HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2016 January 26.

Published in final edited form as:

Epidemiology. 2014 November ; 25(6): 843–850. doi:10.1097/EDE.0000000000000170.

Modification of the effect of ambient air pollution on pediatric asthma emergency visits: susceptible subpopulations

Matthew J Strickland[1], **Mitchel Klein**[1], **W Dana Flanders**[2], **Howard H Chang**[3], **James A Mulholland**[4], **Paige E Tolbert**[1], and **Lyndsey A Darrow**[2]

[1]Department of Environmental Health, Rollins School of Public Health, Emory University

[2]Department of Epidemiology, Rollins School of Public Health, Emory University

[3]Department of Biostatistics, Rollins School of Public Health, Emory University

[4]Department of Civil and Environmental Engineering, Georgia Institute of Technology

Abstract

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 aged 2–16 years 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 three-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 ration 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.

Corresponding author: Matthew J Strickland, 1518 Clifton Rd NE, Atlanta GA 30322, Phone: 404-712-8912, Fax: 404-727-8744.

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. Additionally, in metropolitan Atlanta there are several long-running air quality measurement campaigns that include, among other more commonly measured pollutants, daily measurements from four monitoring stations of speciated particulate matter less than 2.5 microns in diameter ($PM_{2.5}$). We used these two 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 dataset. Although we examined effect-measure modification for eight different factors, 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 2002–2010, 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 comprised of components of first and last name, date of birth, and child sex enabled linkage of records from the two datasets. 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 dataset) 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 one of the multiple births, to associate with the ED visit.

There were 2,369,760 ED visits among children aged 2–16 years 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 dataset 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 dataset according to information contained on either the birth record or the ED visit record: preterm birth (gestational age < 37 weeks) vs. full-term birth; term low birth weight (< 2500 grams among full-term births) vs. normal birth weight; Medicaid vs. other sources of payment for childbirth; African American vs. all other self-reported maternal races; maternal smoking vs. non-smoking; low maternal education (less than high school education) vs. higher maternal education; Cesarean vs. 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 three-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 eight factors described above, as well as a cubic spline on day of study with 8 degrees of freedom (d.f.) per year; indicator variables for season (4 seasons), day of week, holiday, and lag holiday (indicating whether one of the previous two days was a holiday); and cubic polynomials for three-day moving average maximum temperature (lags 0-1-2) and three-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 (e.g., preterm births vs. full-term births) and created separate models for each stratum. These stratum-specific models contained indicators for the seven 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 two stratum-specific rate ratios are equal are presented when $p < 0.15$. 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 one 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. 2011.[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, i.e., 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 U.S.[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.

Associations between the three-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 interquartile range (IQR) increase in pollutant concentration was observed for ozone (RR = 1.082 per 24.30 ppb increase [95% CI=1.051–1.114]). Also presented in Table 3 are results from two-pollutant models that contained ozone and another pollutant. With the exception of NO_3^-, all the effect estimates decreased slightly with control 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 two-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 two-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). 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 two 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. The 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 one 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 towards 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] 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 (i.e., 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 two years of age in the asthma definition. Whereas we excluded visits to children younger than five years in a previous study,[8] for the present study we included younger children to increase sample 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. 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 Lin et al. study, 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 two 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 dataset of 2.3 million ED visits and given that some children undergo name changes after birth. If associations differ for children who linked compared to 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 to 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 towards 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 two-pollutant models (presented in Table 3), the estimated RRs per interquartile range increase were similar for SO_4^{2-}, NH_4^+, EC, and OC. Although these results may be indicative of a general "non-specific"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 towards 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 relationship 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 inter-alveolar 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 co-morbidity 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 two 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.

Acknowledgments

Sources of financial support: NIEHS K01ES019877, NIEHS R03ES018963, and EPA STAR grant RD834799. The contents of the publication are solely the responsibility of the grantee and do not necessarily represent the official views of the United States Environmental Protection Agency (US EPA). Further, the US EPA does not endorse the purchase of any commercial products or services mentioned in this publication.

