Short-term Associations between Ambient Air Pollutants and Pediatric Asthma Emergency Department Visits

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Rationale: **Certain outdoor air pollutants cause asthma exacerbations in children. To advance understanding of these relationships, further characterization of the dose–response and pollutant lag effects are needed, as are investigations of pollutant species beyond the commonly measured criteria pollutants.**

Objectives: **Investigate short-term associations between ambient air pollutant concentrations and emergency department visits for pediatric asthma.**

Methods: **Daily counts of emergency department visits for asthma or wheeze among children aged 5 to 17 years were collected from 41 Metropolitan Atlanta hospitals during 1993–2004 (n = 91,386 visits). Ambient concentrations of gaseous pollutants and speciated particulate matter were available from stationary monitors during this time period. Rate ratios for the warm season (May to October) and cold season (November to April) were estimated using Poisson generalized linear models in the framework of a case-crossover analysis.**

Measurements and Main Results: **Both ozone and primary pollutants from traffic sources were associated with emergency department visits for asthma or wheeze; evidence for independent effects of ozone and primary pollutants from traffic sources were observed in multipollutant models. These associations tended to be of the highest magnitude for concentrations on the day of the emergency department visit and were present at relatively low ambient concentrations.**

Conclusions: **Even at relatively low ambient concentrations, ozone and primary pollutants from traffic sources independently contributed to the burden of emergency department visits for pediatric asthma.**

Keywords: ambient particulate matter; asthma; minors; ozone

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Certain outdoor air pollutants can trigger asthma exacerbations. To advance understanding of the relationships between ambient air pollutant concentrations and asthma exacerbations among children, further characterization of the dose–response and pollutant lag effects are needed as are investigations of pollutant species beyond the commonly measured criteria pollutants.

What This Study Adds to the Field

In our large, population-based study we observed that both ozone and primary pollutants from traffic sources independently contributed to the burden of emergency department visits for pediatric asthma. These associations tended to be of the highest magnitude for concentrations on the day of the emergency department visit and were present at relatively low ambient concentrations.

A broad literature supports associations between ambient air pollutant concentrations and asthma exacerbations (1–3). Children are thought to be particularly susceptible to ambient air pollutants, because their lungs and immune systems are not fully developed, they breathe more air per unit body weight and are typically more active than adults, and their peripheral airways are anatomically smaller than adults so that inflammation results in proportionally greater airway obstruction (4–6). To help advance understanding of the relationships between ambient air pollutant concentrations and asthma exacerbations in children, further characterization of the dose–response and pollutant lag effects are needed, as are investigations of pollutant species beyond the commonly measured urban air pollutants (3, 7). Further investigation of pollutant mixtures and effect modification may also provide insights (8, 9); for example, there have been reports of stronger pollution effects during the warm season (10–15) even though pediatric asthma rates peak during the cold season (16). To lessen concerns about uncontrolled confounding, aggressive control for variables, such as meteorology and seasonal asthma trends, is required.

In the present study, we analyzed data from the Study of Particles and Health in Atlanta (SOPHIA) (14, 17–21), one of the largest single-city time-series studies of the health effects of urban air pollutants, to investigate short-term associations between ambient air pollutant concentrations and pediatric emergency department visits for asthma or wheeze in metropolitan Atlanta, Georgia, during 1993–2004. Our study takes advantage of daily measurements of components of particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), a resource not typically available to investigators, which enables us to distinguish among the various compounds that comprise $PM_{2.5}$. We investigated effect modification by season and potential confounding by ambient pollen concentrations and upper respiratory infections, because it is well known that these factors can trigger asthma exacerbations (9). The extent to which ambient pollen concentrations and circulating respiratory viruses confound associations between air pollutant concentrations and asthma exacerbations depends on the nature of the associations between short-term

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changes in these risk factors and changes in air pollutant concentrations. We also present several characterizations of dose–response relationships, descriptions of pollution lag effects, and results from multipollutant models and models of pollutant interactions. Some of the results from this study have been previously reported in the form of an abstract (22).

METHODS

We obtained data on emergency department visits from metropolitan Atlanta hospitals during 1993–2004 (18). Using the International Classification of Diseases, 9th Revision, we defined emergency department visits for pediatric asthma as all visits with a code for asthma (493.0–493.9) or wheeze (786.09 before October 1, 1998; 786.07 after October 1, 1998) that did not have a code for an external injury or poisoning (E800–E999) among children aged 5 to 17 years (n = 91,386). We also identified emergency department visits for acute respiratory infections (codes 460.0–466.0) that did not have a code for asthma or wheeze among children aged 5 to 17 years (n = 154,300).

Daily concentrations of ambient 1-hour maximum carbon monoxide, nitrogen dioxide, and sulfur dioxide; 8-hour maximum ozone; and 24-hour average particulate matter less than 10 μm in diameter (PM_{10}), coarse particles between 2.5 and 10 μm in diameter ($PM_{10–2.5}$), $PM_{2.5}$, and the $PM_{2.5}$ components sulfate, elemental carbon, organic carbon, and water-soluble metals (comprised of water-soluble chromium, copper, iron, manganese, nickel, and vanadium) were obtained from several networks of ambient monitors (14, 21, 23). These pollutants reflect many of the predominant sources of air pollution in Atlanta (24, 25). Daily measurements of $PM_{10–2.5}$, $PM_{2.5}$, and the $PM_{2.5}$ components began in August 1998. We used population-weighting to combine daily pollutant measurements across monitors (26). Daily ambient airborne pollen concentrations were obtained from the Atlanta Allergy and Asthma Clinic.

