates were elevated and all confidence intervals excluded the null. The strongest association per IQR increase in pollutant concentration was observed for ozone (RR = 1.082 per 24.30 ppb increase [95% CI = 1.051 to 1.114]). Also presented in Table 3 are results from 2-pollutant models that contained ozone and another pollutant. With the exception of NO_3^-, all the effect estimates decreased slightly with control

TABLE 1. Number of Emergency Department (ED) Visits for Asthma or Wheeze Among Children Aged 2 to 16 years in 20-county Atlanta, 1 January 2002 to 30 June 2010

	No. (%)
Gestational age	
Preterm (gestational age <37 weeks)	18,641 (17)
Full-term (gestational age ≥37 weeks)	91,117 (83)
Birth weight (limited to full-term infants)	
Low birth weight (≤2,500 g)	3,890 (4)
Normal birth weight (>2,500 g)	87,227 (96)
Medicaid	
Yes	56,573 (52)
No	53,185 (48)
African American maternal race	
Yes	62,739 (57)
No	47,019 (43)
Maternal smoking	
Yes	10,454 (10)
No	99,304 (90)
Maternal education	
Less than high school	31,338 (29)
High school or more	78,420 (71)
Delivery method	
Cesarean	29,337 (27)
Vaginal	80,421 (73)
ED visit for bronchiolitis during infancy	
Yes	5,902 (5)
No	103,856 (95)

TABLE 2. Descriptive Statistics for 3-day Moving Average Population-weighted Average Ambient Air Pollutant Concentrations in 20-county Atlanta, 1 January 2002 to 30 June 2010

	Mean (SD)	Interquartile Range	Percent of Days Missing	No. Monitors
1-hour CO (ppm)	0.45 (0.20)	0.23	0	5
1-hour NO_2 (ppb)	20.17 (6.32)	8.50	0	6
8-hour O_3 (ppb)	42.22 (15.70)	24.03	0	5[a]
24-hour PM_{10} (μg/m^3)	20.74 (7.74)	10.40	7	9[b]
24-hour $PM_{2.5}$ (μg/m^3)	13.30 (5.42)	6.60	0	11[c]
24-hour SO_4^{2-} (μg/m^3)	3.86 (2.26)	2.44	0	6[d]
24-hour NO_3^- (μg/m^3)	0.70 (0.50)	0.51	0	6[d]
24-hour NH_4^+ (μg/m^3)	1.36 (0.65)	0.71	0	6[d]
24-hour EC (μg/m^3)	0.81 (0.36)	0.45	1	6[d]
24-hour OC (μg/m^3)	3.07 (1.02)	1.29	1	6[d]

[a]Daily ozone measurements from 2 year-round monitors, 2 March-October monitors, and 1 year-round monitor that started in mid-2009.
[b]PM_{10} measured daily at one monitor and every sixth day at 8 monitors.
[c]$PM_{2.5}$ measured daily at 7 monitors and every third day at 4 monitors.
[d]$PM_{2.5}$ components measured daily at 4 monitors and every third day at 2 monitors.
ppb, parts per billion; ppm, parts per million; μg/m^3, micrograms per cubic meter.

TABLE 3. Associations Between Emergency Department Visits for Asthma or Wheeze and Interquartile Range (IQR) Increases in 3-day Moving Average Population-weighted Average Ambient Air Pollutant Concentrations

		Single-pollutant Model	2-pollutant Model with Control for O_3
	IQR	RR per IQR (95% CI)	RR per IQR (95% CI)
CO	0.23 ppm	1.026 (1.013–1.038)	1.023 (1.010–1.036)
NO_2	8.50 ppb	1.041 (1.025–1.058)	1.033 (1.016–1.050)
O_3	24.03 ppb	1.082 (1.051–1.114)	—
PM_{10}	10.40 μg/m^3	1.029 (1.014–1.044)	1.016 (1.001–1.032)
$PM_{2.5}$	6.60 μg/m^3	1.032 (1.019–1.044)	1.022 (1.009–1.035)
SO_4^{2-}	2.44 μg/m^3	1.029 (1.017–1.041)	1.019 (1.006–1.032)
NO_3^-	0.51 μg/m^3	1.008 (0.997–1.020)	1.009 (0.997–1.020)
NH_4^+	0.71 μg/m^3	1.021 (1.012–1.032)	1.013 (1.002–1.024)
EC	0.45 μg/m^3	1.020 (1.008–1.032)	1.016 (1.004–1.028)
OC	1.29 μg/m^3	1.026 (1.014–1.038)	1.019 (1.007–1.031)

for ozone. Primary pollutants (CO, NO_2, and EC) tended to have less attenuation than secondary pollutants that peak in summer (SO_4^{2-} and NH_4^+) and the pollutants of mixed origin (PM_{10}, $PM_{2.5}$, and OC). In every 2-pollutant model, the RR for ozone (per IQR increase) was higher than the RR for the other pollutant (results not shown). Confidence interval widths did not meaningfully increase in the 2-pollutant models, which suggests that collinearity was not a problem.