References

1. U.S. EPA. Integrated Science Assessment of ozone and related photochemical oxidants (final report). Washington, D.C: 2013. EPA/600/R-10/076F
2. U.S. EPA. Integrated Science Assessment for Particulate Matter. Washington, D.C: 2009. EPA/600/R-08/139F
3. Lovinsky-Desir S, Miller RL. Epigenetics, asthma, and allergic diseases: a review of the latest advancements. Curr Allergy Asthma Rep. 2012; 12(3):211–20. [PubMed: 22451193]
4. Jones M. Effect of preterm birth on airway function and lung growth. Paediatr Respir Rev. 2009; 10(Suppl 1):9–11. [PubMed: 19651391]
5. Harding R, Maritz G. Maternal and fetal origins of lung disease in adulthood. Semin Fetal Neonatal Med. 2012; 17(2):67–72. [PubMed: 22277111]
6. U.S. EPA. National Ambient Air Quality Standards (NAAQS). [Accessed Febuary 3, 2014] http://www.epa.gov/air/criteria.html
7. Ivy D, Mulholland JA, Russell AG. Development of Ambient Air Quality Population-Weighted Metrics for Use in Time-Series Health Studies. J Air Waste Manag Assoc. 2008; 58:711–720. [PubMed: 18512448]
8. Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, Waller LA, Sarnat SE, Mulholland JA, Tolbert PE. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. Am J Respir Crit Care Med. 2010; 182(3):307–16. [PubMed: 20378732]
9. Flanders WD, Klein M, Darrow LA, Strickland MJ, Sarnat SE, Sarnat JA, Waller LA, Winquist A, Tolbert PE. A method for detection of residual confounding in time-series and other observational studies. Epidemiology. 2011; 22(1):59–67. [PubMed: 21068669]
10. Schaaf JM, Liem SM, Mol BW, Abu-Hanna A, Ravelli AC. Ethnic and racial disparities in the risk of preterm birth: a systematic review and meta-analysis. Am J Perinatol. 2013; 30(6):433–50. [PubMed: 23059494]
11. Peel JL, Tolbert PE, Klein M, Metzger KB, Flanders WD, Todd K, Mulholland JA, Ryan PB, Frumkin H. Ambient air pollution and respiratory emergency department visits. Epidemiology. 2005; 16(2):164–74. [PubMed: 15703530]
12. Samoli E, Nastos PT, Paliatsos AG, Katsouyanni K, Priftis KN. Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. Environ Res. 2011; 111(3):418–424. [PubMed: 21296347]
13. Burra TA, Moineddin R, Agha MM, Glazier RH. Social disadvantage, air pollution, and asthma physician visits in Toronto, Canada. Environ Res. 2009; 109(5):567–74. [PubMed: 19406394]
14. National Heart Lung and Blood Institute. Expert panel report 3: Guidelines for the diagnosis and management of asthma. Bethesda, MD: 2007. NIH publication no. 07-4051