In the framework of a case-crossover analysis, associations between ambient air pollutant concentrations and pediatric asthma emergency department visits were estimated by Poisson generalized linear models that accounted for overdispersion (27). The dependent variable was the hospital-specific daily count of pediatric asthma visits. In most analyses, the 3-day moving average pollutant concentration (the average of concentrations today [lag 0], yesterday [lag 1], and 2 days ago [lag 2]) was modeled linearly (14). To further describe associations we examined the 3-day moving average using quintiles; the 3-day moving average using a loess smoother (from a generalized additive model) (28, 29); and the 8-day moving average concentration (lags 0–7) constrained using a third-degree polynomial (30). For all analyses we created separate warm season (May through October) and cold season (November through April) models. All models included a cubic polynomial for day-of-season, the moving average of dew point (lags 0–2), and the moving average of minimum temperature (lags 1 and 2); indicator variables for year, month, day of week, hospital, and lag 0 maximum temperature (for each degree of Celsius); and interactions between month and year, month and lag 0 maximum temperature, and month and day of week. Additional terms for dew point and minimum temperature were included in distributed lag models to coincide with the pollutant averaging period. We investigated confounding by upper respiratory infections (the logarithm of the daily count of upper respiratory infections) and pollen concentrations (various lags of ambient ragweed, pine, oak, juniper, grass, and birch concentrations) by assessing whether their inclusion changed the pollutant regression coefficient estimates. We examined the sensitivity of our results to alternative model specifications and evaluated model misspecification by estimating associations with pollutant concentrations on the day after the emergency department visit. The sensitivity analyses include results from time-series models, which are based on models analogous to those we presented in earlier publications (14, 18, 20, 31); "traditional" case-crossover models that include the three-way interactions between year, month, and day-of-week; traditional case-crossover models with bimonthly (rather than monthly) time windows to further account for temporal trends; and our primary analytic approach without control for the daily count of emergency department visits for (nonasthma) respiratory infections. Generalized additive models were implemented using R 2.8.1 (Vienna, Austria); all other analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Mean counts of emergency department visits for asthma or wheeze among children aged 5 to 17 years were 18.9 per day during the warm season (May through October) and 22.8 per day during the cold season (November through April). The seasonal difference in upper respiratory infections was more pronounced, with mean counts of 21.5 per day during the warm season and 34.6 per day during the cold season. Descriptive statistics for ambient air pollutant concentrations and maximum temperature are shown in Table 1. All pollutants had some seasonal variability, although the mean concentrations of nitrogen dioxide, carbon monoxide, and $PM_{2.5}$ elemental carbon (all markers of pollution from combustion engines) were similar between the warm and cold season.

TABLE 1. DESCRIPTIONS (MEAN, STANDARD DEVIATION, INTERQUARTILE RANGE, PERCENT MISSING AND NUMBER OF MONITORS) OF POPULATION-WEIGHTED AMBIENT AIR POLLUTANT CONCENTRATIONS AND MAXIMUM TEMPERATURE*

	Overall (Jan–Dec) Mean ± SD	Warm Season (May–Oct) Mean ± SD	Cold Season (Nov–Apr) Mean ± SD	IQR	Percent Missing	Number of Monitors
8-h ozone, ppb†	45.4 ± 20.0	55.2 ± 19.2	34.5 ± 14.6	29.2	4	5
1-h nitrogen dioxide, ppb†	23.3 ± 9.7	22.0 ± 9.4	24.5 ± 9.8	12.9	<1	6
1-h carbon monoxide, ppm†	0.9 ± 0.5	0.9 ± 0.4	1.0 ± 0.6	0.6	5	4
1-h sulfur dioxide, ppb†	10.8 ± 9.5	9.6 ± 8.7	12.0 ± 10.2	11.5	0	5
24-h PM_{10}, μg/m³‡	23.8 ± 11.5	27.6 ± 11.6	20.0 ± 10.0	14.6	1	9
24-h $PM_{10–2.5}$, μg/m³§	9.0 ± 5.0	9.7 ± 4.7	8.3 ± 5.3	5.9	7	1
24-h $PM_{2.5}$, μg/m³§	16.4 ± 7.4	18.4 ± 7.6	14.3 ± 6.5	9.2	<1	11
24-h $PM_{2.5}$ sulfate, μg/m³§	4.6 ± 3.1	5.9 ± 3.5	3.2 ± 1.8	3.5	1	6
24-h $PM_{2.5}$ elemental carbon, μg/m³§	0.9 ± 0.6	0.8 ± 0.6	0.9 ± 0.6	0.7	<1	6
24-h $PM_{2.5}$ organic carbon, μg/m³§	4.9 ± 3.4	4.8 ± 2.7	5.0 ± 4.0	3.4	<1	6
24-h $PM_{2.5}$ water-soluble metals, μg/m³§	0.030 ± 0.023	0.039 ± 0.025	0.020 ± 0.016	0.025	9	1
Maximum temperature, °C	22.4 ± 8.4	28.5 ± 4.6	16.1 ± 6.6	13	0	1

Definition of abbreviations: IQR = interquartile range; PM = particulate matter less than 10, 2.5, or 10–2.5 μm in aerodynamic diameter.

* Because the means presented are population-weighted spatial averages, they may differ from the means of concentrations measured at urban central site monitors. For comparison, the mean central site concentrations were as follows: ozone, 47.3 ppb; nitrogen dioxide, 43.2 ppb; carbon monoxide, 1.6 ppm; sulfur dioxide, 15 ppb; PM_{10}, 26.6 μg/m³; $PM_{10–2.5}$, 9 μg/m³; $PM_{2.5}$, 17.1 μg/m³; $PM_{2.5}$ sulfate, 4.9 μg/m³; $PM_{2.5}$ elemental carbon, 1.6 μg/m³; $PM_{2.5}$ organic carbon, 4.4 μg/m³; $PM_{2.5}$ water soluble metals, 0.030 μg/m³.

† Measurements available during January 1, 1993 to December 31, 2004 (n = 4,383). Ozone was not measured December 1994 to February 1995 and December 1995 to February 1996.

‡ Measurements available during January 1, 1996, to December 31, 2004 (n = 3,288).

§ Measurements available during August 1, 1998, to December 31, 2004 (n = 2,345).

Rate ratio estimates for associations between ambient air pollutant concentrations and pediatric asthma emergency department visits were similar regardless of whether pollen concentrations were included in the model as covariates; we examined various lags of pollen concentrations both continuously and using indicator variables for the top 5 and 10% of days. Therefore, covariates for pollen were not included in our final regression models. Results from our primary analysis, with pollutant concentrations characterized as 3-day moving averages and rate ratios corresponding to interquartile range changes in pollutant concentrations, are presented in Table 2. Models for 11 pollutants were created for each season, and we observed 10 significant positive associations ($P < 0.05$) during the warm season and 1 during the cold season. Further examination of dose–response relationships included season-specific rate ratios for pollutant concentration quintiles, presented in Table 3, and loess dose–response curves for the 10 significant warm season associations from Table 2, which are presented in Figure 1. Ozone was strongly associated with emergency department visits for pediatric asthma during the summer; the cold season ozone association was elevated but not significant. Within the cold season, we observed evidence for an effect during the more temperate months (November, March, and April) and no evidence for an effect during the coldest 3 months (December, January, and February) (*see* footnote in Table 2). As shown by both the quintile analysis and the loess dose–response curves, evidence for a dose–response relationship with ozone was present at concentrations as low as 30 parts per billion. Several markers of pollution from combustion engines (carbon monoxide, nitrogen dioxide, $PM_{2.5}$ elemental carbon, and $PM_{2.5}$ water-soluble metals) were associated with emergency department visits for pediatric asthma during the warm season, as were sulfur dioxide, PM_{10}, $PM_{2.5}$, and $PM_{2.5}$ sulfate (a secondary pollutant derived largely from coal burning). $PM_{10-2.5}$ was associated with pediatric asthma emergency department visits during the cold season; the lower bound confidence interval for the $PM_{10-2.5}$ association was very close to 1.0, although the point estimates for $PM_{10-2.5}$ were elevated during both seasons.