Examination of stratum-specific associations from single-pollutant models suggested heterogeneity in the effect of ambient air pollutant concentrations for some susceptibility factors (Figure 1; numerical results in eTable 2, http://links.lww.com/EDE/A828). The point estimates for children born preterm and for children born to African American mothers tended to be farther from the null than the corresponding point estimates for their counterparts. Confidence intervals for the term low birth weight children were very wide owing to the small number of ED visits in this stratum (n = 3,890). We did not observe strong evidence for heterogeneity in the RRs across levels of Medicaid or maternal education (the 2 main indictors of socioeconomic status) or by maternal smoking, delivery method, or history of an ED visit for bronchiolitis during infancy.

After observing evidence for effect-measure modification by gestational age and by maternal race, we investigated susceptibility by these factors jointly. ED visits for asthma or wheeze numbered 40,569 for full-term birth and non-African American maternal race; 6,450 for preterm birth and non-African American maternal race; 50,548 for full-term birth and African American maternal race; and 12,191 for preterm birth and African American maternal race. Stratum-specific RRs and 95% CIs per IQR increase in pollution are presented for each combination of factors in Figure 2 and eTable 3 (http://links.lww.com/EDE/A828). *P* values in Figure 2 provide a measure of the consistency between the data and the null hypothesis that the RR in the group hypothesized to be least susceptible (full-term births and non-African American maternal race) is equal to the RR in the group hypothesized to be the most susceptible (preterm births and African American maternal race). For all pollutants except NO_3^-, for which there was no association in the overall model (Table 3), there was a tendency for the RR to increase as the number of susceptibility factors increased, as both gestational age and maternal race appeared to affect susceptibility. The largest difference in RRs (comparing the lowest susceptibility group with the highest susceptibility group) was observed for ozone. Among children born full-term to non-African American mothers, the RR for an IQR increase in ozone (24.30 ppb) was 1.025 (95% CI = 0.970–1.083), whereas for children born preterm to African American mothers the RR was 1.138 (1.077–1.203).

Although the patterns of heterogeneity were consistent across sensitivity analyses, the magnitude of the RRs was sensitive to the number of knots in the cubic spline. Shown in Table 4 are the RRs and confidence intervals per IQR increase comparing the associations reported in Table 3 (single-pollutant models that contained 8 degrees of freedom per year in the cubic spline) with results from single-pollutant models that contained either 6 degrees of freedom per year (less aggressive control) or 12 degrees of freedom per year (more aggressive control) in the cubic spline. Also presented are associations for IQR increases in pollutant levels occurring 1 day in the future. Whereas the RRs from the models with 6 and with 8 degrees of freedom per year were similar, the RRs from the models with 12 degrees of freedom per year were closer to the null. We examined several other control scenarios as well, and we observed that RRs were sensitive to model specification when the cubic spline contained fewer than 5 degrees of freedom per year (results not shown). The associations with the future pollutant concentrations were not highly sensitive—adding parameters to the cubic spline resulted in changes only in the third decimal point of the estimated RRs. Although adding control for ozone to the models caused the estimated associations for the future pollutant concentrations to shift toward the null slightly (results not shown), the general pattern described above held. Together, these results suggest that if the associations between the future pollutant levels and the outcome are due to uncontrolled confounding, then the confounders are more likely to be at short time-scales (risk factors with short-term variability) rather than low-frequency (season or trend), since adding parameters to the cubic spline did not appreciably change the estimated associations with the future pollutant concentrations.