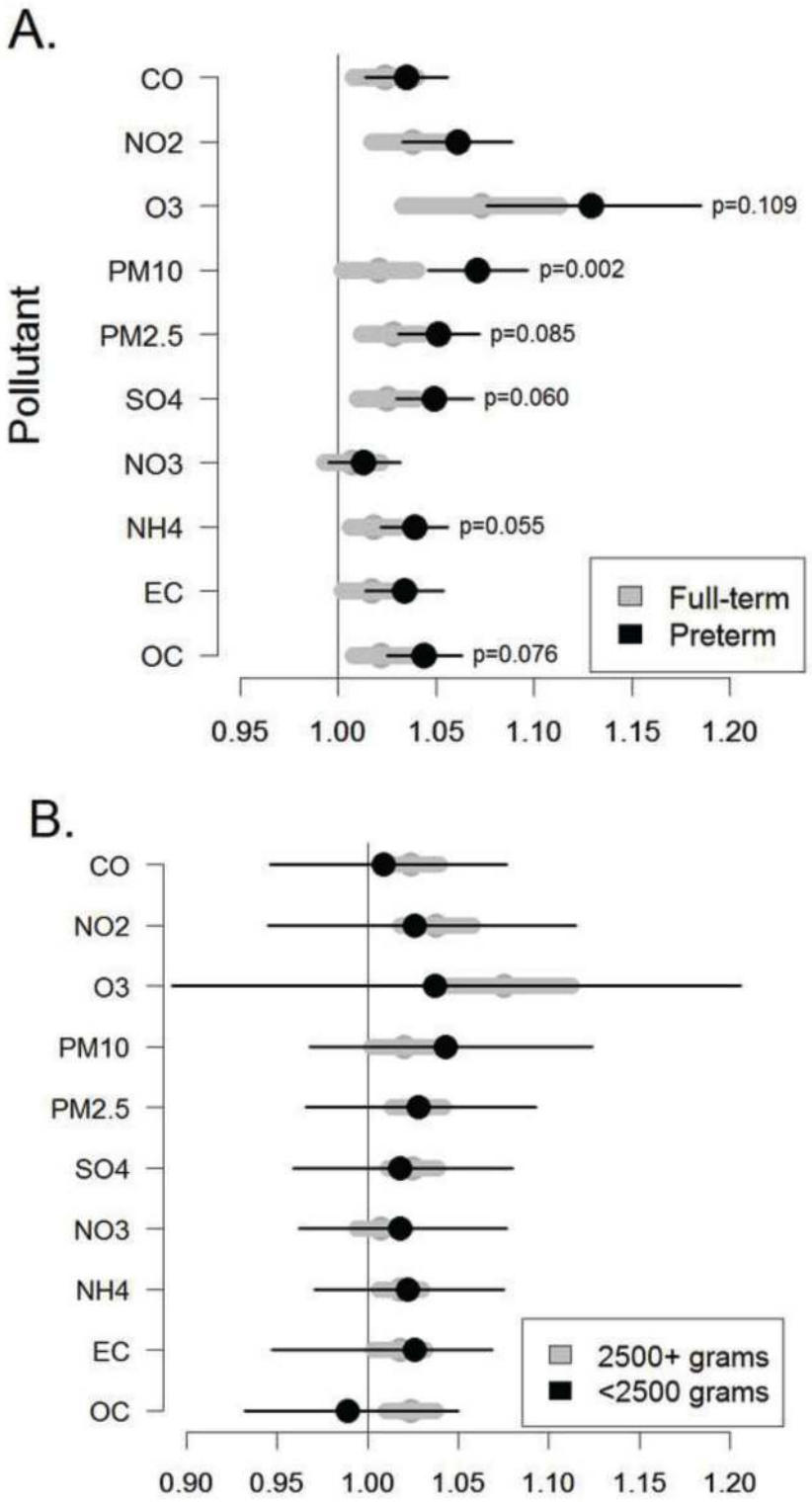
15. Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, Kaufman J. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. Environ Health Perspect. 2006; 114(2): 277–81. [PubMed: 16451867]
16. Lin S, Bell EM, Liu W, Walker RJ, Kim NK, Hwang SA. Ambient ozone concentration and hospital admissions due to childhood respiratory diseases in New York State, 1991–2001. Environ Res. 2008; 108(1):42–7. [PubMed: 18656858]
17. Dominici F, McDermott A, Hastie TJ. Improved semiparametric time-series models of air pollution and mortality. J Am Stat Assoc. 2004; 99:938–948.
18. Peng RD, Dominici F, Louis TA. Model choice in time series studies of air pollution and mortality. J R Statist Soc A. 2006; 169(Part 2):179–203.
19. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology. 2010; 21(3):383–8. [PubMed: 20335814]
20. Goldman GT, Mulholland JA, Russell AG, Srivastava A, Strickland MJ, Klein M, Waller LA, Tolbert PE, Edgerton ES. Ambient air pollutant measurement error: characterization and impacts in a time-series epidemiologic study in Atlanta. Environ Sci Technol. 2010; 44(19):7692–8. [PubMed: 20831211]
21. Strickland MJ, Gass KM, Goldman GT, Mulholland JA. Effects of ambient air pollution measurement error on health effect estimates in time-series studies: a simulation-based analysis. J Expo Sci Environ Epidemiol. 2013
22. Sheppard L, Slaughter JC, Schildcrout J, Liu LJ, Lumley T. Exposure and measurement contributions to estimates of acute air pollution effects. J Expo Anal Environ Epidemiol. 2005; 15(4):366–76. [PubMed: 15602584]
23. U.S. EPA. Integrated Science Assessment for Sulfur Oxides - Health Criteria (Final Report). Washington, D.C: 2008. EPA/600/R-08/047F
24. Maritz GS, Cock ML, Louey S, Suzuki K, Harding R. Fetal growth restriction has long-term effects on postnatal lung structure in sheep. Pediatr Res. 2004; 55(2):287–95. [PubMed: 14630984]
25. Maritz GS, Cock ML, Louey S, Joyce BJ, Albuquerque CA, Harding R. Effects of fetal growth restriction on lung development before and after birth: a morphometric analysis. Pediatr Pulmonol. 2001; 32(3):201–10. [PubMed: 11536449]
26. Dessi A, Ottonello G, Fanos V. Physiopathology of intrauterine growth retardation: from classic data to metabolomics. J Matern Fetal Neonatal Med. 2012; 25(Suppl 5):13–8. [PubMed: 23025763]
27. Pei L, Chen G, Mi J, Zhang T, Song X, Chen J, Ji Y, Li C, Zheng X. Low birth weight and lung function in adulthood: retrospective cohort study in China, 1948–1996. Pediatrics. 2010; 125(4):e899–905. [PubMed: 20211946]
28. Edwards CA, Osman LM, Godden DJ, Campbell DM, Douglas JG. Relationship between birth weight and adult lung function: controlling for maternal factors. Thorax. 2003; 58(12):1061–5. [PubMed: 14645976]
29. Suresh S, Mamun AA, O'Callaghan M, Sly PD. The impact of birth weight on peak lung function in young adults. Chest. 2012; 142(6):1603–10. [PubMed: 22539648]
30. Wendt JK, Symanski E, Stock TH, Chan W, Du XL. Association of short-term increases in ambient air pollution and timing of initial asthma diagnosis among medicaid-enrolled children in a metropolitan area. Environ Res. 2014; 131(1):50–8. [PubMed: 24657516]
31. Glad JA, Brink LL, Talbott EO, Lee PC, Xu X, Saul M, Rager J. The relationship of ambient ozone and PM(2. 5) levels and asthma emergency department visits: possible influence of gender and ethnicity. Arch Environ Occup Health. 2012; 67(2):103–8. [PubMed: 22524651]
32. Yap PS, Gilbreath S, Garcia C, Jareen N, Goodrich B. The influence of socioeconomic markers on the association between fine particulate matter and hospital admissions for respiratory conditions among children. Am J Public Health. 2013; 103(4):695–702. [PubMed: 23409878]
33. Seal E, McDonnell WF, House DE, Salaam SA, Dewitt PJ, Butler SO, Green J, Raggio L. The pulmonary response of white and black adults to six concentrations of ozone. Am Rev Respir Dis. 1993; 147(4):804–810. [PubMed: 8466113]