Figure 2 displays rate ratio estimates for day-specific lags (lags 0–7) for associations between ambient air pollutant concentrations and pediatric asthma emergency department visits for the 10 significant warm season associations from Table 2. The rate ratio and confidence interval summarizing the overall 8-day association are also presented for each pollutant. For 7 of the 10 associations, the lag-specific rate ratio of the highest magnitude was lag 0 (the pollutant concentration on the day of the emergency department visit). For the other three associations (PM_{10}, $PM_{2.5}$ elemental carbon, and $PM_{2.5}$ water-soluble metals), the lag-specific rate ratios were more uniformly distributed over the 8-day period. For all pollutants the confidence intervals are widest at lag 0, because the shape of the dose–response was constrained to follow a cubic polynomial (over lags 0–13), and the uncertainty of the estimates is greatest at the boundaries.

We created multipollutant models, including several two-pollutant models that paired ozone with another pollutant representing a particular source. A table of partial correlations between the various pollutants is available in the online data supplement. Warm season two-pollutant models are presented in Figure 3. The association between ozone and asthma emergency department visits observed in the single-pollutant models persisted across the various two-pollutant models, and although the point estimates were attenuated, we observed evidence for an effect of primary traffic pollutants on asthma exacerbations independent of the effect of ozone. Carbon monoxide showed the strongest association of the three markers of pollution from traffic sources examined in two-pollutant models. Although significant associations were observed with warm season $PM_{2.5}$ sulfate and cold season $PM_{10-2.5}$ in single-pollutant models, these associations were not present in the two-pollutant models. We also explored two-pollutant models that allowed for interactions between ozone and each of the other pollutants; however, we did not observe evidence suggesting interaction in these models (results not shown).

We included the logarithm of the daily count of upper respiratory infections as an additional covariate in all of our models. As presented in Table 4, inclusion of this covariate tended to attenuate the estimated rate ratios, particularly during the warm season. Results from several alternative statistical models are also presented in Table 4. Broadly, these models

TABLE 2. RATE RATIOS AND 95% CONFIDENCE INTERVALS FROM POISSON GENERALIZED LINEAR MODELS FOR INTERQUARTILE RANGE INCREASES IN THREE-DAY MOVING AVERAGE POPULATION-WEIGHTED AMBIENT AIR POLLUTANT CONCENTRATIONS*

	Overall RR (95% CI) (Jan–Dec)	Warm Season RR (95% CI) (May–Oct)	Cold Season RR (95% CI) (Nov–Apr)
Ozone[†‡]	**1.062 (1.031–1.093)**	**1.082 (1.043–1.123)**	1.044 (0.992–1.098)
Nitrogen dioxide[†]	**1.036 (1.018–1.055)**	**1.066 (1.038–1.095)**	1.016 (0.992–1.040)
Carbon monoxide[†]	**1.023 (1.006–1.041)**	**1.068 (1.034–1.102)**	1.005 (0.985–1.025)
Sulfur dioxide[†]	1.012 (0.994–1.030)	**1.030 (1.002–1.058)**	1.001 (0.978–1.025)
PM_{10}[§]	**1.020 (1.003–1.038)**	**1.026 (1.001–1.051)**	1.018 (0.994–1.043)
$PM_{10-2.5}$[‖]	**1.034 (1.011–1.057)**	1.025 (0.991–1.059)	**1.041 (1.010–1.073)**
$PM_{2.5}$[‖]	**1.020 (1.002–1.039)**	**1.043 (1.016–1.070)**	1.005 (0.978–1.031)
$PM_{2.5}$ sulfate[‖]	1.014 (0.995–1.033)	**1.027 (1.004–1.049)**	0.991 (0.953–1.029)
$PM_{2.5}$ elemental carbon[‖]	1.015 (0.997–1.033)	**1.041 (1.010–1.072)**	1.003 (0.981–1.026)
$PM_{2.5}$ organic carbon[‖]	1.008 (0.994–1.021)	**1.034 (1.007–1.062)**	1.000 (0.985–1.016)
$PM_{2.5}$ water-soluble metals[‖]	**1.021 (1.000–1.042)**	**1.029 (1.003–1.055)**	1.005 (0.968–1.043)

Definition of abbreviations: CI = confidence interval; PM = particulate matter less than 10, 2.5, or 10–2.5 μm in aerodynamic diameter; RR = rate ratio.

Bold typeface indicates confidence intervals that do not include the null value.

* *See* interquartile ranges presented in Table 1.

† Measurements available January 1993 to December 2004.

‡ When the cold season was divided into the more temperate months (March, April, November) versus the coldest months (December, January, February) we observed rate ratios of 1.107 (1.035–1.184) for November-March-April and 0.968 (0.895–1.047) for December-January-February.

§ Measurements available January 1996 to December 2004.

‖ Measurements available August 1998 to December 2004.

TABLE 3. RATE RATIOS AND 95% CONFIDENCE INTERVALS FOR QUINTILES OF THREE-DAY MOVING AVERAGE POPULATION-WEIGHTED AMBIENT AIR POLLUTANT CONCENTRATIONS