DISCUSSION

In our study, outdoor air pollutant concentrations were associated with increases in pediatric emergency department visits for asthma or wheeze. Of note was the particularly strong association with ambient ozone concentrations, a finding that is consistent with our previous studies from Atlanta[8,11]

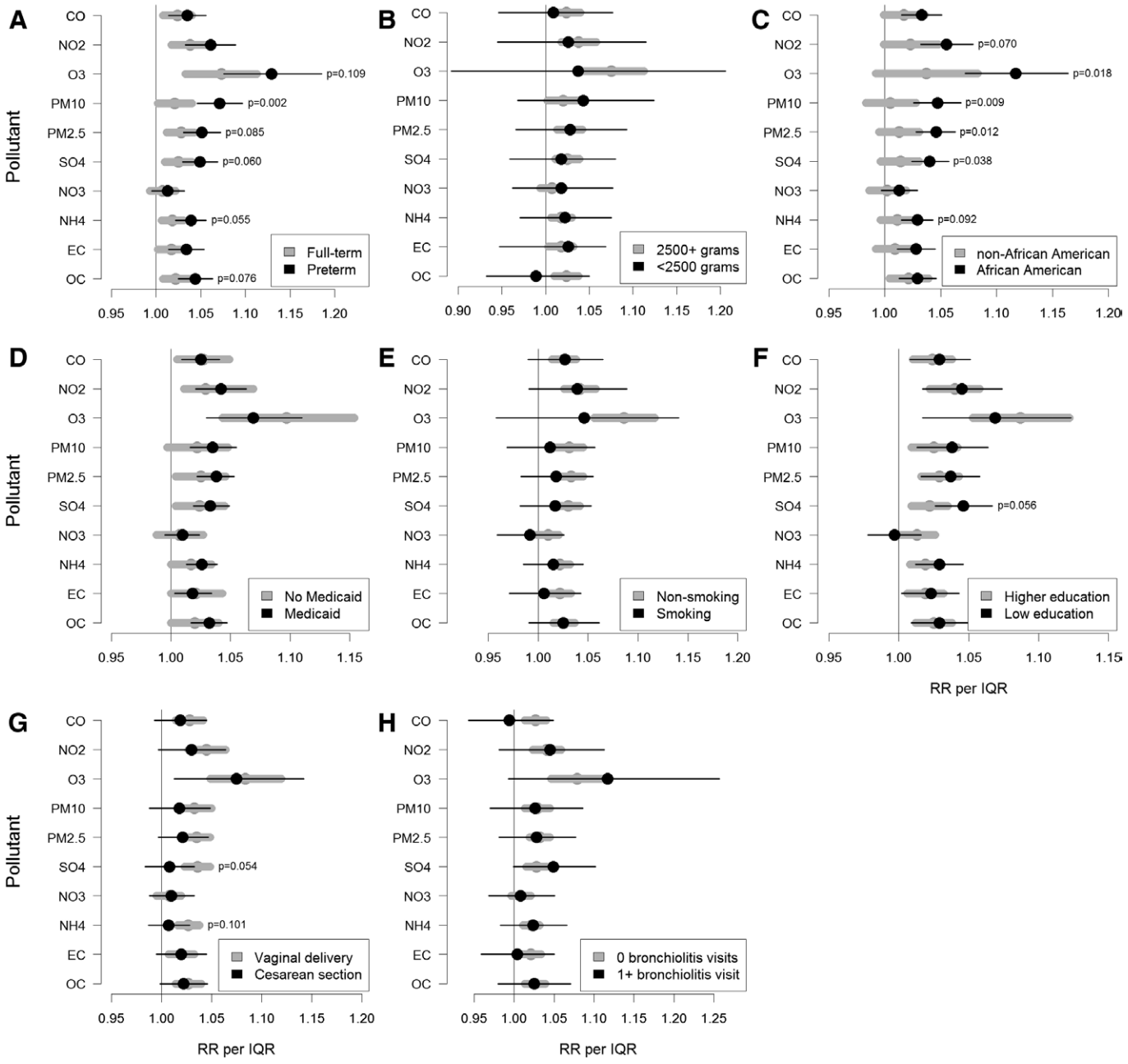

FIGURE 1. Stratum-specific rate ratios and 95% confidence intervals for associations of emergency department visits for asthma or wheeze with interquartile range increases in 3-day moving average population-weighted average ambient air pollutant concentrations. Stratification factors are (A) gestational age; (B) term birth weight; (C) maternal race; (D) medicaid status; (E) maternal education; (F) maternal smoking; (G) delivery method; and (H) ED visit for infant bronchiolitis. The *P* value for the null hypothesis that the 2 stratum-specific rate ratios are equal is reported for all *P* less than 0.15.

and much of the scientific literature,[1] although associations with ozone have not been observed in some studies.[12,13] We also observed consistently stronger associations among children born preterm and children with African American mothers. Further investigation of these factors suggested that the RRs for children with both susceptibility factors (ie, preterm birth and African American maternal race) were elevated in comparison to children with neither susceptibility factor.