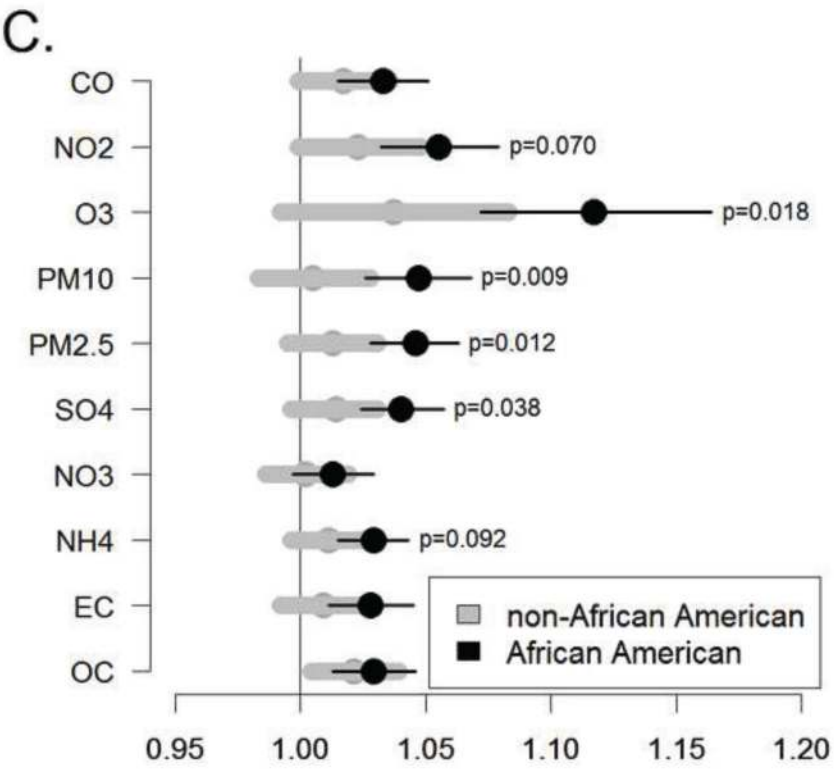
34. Que LG, Stiles JV, Sundy JS, Foster WM. Pulmonary function, bronchial reactivity, and epithelial permeability are response phenotypes to ozone and develop differentially in healthy humans. J Appl Physiol. 2011; 111(3):679–687. [PubMed: 21700892]