	Warm Season RR (95% CI)*	Cold Season RR (95% CI)*
Ozone, ppb†		
Q2 (26.3 to <38.7)	1.002 (0.953–1.054)	1.039 (0.998–1.081)
Q3 (38.7 to <51.5)	1.016 (0.961–1.074)	**1.097 (1.037–1.161)**
Q4 (51.5 to <67)	1.061 (0.999–1.127)	**1.151 (1.065–1.243)**
Q5 (67 to ≤147.5)	**1.111 (1.038–1.189)**	**1.150 (1.013–1.306)**
Nitrogen dioxide, ppb†		
Q2 (28 to <37.1)	1.033 (0.999–1.069)	0.996 (0.964–1.030)
Q3 (37.1 to <46)	**1.040 (1.000–1.081)**	0.984 (0.950–1.020)
Q4 (46 to <57.1)	**1.087 (1.044–1.131)**	1.024 (0.985–1.064)
Q5 (57.1 to ≤181)	**1.087 (1.036–1.140)**	1.014 (0.973–1.056)
Carbon monoxide, ppm†		
Q2 (0.70 to <1.01)	1.019 (0.986–1.054)	1.010 (0.977–1.045)
Q3 (1.01 to <1.05)	**1.046 (1.008–1.086)**	**1.040 (1.005–1.076)**
Q4 (1.05 to <2.30)	**1.097 (1.049–1.147)**	1.005 (0.969–1.042)
Q5 (2.30 to ≤7.70)	**1.112 (1.054–1.174)**	1.021 (0.981–1.064)
Sulfur dioxide, ppb†		
Q2 (3.1 to <7)	1.021 (0.988–1.055)	0.968 (0.935–1.002)
Q3 (7 to <13)	**1.041 (1.007–1.077)**	0.998 (0.964–1.034)
Q4 (13 to <24.2)	**1.048 (1.010–1.087)**	0.982 (0.947–1.017)
Q5 (24.2 to ≤149)	1.008 (0.967–1.051)	0.987 (0.949–1.026)
PM_{10} ($\mu g/m^3$)‡		
Q2 (16 to <21.9)	1.014 (0.968–1.061)	1.008 (0.978–1.038)
Q3 (21.9 to <28	1.029 (0.981–1.080)	0.996 (0.963–1.030)
Q4 (28 to <36)	1.027 (0.979–1.078)	1.017 (0.977–1.059)
Q5 (36 to ≤98.4)	**1.059 (1.006–1.116)**	1.047 (0.991–1.106)
$PM_{10-2.5}$ ($\mu g/m^3$)§		
Q2 (5 to <7.1)	0.975 (0.924–1.028)	0.972 (0.930–1.012)
Q3 (7.1 to <9.3)	0.986 (0.934–1.040)	1.006 (0.960–1.054)
Q4 (9.3 to <12.3)	0.964 (0.909–1.022)	1.045 (0.996–1.097)
Q5 (12.3 to ≤50.4)	1.005 (0.942–1.072)	**1.075 (1.015–1.139)**
$PM_{2.5}$ ($\mu g/m^3$)§		
Q2 (10 to <13.7)	0.993 (0.943–1.047)	0.985 (0.952–1.019)
Q3 (13.7 to <17.6)	1.008 (0.956–1.062)	0.979 (0.943–1.017)
Q4 (17.6 to <23.8)	1.018 (0.966–1.073)	1.006 (0.960–1.049)
Q5 (23.8 to ≤65.8)	1.052 (0.995–1.112)	1.050 (0.997–1.106)
$PM_{2.5}$ sulfate ($\mu g/m^3$)§		
Q2 (2.2 to <3.3)	1.032 (0.951–1.120)	0.987 (0.950–1.025)
Q3 (3.3 to <4.6)	1.048 (0.968–1.135)	1.045 (0.998–1.094)
Q4 (4.6 to <7.2)	1.061 (0.978–1.150)	1.008 (0.944–1.077)
Q5 (7.2 to ≤21.9)	1.082 (0.995–1.177)	1.027 (0.931–1.133)
$PM_{2.5}$ elemental carbon ($\mu g/m^3$)§		
Q2 (0.78 to <1.13)	0.981 (0.936–1.028)	1.034 (0.994–1.076)
Q3 (1.13 to <1.55)	1.023 (0.977–1.071)	1.027 (0.984–1.072)
Q4 (1.55 to <2.25)	**1.050 (1.004–1.107)**	1.014 (0.971–1.058)
Q5 (2.25 to ≤11.89)	**1.056 (1.000–1.115)**	1.039 (0.990–1.091)
$PM_{2.5}$ organic carbon ($\mu g/m^3$)§		
Q2 (2.54 to <3.41)	1.024 (0.976–1.073)	0.983 (0.942–1.025)
Q3 (3.41 to <4.32)	**1.070 (1.020–1.122)**	1.028 (0.983–1.075)
Q4 (4.32 to <5.82)	**1.078 (1.024–1.135)**	0.993 (0.950–1.038)
Q5 (5.82 to ≤25.93)	**1.065 (1.006–1.128)**	1.017 (0.972–1.063)
$PM_{2.5}$ water-soluble metals ($\mu g/m^3$)§		
Q2 (0.0123 to <0.0195)	1.026 (0.946–1.112)	0.992 (0.953–1.032)
Q3 (0.0195 to <0.0276)	1.081 (0.999–1.170)	1.004 (0.958–1.053)
Q4 (0.0276 to <0.0436)	**1.113 (1.026–1.206)**	1.036 (0.978–1.096)
Q5 (0.0436 to ≤0.202)	**1.119 (1.028–1.218)**	1.009 (0.934–1.090)

Definition of abbreviations: CI = confidence interval; PM = particulate matter less than 10, 2.5, or 10–2.5 μm in aerodynamic diameter; RR = rate ratio.

Bold typeface indicates confidence intervals that do not include the null value.

* Relative to the first quintile (concentrations less than the lower bound of the second quintile).

† Measurements available January 1993 to December 2004.

‡ Measurements available August 1998 to December 2004.

§ Measurements available August 1998 to December 2004.

supported the conclusions from our primary single-pollutant models. Asthma emergency department visits were associated with ambient ozone concentrations and with several traffic-related primary pollutants and $PM_{2.5}$ sulfate concentrations during the warm season and with $PM_{10-2.5}$ during the cold season. Table 4 also presents associations between lag -1 (tomorrow's) pollutant concentrations and pediatric asthma emergency department visits for the primary model (controlling for the 3-day average concentration on lags 0, 1, and 2). We used these estimates, which were generally compatible with the null, as a diagnostic tool to assess model misspecification; a well-specified model should have a rate ratio estimate close to the null value for the lag -1 pollutant concentration.

DISCUSSION

In our large study we analyzed over 90,000 emergency department visits for pediatric asthma in relation to ambient air pollutant concentrations. We controlled tightly for meteorology and seasonal asthma trends, and we observed several positive, statistically significant associations between ambient air pollutant concentrations and the rate of pediatric asthma emergency department visits in Atlanta. Ozone was associated with emergency department visits for asthma during the warm season and during the temperate cold season months (November, March, and April). We also observed associations with several traffic-related primary pollutants during the warm season. These pollutants have been found to cause asthma exacerbations and airway inflammation in observational and experimental studies (32–36); as supported by both the quintile analysis and the smooth estimates of dose–response, we observed evidence that associations were present at relatively low ambient concentrations. Further, results from two-pollutant models support the conclusion that ambient concentrations of both ozone and traffic-related primary pollutants independently contribute to the burden of asthma exacerbations. Among the three markers of primary traffic pollution that we investigated in two-pollutant models, the rate ratio of the highest magnitude was for carbon monoxide. Because levels of carbon monoxide present in ambient air do not pose appreciable health risks, carbon monoxide concentrations are likely a surrogate for other pollutants emitted from combustion sources more plausibly linked to asthma. Estimates from distributed lag models suggested there were both immediate and lagged effects for these pollutants, with the association of highest magnitude tending to occur on the day of the emergency department visit.