Our use of linked birth records and ED visits to investigate subgroup-specific pollutant associations is novel, and the large number of ED visits (n = 109,758) enabled us to estimate most effects with good precision. We achieved this large sample size, in part, by including children as young as 2 years of age in the asthma definition. Whereas we excluded visits to children younger than 5 years in a previous study,[8] for the present study we included younger children to increase sample

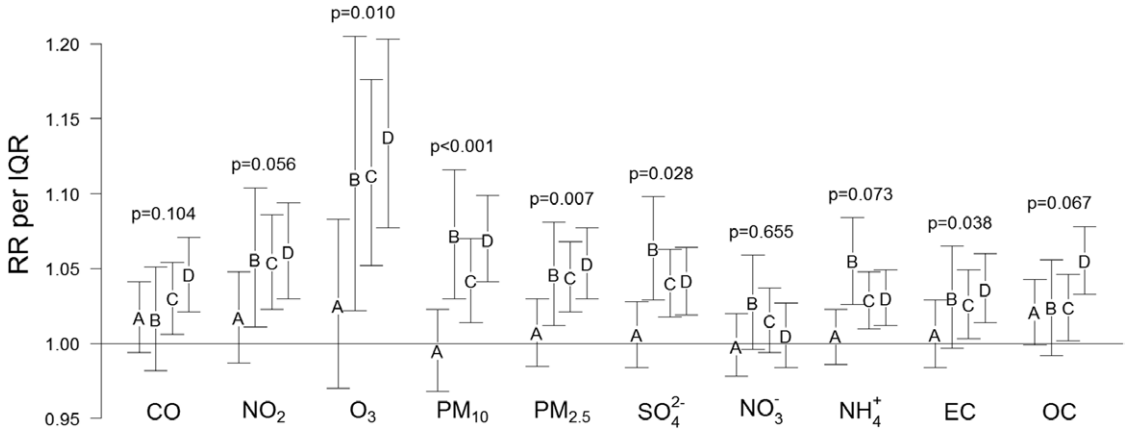

FIGURE 2. Stratum-specific rate ratios and 95% confidence intervals for associations of emergency department visits for asthma or wheeze with interquartile range increases in 3-day moving average population-weighted average ambient air pollutant concentrations. Stratification factors are (A) full-term birth and other maternal race; (B) preterm birth and other maternal race; (C) full-term birth and African American maternal race; and (D) preterm birth and African American maternal race. For each pollutant, the *P* value is presented for the null hypothesis that the rate ratio for stratum A is equal to the rate ratio for stratum D.

TABLE 4. Associations of Emergency Department Visits for Asthma or Wheeze with 3-day Moving Average Population-weighted Average Ambient Air Pollutant Concentrations and with Pollutant Concentrations 1 Day in the Future: Sensitivity to Varying Control in the Regression Time Spline[a]