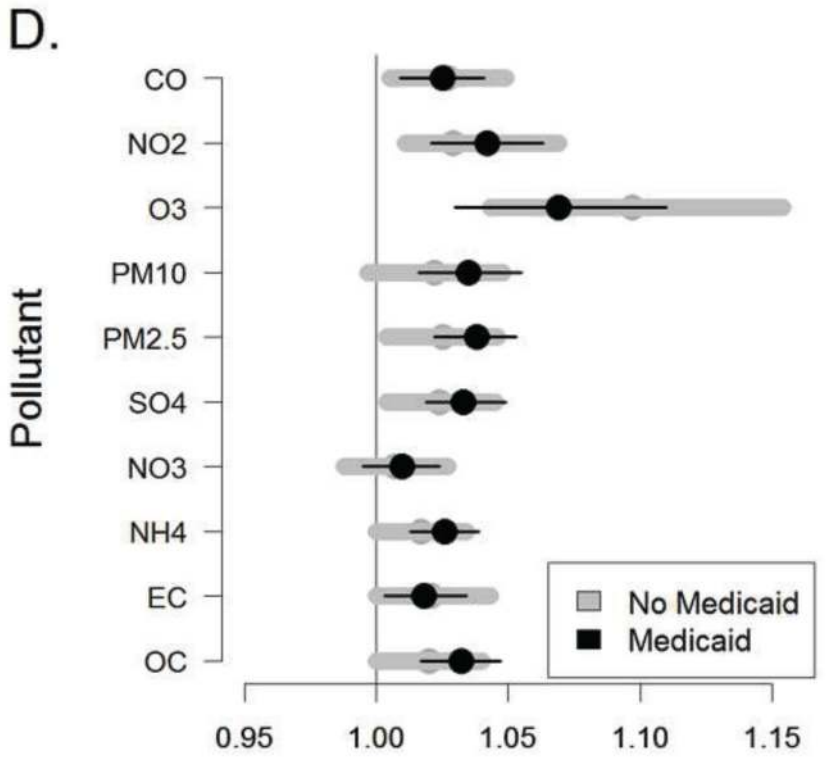
35. Vawda S, Mansour R, Takeda A, Funnell P, Kerry S, Mudway I, Jamaludin J, Shaeen S, Griffiths C, Walton R. Associations between inflammatory and immune response genes and adverse respiratory outcomes following exposure to outdoor air pollution: a HuGE systematic review. Am J Epidemiol. 2014; 179(4):432–442. [PubMed: 24243740]

