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# Acute Effects of Ambient Air Pollution on Asthma Emergency Department Visits in Ten U.S. States

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**Background:** Previous studies of short-term ambient air pollution exposure and asthma morbidity in the United States have been limited to a small number of cities and/or pollutants and with limited consideration of effects across ages.

**Objectives:** To estimate acute age group-specific effects of fine and coarse particulate matter (PM), major PM components, and gaseous pollutants on emergency department (ED) visits for asthma during 2005–2014 across the United States.

**Methods:** We acquired ED visit and air quality data in regions surrounding 53 speciation sites in 10 states. We used quasi-Poisson log-linear time-series models with unconstrained distributed exposure lags to estimate site-specific acute effects of air pollution on asthma ED visits overall and by age group (1–4, 5–17, 18–49, 50–64, and 65+ y), controlling for meteorology, time trends, and influenza activity. We then used a Bayesian hierarchical model to estimate pooled associations from site-specific associations.

**Results:** Our analysis included 3.19 million asthma ED visits. We observed positive associations for multiday cumulative exposure to all air pollutants examined [e.g., 8-d exposure to $PM_{2.5}$: rate ratio of 1.016 with 95% credible interval (CI) of (1.008, 1.025) per 6.3-$\mu g/m^3$ increase, $PM_{10–2.5}$: 1.014 (95% CI: 1.007, 1.020) per 9.6-$\mu g/m^3$ increase, organic carbon: 1.016 (95% CI: 1.009, 1.024) per 2.8-$\mu g/m^3$ increase, and ozone: 1.008 (95% CI: 0.995, 1.022) per 0.02-ppm increase]. $PM_{2.5}$ and ozone showed stronger effects at shorter lags, whereas associations of traffic-related pollutants (e.g., elemental carbon and oxides of nitrogen) were generally stronger at longer lags. Most pollutants had more pronounced effects on children (<18 y old) than adults; $PM_{2.5}$ had strong effects on both children and the elderly (>64 y old); and ozone had stronger effects on adults than children.

**Conclusions:** We reported positive associations between short-term air pollution exposure and increased rates of asthma ED visits. We found that air pollution exposure posed a higher risk for children and older populations. https://doi.org/10.1289/EHP11661

## Introduction

Ambient air pollution poses great risks to human health. Exposure to ambient air pollution contributes 4 million deaths with 140 million disability-adjusted life-years (DALYs) each year.[1,2] Despite a reduction of air pollution among developed countries over the past decades, there has been a substantial increase in exposure levels in many other parts of the world.[3,4] Global age-standardized exposure levels to ambient particulate matter (PM) and ozone ($O_3$), two major air pollutants regulated worldwide, increased 41% and 3% over the period 1990–2017, respectively.[1] Over 90% of the world's population lives in places where air quality concentrations exceed the World Health Organization's ambient air quality guideline limits.[5] There is substantial epidemiological evidence regarding adverse health effects of air pollution exposure, especially for respiratory and cardiovascular outcomes, even at low concentrations.[6]

Asthma is a lifelong inflammatory disease of the airways that is characterized by reversible airflow obstruction and bronchospasm with recurrent symptoms of coughing, wheezing, shortness of breath, and chest tightness. In severe cases, the symptoms may be triggered multiple times per week or even within a day. Asthma is the most prevalent chronic respiratory disease, and the most common chronic disease among children, affecting 260 million people and causing 460 thousand deaths worldwide in 2019.[2] In the United States, asthma affected 25 million people and was associated with more than 3,500 deaths in 2019.[7] There is an estimated $81 billion annual economic cost associated with asthma, including medical costs and indirect costs of loss of work and school days.[8]

Accumulating epidemiological evidence points to the influence of short-term exposure to ambient air pollution on exacerbation of asthma—particularly among children and the elderly—reflected by increased emergency department use.[9–12] Traffic-related air pollution, e.g., certain particulate matter (PM) components, oxides of nitrogen ($NO_x$), and carbon monoxide (CO), may play a particular role.[13] However, meta-analyses and systematic reviews on the topic have reported high heterogeneity in studies investigating these associations.[9] Differential characteristics (e.g., air pollution concentration, composition, and exposure, as well as outcome definition), study population (e.g., population susceptibility, access to health care), and analytical methods employed across studies are possible driving factors behind the observed heterogeneity.[14,15] In the United States, for example, air pollution–asthma morbidity studies have been limited to a small number of cities[16–21] and pollutants.[22–26] Studies have also typically been restricted to only hospitalization outcomes[27–29] or only the young population.[30–35] There remains a need to comprehensively examine associations between short-term exposure to air pollution and asthma-related morbidity, particularly using a multisite design that employs consistent exposure and outcome assessment methods across locations and that thus enables a rigorous assessment of pooled effects as well as possible effect heterogeneity.