	6 df per Year		8 df per Year		12 df per Year	
	Lag 0-1-2 Concentration	Future Concentration	Lag 0-1-2 Concentration	Future Concentration	Lag 0-1-2 Concentration	Future Concentration
	RR per IQR (95% CI)	RR per IQR (95% CI)	RR per IQR (95% CI)[b]	RR per IQR (95% CI)	RR per IQR (95% CI)	RR per IQR (95% CI)
CO	1.026 (1.014–1.039)	1.006 (0.999–1.039)	1.026 (1.013–1.038)	1.007 (1.000–1.015)	1.007 (0.995–1.020)	1.004 (0.996–1.012)
NO_2	1.038 (1.022–1.055)	1.008 (0.999–1.017)	1.041 (1.025–1.058)	1.010 (1.001–1.019)	1.014 (0.998–1.031)	1.005 (0.995–1.014)
O_3	1.074 (1.044–1.105)	0.999 (0.984–1.014)	1.082 (1.051–1.114)	1.003 (0.988–1.018)	1.053 (1.021–1.085)	1.001 (0.986–1.016)
PM_{10}	1.032 (1.018–1.047)	1.017 (1.007–1.027)	1.029 (1.014–1.044)	1.017 (1.007–1.027)	1.001 (0.986–1.017)	1.016 (1.006–1.026)
$PM_{2.5}$	1.031 (1.019–1.043)	1.011 (1.003–1.020)	1.032 (1.019–1.044)	1.013 (1.004–1.022)	1.010 (0.997–1.022)	1.010 (1.001–1.019)
SO_4^{2+}	1.032 (1.021–1.044)	1.010 (1.002–1.019)	1.029 (1.017–1.041)	1.010 (1.001–1.018)	1.015 (1.003–1.027)	1.007 (0.998–1.016)
NO_3^-	1.009 (0.998–1.020)	0.995 (0.987–1.003)	1.008 (0.997–1.020)	0.997 (0.989–1.005)	1.002 (0.990–1.013)	0.997 (0.989–1.005)
NH_4^+	1.026 (1.016–1.036)	1.009 (1.001–1.017)	1.022 (1.012–1.032)	1.008 (1.000–1.016)	1.011 (1.001–1.021)	1.007 (0.999–1.015)
EC	1.025 (1.013–1.036)	1.010 (1.002–1.017)	1.020 (1.008–1.032)	1.009 (1.001–1.017)	1.000 (0.988–1.012)	1.007 (0.999–1.014)
OC	1.026 (1.014–1.037)	1.011 (1.003–1.018)	1.026 (1.014–1.038)	1.011 (1.004–1.019)	1.004 (0.992–1.016)	1.008 (1.000–1.015)

[a]Rate ratios scaled to interquartile range increases in 3-day moving average population-weighted average ambient air pollutant concentrations: 0.23 ppm for CO, 8.50 ppb for NO_2, 24.03 ppb for ozone, 10.40 μg/m³ for PM_{10}, 6.60 μg/m³ for $PM_{2.5}$, 2.44 μg/m³ for SO_4^{2-}, 0.51 μg/m³ for NO_3^-, 0.71 μg/m³ for NH_4^+, 0.45 μg/m³ for EC, and 1.29 μg/m³ for OC.
[b]Results from primary analysis.
df indicates degrees of freedom.

size, even though it likely resulted in the inclusion of some ED visits diagnosed as asthma that were in fact reactive airway disease.[14] To our knowledge, no directly comparable results have been published; related work includes studies by Karr et al[15] and Lin et al,[16] both of whom used linked records to investigate health effects of outdoor air pollutant concentrations. In their case-crossover analysis of 19,109 wintertime bronchiolitis hospitalizations, Karr et al[15] reported that short-term associations with ambient air pollutants were largely consistent with the null, although some RRs were observed to be elevated for children who were born very premature (25–29 weeks of gestation). In the study by Lin et al,[16] the authors conducted a spatial analysis to investigate associations between lifetime average ozone concentrations and lifetime risk of hospitalization. Effects were found to be stronger among children whose mothers had low education, had Medicaid/self-paid births, or were Hispanic (relative to their counterparts).

Some caveats limit the strength of the conclusions that can be drawn from our analyses. Selection of the appropriate amount of smoothing is a challenge in air pollution epidemiology time-series studies, particularly when the temporal correlation of both the outcome and the exposure are high.[17,18] Our use of future pollution levels as a method to detect unmeasured and residual confounding is well-supported by theory,[9,19]

although in this analysis the coefficients for the future pollution levels were not sensitive to changes in the parameterization of the cubic spline, which limited their usefulness in guiding model selection. Apart from PM_{10}, the associations with the future pollution levels, although slightly elevated, were generally consistent with no association, so these results provide some assurance that confounding (if present) was unlikely to be strong. Given the insensitivity of the future pollution coefficient to the parameterization of the time spline, if confounding was present it was presumably caused by a factor that varied systematically with short-term changes in air pollution levels. We investigated 2 factors that have sharp seasonal peaks—pollen concentrations and influenza epidemics—and neither was a confounder. The slightly elevated associations with the future pollution levels could also indicate issues with model misspecification; for example, misspecification of concentration-response or pollutant lag effects will cause associations to be observed with future variables.[9]

Another concern relates to the generalizability of our findings, as only 69.1% of ED visits that could plausibly link to a birth record were successfully linked. Because of residential mobility, we would not expect all ED visits to link to the birth records (even with perfect linkage); further, we would not expect perfect linkage given the inevitability of data entry errors in a data set of 2.3 million ED visits and given that some children undergo name changes after birth. If associations differ for children who linked compared with children who did not link then the overall effect estimates reported in our study will not be representative of effects in the entire population. When we investigated this issue, we observed that the RRs from single-pollutant models were somewhat larger for the subset of ED visits that did not link. Thus, the RRs reported in our study may be lower than they would have otherwise been with perfect linkage. Drawing inference about how the stratum-specific results were affected is more difficult because (given the lack of a linkage) we do not know how the distribution of these covariates on the unlinked records would compare with that of the linked records.