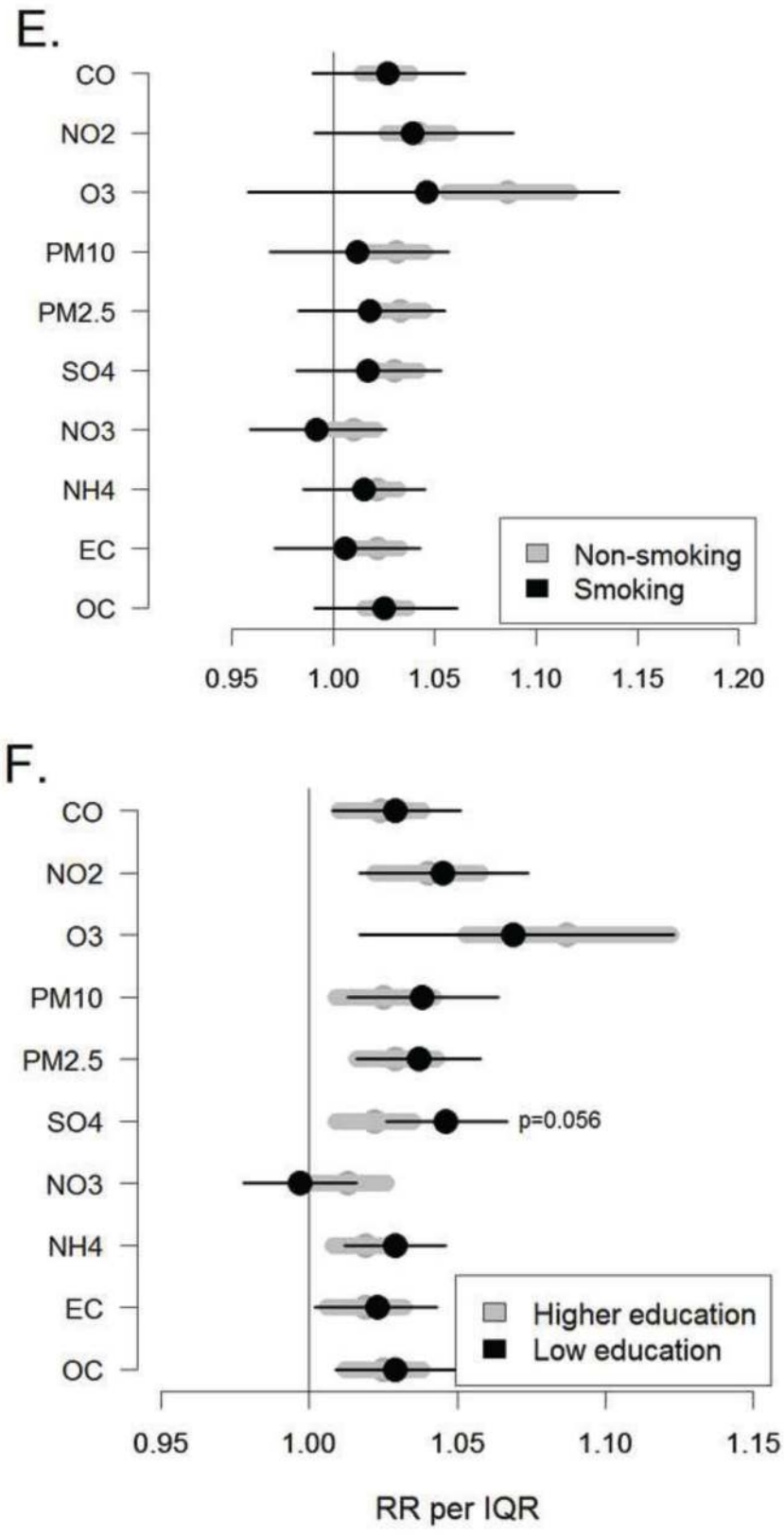
36. Moreno-Macias H, Dockery DW, Schwartz J, Gold DR, Laird NM, Sienra-Monge JJ, Del Rio-Navarro BE, Ramirez-Aguilar M, Barraza-Villarreal A, London SJ, Romieu I. Ozone exposure, vitamin C intake, and genetic susceptibility of asthmatic children in Mexico City: a cohort study. Respir Res. 2013; 14:14. [PubMed: 23379631]