We also observed associations with 3-day moving average concentrations of warm season sulfur dioxide, warm season $PM_{2.5}$ sulfate, warm season $PM_{2.5}$ organic carbon, and cold season coarse particles ($PM_{10-2.5}$). None of these warm season results were significant in two-pollutant models that also contained 3-day moving average ozone concentrations; however, many of the lag-specific point estimates (from the distributed lag models) were positive at lag 3 and longer, thereby raising the possibility that some pollutants might have shown effects had we created multipollutant models that spanned longer lag periods. We are particularly suspicious of the sulfur dioxide result, because local plume touchdowns strongly impact measured sulfur dioxide concentrations, and consequently it is challenging to develop a daily sulfur dioxide metric that could be considered representative of the urban airshed based on measurements from only five monitoring stations. Further, in previous epidemiologic and experimental studies, ambient concentrations of sulfur dioxide and $PM_{2.5}$ sulfate have not been consistently associated with impaired pediatric respiratory function (6, 37, 38). Respiratory function decline and increased

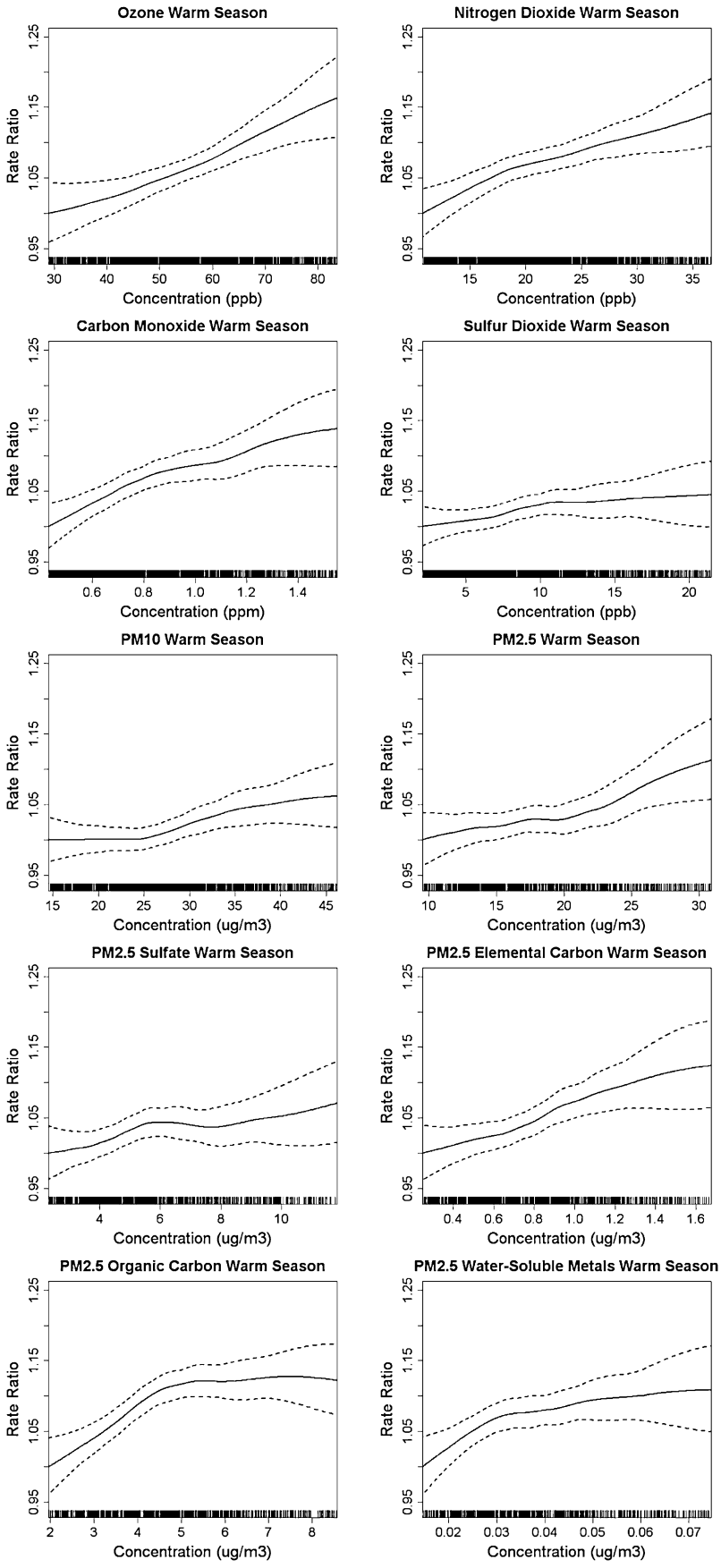

Figure 1. Loess dose–response estimates (*solid line*) and twice-standard error estimates (*dashed lines*) from generalized additive models for associations between 3-day moving average air pollutant concentrations and emergency department visits for pediatric asthma. The reference (denominator) for the rate ratio is the estimated rate at the 5th percentile of the pollutant concentration. Estimates are only presented for the 5th percentile through the 95th percentile of pollutant concentrations because of instability in the dose–response estimates at the distribution tails.