Caveats also apply to the interpretation of results from single-pollutant models. The concentrations of several pollutants were correlated, so a particular single-pollutant result could be confounded by other pollutants; we presented results showing that some single-pollutant results were confounded by ozone. There are measurement error issues affecting interpretation as well. Twenty-county metropolitan Atlanta is large, and the population-weighted average concentrations are affected by spatial errors. These errors occur because the network of monitors is not sufficiently dense to fully capture the spatial heterogeneity and variability of a pollutant. Population-weighted average concentrations of primary pollutants (CO, NO_2, and EC) tend to have more spatial error than those of secondary pollutants (O_3, SO_4^{2-}, NO_3^-, and NH_4^+) and those of mixed origin (PM_{10}, $PM_{2.5}$, and OC).[20] The net impact of these errors is to cause the expected value of the estimated RRs to be biased toward the null, with larger errors resulting in proportionally greater attenuation.[21,22] Among the $PM_{2.5}$ components examined, we did not see evidence for an association with NO_3^-. In the 2-pollutant models (presented in Table 3), the estimated RRs per IQR increase were similar for SO_4^{2-}, NH_4^+, EC, and OC. Although these results may be indicative of a general "nonspecific" effect of $PM_{2.5}$, it is important to keep in mind that the $PM_{2.5}$ components have different amounts of spatial error and that the amount bias toward the null likely differed by component. Because the spatial errors associated with sulfur dioxide concentrations are very large,[20] we chose not to investigate the health effects of sulfur dioxide in this analysis, even though the U.S. EPA has concluded that a causal relation exists between short-term exposure to sulfur dioxide and respiratory morbidity.[23] In future work, we will investigate the health effects of sulfur dioxide in Atlanta using a smaller spatial domain.

Although we did not investigate a specific biological mechanism, there are plausible reasons why children born premature could suffer increased susceptibility to air pollutants throughout childhood. Structurally, the human lung is not fully developed until age 2 or 3 years, and lung growth continues throughout adolescence. Experimental studies have shown that fetal sheep subjected to intrauterine growth restriction have impaired alveolarization, thicker interalveolar septa, and a thicker blood-air barrier.[24,25] Exposures during gestation and early postnatal life can result in long-term epigenetic changes,[4,5,26] and several epidemiologic studies have shown decrements in adult lung function associated with low birth weight (a common comorbidity for children born preterm).[27–29] We also observed effect-measure modification by maternal race. In a small number of previous studies, investigators found evidence that associations between short-term changes in ambient air pollutant concentrations and asthma exacerbations were higher for African Americans[30,31] and for children who had markers of low socioeconomic status.[13,32] Although race might be considered a proxy for socioeconomic status, in our study we did not observe effect-measure modification by Medicaid or maternal education, both of which would appear to be more direct measures of socioeconomic status than race. Whereas investigators in the previously referenced studies[13,30–32] had data on race or socioeconomic status (but not both), we were able to estimate effect modification by race and socioeconomic status in the same population, which is a contribution of our study. Further evidence supporting effect modification by race comes from 2 controlled ozone exposure studies in which African American men exhibited greater decrements in lung function following exposure than either white men or African American women.[33,34] Although the mechanisms underlying these observed differences have not been fully elaborated, several genetic factors have been investigated,[35] and some factors reported to affect susceptibility to ozone (such as

micronutrient deficiencies[36] and elevated body mass index)[37] may be more prevalent in African American populations. Further research is needed to clarify how race may affect susceptibility.

All the factors we investigated as potential effect-measure modifiers are associated with asthma. Further, many are common, and so any elevation in susceptibility associated with these factors would be meaningful from a public health standpoint. Although additional research is needed to investigate whether the effect-measure modification we observed is present in other settings, broadly speaking our results support the hypothesis that susceptibility to ambient air pollutant concentrations varies among children, and that premature children and children born to African American mothers are at higher risk.

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