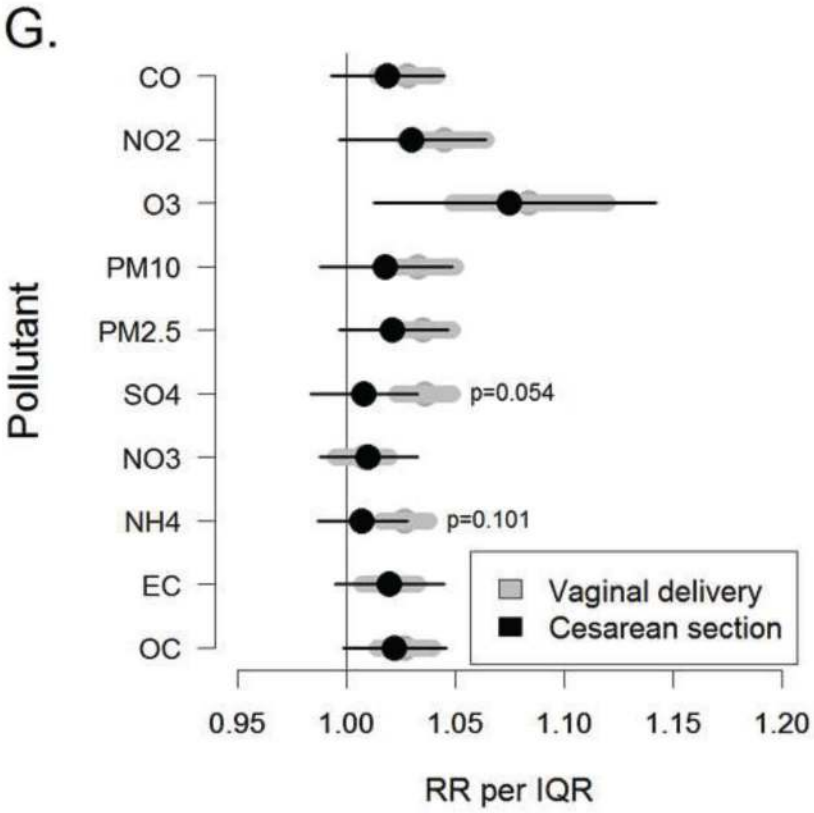
37. Bennett WD, Hazucha MJ, Folinsbee LJ, Bromberg PA, Kissling GE, London SJ. Acute pulmonary function response to ozone in young adults as a function of body mass index. Inhal Toxicol. 2007; 19(14):1147–1154. [PubMed: 17987466]











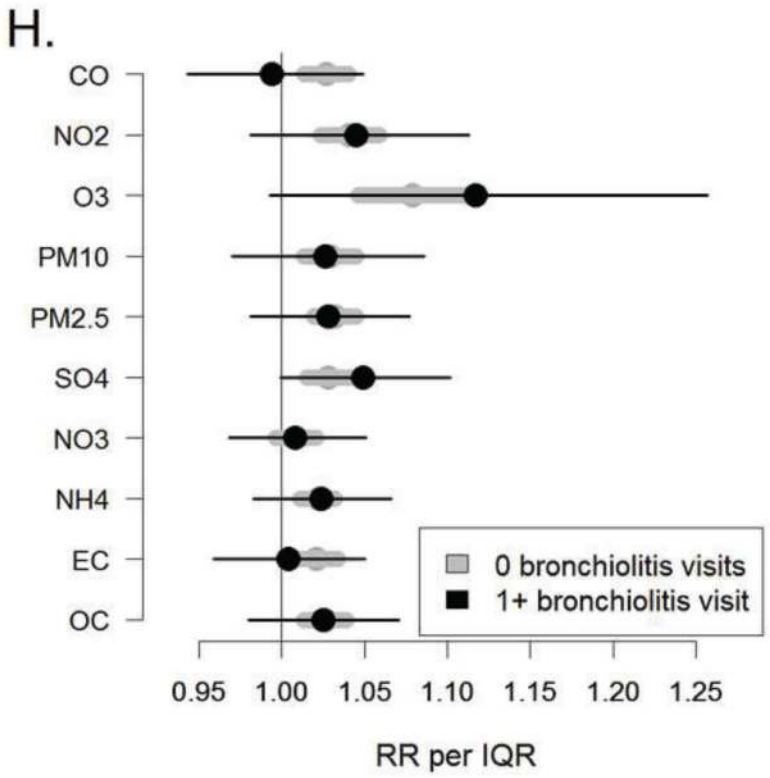


Figure 1.