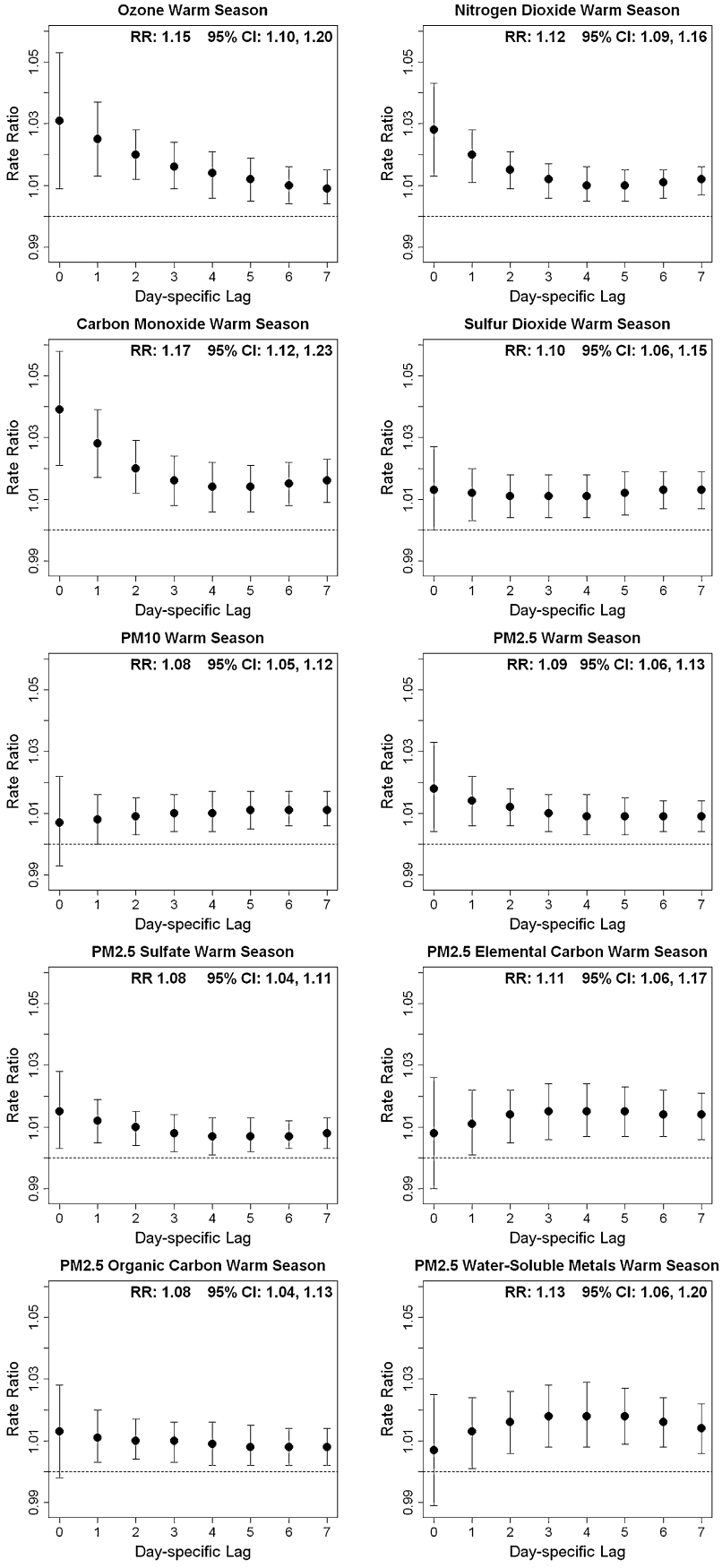

Figure 2. Constrained cubic polynomial distributed lag models. The rate ratio and 95% confidence interval displayed for each pollutant correspond to an interquartile range increase in the cumulative ambient pollutant concentration during the 8-day period of interest (lags 0–7). Point estimates and 95% confidence intervals are also presented graphically for the lag-specific rate ratios. To enhance the stability of the distributed lag estimates, the cubic polynomial was fit to lags 0–13; however, the rate ratios and 95% confidence intervals presented in the Figure correspond to the effects of lags 0–7 only.

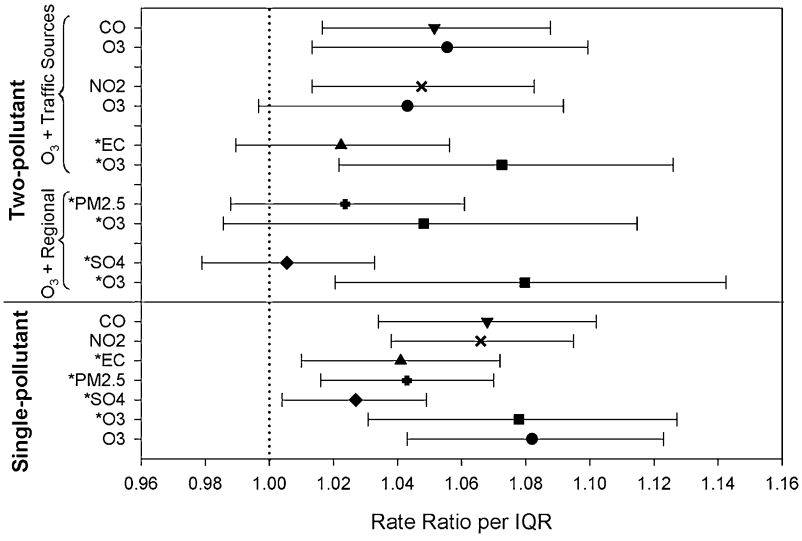

Figure 3. Warm season rate ratios and 95% confidence intervals for interquartile range increases in 3-day moving average ambient air pollutant concentrations for single-pollutant and two-pollutant models. CO = carbon monoxide; EC = $PM_{2.5}$ elemental carbon; NO2 = nitrogen dioxide; O3 = ozone; $PM_{2.5}$ = particulate matter less than 2.5 μm in aerodynamic diameter; SO4 = $PM_{2.5}$ sulfate. *Time period limited to August 1, 1998, to December 31, 2004.

risks of asthma exacerbation associated with ambient $PM_{10-2.5}$ and $PM_{2.5}$ organic carbon concentrations have been reported in previous studies (39–42), although there have been relatively few investigations of these pollutants compared with the body of work on PM_{10} and $PM_{2.5}$. Both $PM_{10-2.5}$ and $PM_{2.5}$ organic carbon are comprised of several different compounds, with $PM_{10-2.5}$ concentrations in Atlanta being largely comprised of metal oxides and crustal material (43), and $PM_{2.5}$ organic carbon consisting of mixture of compounds of both primary and secondary origin (26, 44, 45).

TABLE 4. SENSITIVITY ANALYSES: RATE RATIOS AND 95% CONFIDENCE INTERVALS FOR INTERQUARTILE RANGE INCREASES IN THREE-DAY MOVING AVERAGE POPULATION-WEIGHTED AMBIENT AIR POLLUTANT CONCENTRATIONS