Stratum-specific rate ratios and 95% confidence intervals for associations of emergency department visits for asthma or wheeze with interquartile range increases in three-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 two stratum-specific rate ratios are equal is reported for all $p < 0.15$.

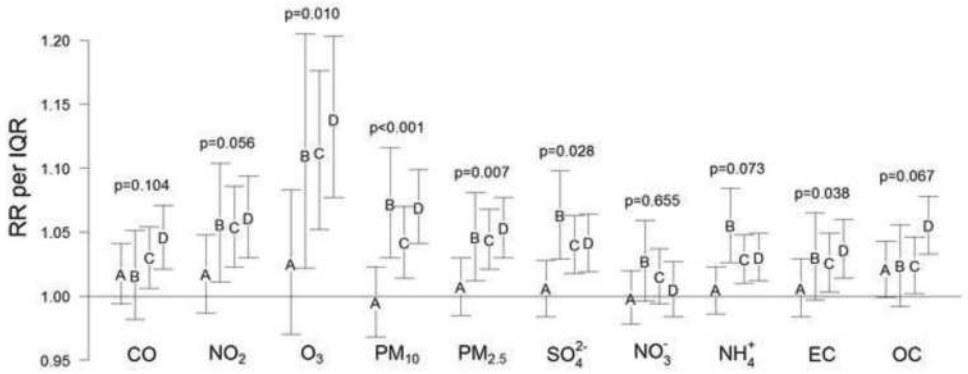


Figure 2.

Stratum-specific rate ratios and 95% confidence intervals for associations of emergency department visits for asthma or wheeze with interquartile range increases in three-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 1

Number of emergency department (ED) visits for asthma or wheeze among children aged 2–16 years in 20-county Atlanta, 1 January 2002 – 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 (≤2500 grams)	3,890 (4)
Normal Birth Weight (> 2500 grams)	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 three-day moving average population-weighted average ambient air pollutant concentrations in 20-county Atlanta, 1 January 2002 – 30 June, 2010.

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

ppm, parts per million; ppb, parts per billion, $\mu g/m^3$, micrograms per cubic meter.

[a] Daily ozone measurements from two year-round monitors, two March-October monitors, and one year-round monitor that started in mid-2009.

[b] PM_{10} measured daily at one monitor and every sixth day at eight monitors.

[c] $PM_{2.5}$ measured daily at seven monitors and every third day at four monitors.

[d] $PM_{2.5}$ components measured daily at four monitors and every third day at two monitors.

Table 3

Associations between emergency department visits for asthma or wheeze and interquartile range (IQR) increases in three-day moving average population-weighted average ambient air pollutant concentrations.

	IQR	Single-pollutant model RR per IQR (95% CI)	Two-pollutant model with control for O_3 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)

Table 4

Associations of emergency department visits for asthma or wheeze with three-day moving average population-weighted average ambient air pollutant concentrations and with pollutant concentrations one day in the future: sensitivity to varying control in the regression time spline.[3]

	6 df per year		8 df per year		12 df per year	
	Lag 0-1-2 concentration RR per IQR (95% CI)	Future concentration RR per IQR (95% CI)	Lag 0-1-2 concentration RR per IQR (95% CI)[b]	Future concentration RR per IQR (95% CI)	Lag 0-1-2 concentration RR per IQR (95% CI)	Future concentration 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)

df, degrees of freedom;

[a] Rate ratios scaled to interquartile range increases in three-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/m^3 for PM_{10}, 6.60 μg/m^3 for $PM_{2.5}$, 2.44 μg/m^3 for SO_4^{2-}, 0.51 μg/m^3 for NO_3^-, 0.71 μg/m^3 for NH_4^+, 0.45 μg/m^3 for EC, and 1.29 μg/m^3 for OC.

[b] Results from primary analysis.