			Alternative Model Specifications			
	Base Model* RR (95% CI)	No URI Control† RR (95% CI)	Time-series‡ RR (95% CI)	Case-crossover§ RR (95% CI)	Bi-monthly windows‖ RR (95% CI)	Lag -1 Pollution¶ RR (95% CI)
Warm season (May–October)						
Ozone	**1.082 (1.043–1.123)**	**1.106 (1.066–1.147)**	**1.071 (1.025–1.119)**	**1.092 (1.049–1.137)**	**1.058 (1.014–1.104)**	1.015 (0.991–1.039)
Nitrogen dioxide	**1.066 (1.038–1.095)**	**1.073 (1.045–1.102)**	**1.058 (1.028–1.088)**	**1.096 (1.065–1.127)**	**1.065 (1.034–1.098)**	1.000 (0.981–1.019)
Carbon monoxide	**1.068 (1.034–1.102)**	**1.073 (1.039–1.107)**	**1.062 (1.030–1.096)**	**1.090 (1.054–1.127)**	**1.053 (1.016–1.092)**	1.009 (0.988–1.031)
Sulfur dioxide	**1.030 (1.002–1.058)**	**1.033 (1.006–1.062)**	1.021 (0.992–1.051)	1.009 (0.981–1.039)	1.014 (0.984–1.046)	1.007 (0.990–1.025)
PM_{10}	**1.026 (1.001–1.051)**	**1.043 (1.018–1.068)**	**1.031 (1.005–1.058)**	**1.057 (1.030–1.085)**	1.022 (0.994–1.050)	**1.024 (1.005–1.043)**
$PM_{10-2.5}$	1.025 (0.991–1.059)	1.032 (0.998–1.067)	1.028 (0.992–1.065)	**1.062 (1.026–1.099)**	0.984 (0.945–1.024)	1.004 (0.983–1.025)
$PM_{2.5}$	**1.043 (1.016–1.070)**	**1.060 (1.033–1.088)**	**1.041 (1.012–1.071)**	**1.043 (1.015–1.072)**	1.015 (0.984–1.046)	**1.024 (1.004–1.045)**
$PM_{2.5}$ sulfate	**1.027 (1.004–1.049)**	**1.040 (1.017–1.063)**	**1.025 (1.002–1.048)**	**1.024 (1.000–1.047)**	1.003 (0.977–1.029)	**1.017 (1.001–1.034)**
$PM_{2.5}$ elemental carbon	**1.041 (1.010–1.072)**	**1.051 (1.020–1.083)**	**1.032 (1.000–1.065)**	**1.057 (1.024–1.090)**	1.036 (0.984–1.091)	1.000 (0.979–1.020)
$PM_{2.5}$ organic carbon	**1.034 (1.007–1.062)**	**1.047 (1.020–1.075)**	**1.036 (1.005–1.067)**	**1.050 (1.021–1.079)**	1.019 (0.987–1.052)	1.000 (0.982–1.018)
$PM_{2.5}$ water-soluble metals	**1.029 (1.003–1.055)**	**1.039 (1.013–1.065)**	1.021 (0.996–1.047)	**1.030 (1.004–1.057)**	1.015 (0.986–1.045)	0.992 (0.976–1.009)
Cold season (November–April)						
Ozone	1.044 (0.992–1.098)	**1.062 (1.010–1.118)**	1.013 (0.953–1.077)	1.053 (0.996–1.113)	1.019 (0.961–1.080)	1.004 (0.973–1.036)
Nitrogen dioxide	1.016 (0.992–1.040)	**1.023 (1.000–1.048)**	1.007 (0.982–1.033)	1.020 (0.994–1.047)	1.022 (0.995–1.050)	0.999 (0.983–1.014)
Carbon monoxide	1.005 (0.985–1.025)	1.017 (0.997–1.037)	1.002 (0.982–1.023)	1.003 (0.981–1.025)	1.005 (0.982–1.028)	0.999 (0.986–1.012)
Sulfur dioxide	1.001 (0.978–1.025)	1.000 (0.977–1.024)	1.009 (0.984–1.034)	0.999 (0.975–1.025)	1.014 (0.988–1.040)	1.003 (0.990–1.017)
PM_{10}	1.018 (0.994–1.043)	**1.026 (1.001–1.051)**	1.009 (0.983–1.035)	**1.033 (1.006–1.061)**	1.020 (0.992–1.049)	0.995 (0.976–1.014)
$PM_{10-2.5}$	**1.041 (1.010–1.073)**	**1.036 (1.006–1.068)**	1.018 (0.985–1.052)	**1.073 (1.041–1.107)**	**1.042 (1.004–1.080)**	1.001 (0.981–1.020)
$PM_{2.5}$	1.005 (0.978–1.031)	0.995 (0.969–1.022)	0.999 (0.971–1.028)	1.027 (0.998–1.056)	1.012 (0.982–1.044)	0.982 (0.961–1.003)
$PM_{2.5}$ sulfate	0.991 (0.953–1.029)	0.976 (0.939–1.014)	0.980 (0.941–1.022)	1.026 (0.983–1.070)	1.012 (0.968–1.059)	0.971 (0.943–1.000)
$PM_{2.5}$ elemental carbon	1.003 (0.981–1.026)	1.005 (0.983–1.028)	0.998 (0.974–1.022)	1.014 (0.992–1.037)	1.004 (0.979–1.030)	0.996 (0.981–1.012)
$PM_{2.5}$ organic carbon	1.000 (0.985–1.016)	0.999 (0.984–1.015)	0.998 (0.981–1.105)	1.007 (0.992–1.023)	1.002 (0.985–1.020)	0.994 (0.983–1.010)
$PM_{2.5}$ water-soluble metals	1.005 (0.968–1.043)	1.004 (0.967–1.043)	0.985 (0.949–1.023)	1.017 (0.978–1.058)	0.994 (0.949–1.042)	0.998 (0.974–1.023)

Definition of abbreviations: CI = confidence interval; PM = particulate matter less than 10, 2.5, or 10–2.5 μm in aerodynamic diameter; RR = rate ratio; URI = upper respiratory infections.

Bold typeface indicates confidence intervals that do not include the null value.

* The "base model" is the primary statistical model as described in the Methods section. The results in this column are reproduced from Table 2.

† Model is identical to the base model, except there is no control for pediatric emergency department visits for upper respiratory infections.

‡ Model is does not contain terms for year, month, month × year interactions, month × lag 0 maximum temperature interactions, and month × day-of-week interactions. Instead cubic splines with monthly knots are included to control for long-term and seasonal trends. Daily average temperature and dew point were modeled using cubic splines with knots at the 25th and 75th percentiles. These models are analogous to those presented in earlier publications (14, 18, 20, 31).

§ Model contains three-way interactions between year, month, and day-of-week and does not contain month × lag 0 maximum temperature interactions.

‖ Model is identical to the base model, except that bimonthly (twice-per-month) indicator variables are used instead of monthly indicator variables.

¶ Model is identical to the base model, save for the addition of tomorrow's (lag -1) pollutant concentration, which has been included in the model. The results in this column are the rate ratios estimated for the lag -1 term.

Our tendency to find stronger associations during the warm season is consistent with previous findings (10–15), and although we are unclear about the underlying mechanism for these apparent seasonal differences, it may simply be that during the warm season a greater proportion of asthma exacerbations are caused by air pollution. Rates of emergency department visits for pediatric asthma increase by 60% during the cold season; this increase is largely attributable to exacerbations triggered by viral infections. If the additive effect of air pollution is similar year round, then the attributable fraction (and, correspondingly, the rate ratio) will appear higher during the warm season because there are fewer competing causes of asthma exacerbations during the warm season. Alternatively, it may be that children actually respond more severely to air pollutants during warmer temperatures, perhaps because of some unidentified synergism between the pollutant and a meteorologic or physical factor. Additional contributions to the observed seasonal differences may include nonlinear dose–response functions (e.g., air pollutant concentrations typical during warmer months may be on a steeper part of the dose–response curve) and behavior differences that impact personal pollutant exposures. For example, during the summer children are more likely to play outside, which may lead to a higher correlation between measured ambient concentrations and personal exposures, and consequently result in higher estimated effects of ambient pollutants.

We relied on codes from hospital administrative databases to identify emergency department visits for pediatric asthma. Our definition was relatively broad and included codes for both asthma and wheeze among children aged 5 to 17 years. We excluded children younger than 5 years from our analysis because young children frequently experience transient wheeze, and asthma diagnoses may be suspect (46); however, even among children age 5 years and older, we observed significant hospital-to-hospital variability in the proportion of emergency visits coded as ''asthma'' as opposed to ''wheeze.'' Further, we observed variability in the coding of primary versus secondary diagnoses; for asthma, this typically occurred when a patient presented with both asthma symptoms and a respiratory infection. We conducted subanalyses limited to emergency department visits where asthma or wheeze was reported as the primary diagnosis and observed results similar to those from our primary analytic approach. Because comorbidities were not coded completely and consistently across hospitals, we deemed these data to be of inadequate quality to support analyses where individual visits were stratified according to the presence or absence of a respiratory infection as a comorbidity, even though at the aggregate level the daily count of emergency department visits for respiratory infections was likely an adequate surrogate for the actual burden of respiratory infections in Atlanta. We controlled for the daily count of upper respiratory visits in our statistical models and found it to be an extremely strong predictor of the rate of emergency department visits for pediatric asthma; further, we observed evidence of confounding by respiratory infections, because control for this covariate tended to attenuate the rate ratio estimates, particularly during the warm season.

Although we chose our primary statistical model carefully, all statistical models are misspecified to some degree. Therefore, we reported results from sensitivity analyses using alternative model specifications. Our primary model is based on the case-crossover design, with implementation by Poisson time-series models that account for overdispersion, given that under certain formulations these approaches are nearly identical (27, 47). Traditionally, investigators have implemented the case-crossover design by matching either on day-of-week (48, 49) or temperature (50) within a given month; matching on both day-of-week and temperature is typically not feasible, because data become sparse with too many matching factors. To implement a case-crossover approach in a time-series framework requires terms for the main effects of year, month, and the matching-factor (e.g., a term for each day-of-week); terms for the two-way interactions between year and month, year and day-of-week, and month and day-of-week; and terms for the three-way interactions between year, month, and day-of-week. In developing our primary analytic approach, we explored case-crossover models with matching on year, month, and either day-of-week or lag 0 maximum temperature; however, regardless of the approach, we observed evidence of confounding by within-month trends (e.g., the increasing trend in asthma exacerbations during late August and September because of the ''back-to-school'' effect) (51). To control smoothly for these within-month trends we included a cubic polynomial for day-of-season in the regression models. Given this cubic polynomial, inclusion of the three-way interaction terms no longer meaningfully changed the point estimates for the air pollutant effect. Therefore, we abandoned the three-way interactions (and thereby removed hundreds of parameters from the model) and instead implemented a case-crossover analysis by matching only on month and year. In addition to matching on these factors, we controlled tightly for both day-of-week and lag 0 maximum temperature; our base model included indicator variables for year, month, day-of-week, and lag 0 maximum temperature (for each degree of Celsius), and selected two-way interactions (between month and year; month and day-of-week; and month and lag 0 maximum temperature) that we found to be highly predictive of the pediatric asthma emergency department visit rates.

Although we controlled tightly for meteorology and temporal trends and used a case-only analytic approach, confounding by an unmeasured or inadequately modeled risk factor that varied in a systematic way with short-term fluctuations in ambient air pollutant concentrations could have biased our results. Whereas we cannot dismiss the possibility of confounding by an unmeasured factor, we did conduct extensive analyses to understand the relationships with meteorology, temporal trends, and ambient pollen concentrations in our data. Further, we investigated associations with the lag-1 pollutant concentration (the concentration on the day after the emergency department visit), while controlling for the average concentration on lags 0 to 2, as an approach to evaluate model misspecification (14, 52) because we know that tomorrow's pollutant concentrations are not causally related to today's count of emergency department visits, and any association not caused by chance must be biased.

Measurement error is inherent in all large epidemiologic studies of urban air pollution health effects. Although studies of personal exposures to air pollutants help to advance understanding of biologic responses, from a regulatory standpoint the ambient concentrations are of greatest relevance. One prominent component of error in our study is, therefore, how well the population-weighted spatial average of measurements from urban monitoring stations approximates the ambient concentration across the entire metropolitan Atlanta area. The extent of this measurement error likely varies by pollutant, with primary pollutants (e.g., those from traffic sources) tending to have more measurement error than secondary pollutants (e.g., ozone and $PM_{2.5}$ sulfate) (18, 53). Indeed, in previous work, we observed associations between emergency department visits for cardiovascular disease and spatially heterogeneous pollutants (carbon monoxide and nitrogen dioxide) using measurements from several different air pollution monitors located within 20 miles of the Atlanta population center; however, we did not observe associations when measurements were used from a rural monitor located 38 miles away. Conversely, we observed associations for

the spatially homogeneous pollutants (ozone and $PM_{2.5}$) regardless of whether the measurements were from the rural or urban monitors (18). Also contributing to the measurement error issue is the number of air pollutant monitoring stations, which ranged from only one central monitor (for $PM_{10-2.5}$ and $PM_{2.5}$ water-soluble metals) to 11 monitors (for $PM_{2.5}$). Interpretation of two-pollutant models is complicated by these measurement error issues; the pollutant with the stronger estimated effect (e.g., ozone in our analyses) may not be the more harmful pollutant but may instead be the pollutant that has less measurement error (20). This measurement error also impacts the statistical power to detect effects. In our study we did not find evidence of synergism between ozone and any of the other air pollutants, perhaps because of issues involving measurement error and statistical power.

The findings from our large, population-based time-series study in Atlanta complement previous findings from multicity studies (13, 54). Whereas multicity designs offer a statistically powerful approach for investigating the health effects of ambient air pollutants, large single-city studies provide the opportunity for investigators to better understand and account for the nuances of local data. Further, the SOPHIA study, which has amassed data on over 10,000,000 emergency department visits in metropolitan Atlanta since 1993, affords ample statistical power to detect subtle health effects of ambient air pollutants, including the health effects of $PM_{2.5}$ components. In our study we observed evidence that ambient concentrations of ozone and primary pollutants from traffic sources independently contributed to the burden of emergency department visits for pediatric asthma. Further, these associations were present at relatively low ambient concentrations, reinforcing the need for continued evaluation of the Environmental Protection Agency's National Ambient Air Quality Standards to ensure that the standards are sufficient to protect susceptible individuals.

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