To address these gaps, we conducted a multisite time-series analysis to investigate associations between short-term exposure to ambient air pollution [$PM_{2.5}$ (fine particulate matter less than 2.5 μm in aerodynamic diameter) with its major components, $PM_{10–2.5}$ (coarse particulate matter between 2.5 and 10 μm in aerodynamic diameter), and gaseous pollutants] and risk of asthma emergency department (ED) visits, including those resulting in

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hospital admission, during the period 2005–2014. Study sites were selected based on locations of federal PM speciation stations in 10 U.S. states (Arizona, California, Georgia, Maryland, Missouri, Nevada, New Jersey, New York, North Carolina, and Utah). We further investigated effects of air pollution exposure at different lag times (single-day lags from lag 0 to lag 7 and distributed lags 0–2, 3–6, and 0–7) and compared effects across age groups (1–4, 5–17, 18–49, 50–64, and 65+ y) and regions (the eastern and western United States).

## Data and Methods

### *ED Visits and Hospital Admissions*

We acquired patient-level ED visit data as part of the Environmental Exposures and Health Across the Nation (ENVISION) study.[20,36] The ENVISION database includes outpatient and inpatient billing records from individual states, with key variables for each patient record including date of visit, whether the visit resulted in an admission to the hospital (ED admission), *International Classification of Disease Ninth Revision* (ICD-9) diagnosis codes, patient age, and ZIP code of patient residence.

The ED visit data for this analysis were from 10 U.S. states for 2005–2014: Arizona (Department of Health Services, 2010–2014), California (Department of Health Care Access and Information, 2005–2014), Georgia (Georgia Hospital Association, 2011–2014), Maryland (Department of Health, 2005–2014), Missouri (Department of Health and Senior Services, 2005–2014), Nevada (Division of Health Care Financing and Policy, 2009–2014), New Jersey (Department of Health, Center for Health Statistics & Informatics, 2005–2014), New York (Department of Health, 2005–2014), North Carolina (North Carolina Hospital Discharge Database, 2007–2014), and Utah (Department of Health, 2005–2014). We included patient records with a primary diagnosis of asthma (ICD-9 = 493). The ED visit data were checked for implausible values, facility closures, abnormal distributional trends, and missingness. Implausible values were set to missing, and facility indicators were created to indicate days of hospital operation. Missing values for essential variables, admission date, and patient ZIP codes were excluded from the analysis. Additionally, any visit without at least one ICD diagnosis code was excluded from the analysis. Missingness exclusions were minimal across the 10 states. Categorization of demographic variables were verified against the original data source and data dictionaries; categorical variable levels and processing decisions were standardized across the 10 states of ED visit data.

We restricted the study population to patients with a residential ZIP code within 30 mi of 53 Air Quality System (AQS) PM speciation monitoring sites in the 10 states (Figure S1). Our criteria to select AQS sites to be considered are as follows: *a*) having available air quality measurements for >120 d during the period 2005–2014; *b*) including at least one ZIP-code geographical centroid within 15 mi; *c*) having available primary ED visits (including those resulting in hospital admission) for asthma within 30 mi for >365 d during the period 2005–2014; *d*) having at least 10% of days with nonzero ED visits over the period 2005–2014; *e*) having the longest gap of ED visits shorter than 365 d during 2005–2014; and *f*) having the maximum daily ED visit counts ≥5. We aggregated the patient-level ED visits by day to obtain time-series of daily ED visit counts for the 30-mi area surrounding each monitoring site.

The Emory University institutional review board approved this study and granted an exemption from informed consent requirements, given the minimal risk nature of the study and the infeasibility of obtaining informed consent from individual patients.

### *Air Pollution and Meteorological Data*

Because the AQS monitors only measured $PM_{2.5}$ components every third or sixth day, we applied daily air pollution exposure estimates from a data fusion approach that combines ground observations with chemical transport model simulations from the Community Multiscale Air Quality (CMAQ) model (referred to as *CMAQ-fused* data) as our primary exposure data.[37] The CMAQ-fused data provided estimates at a spatial resolution of 12 km. Data from the CMAQ-fused grid cell overlapping each AQS site location were assigned to the corresponding ED visit time series. The CMAQ-fused air pollutants included PM (daily mean $PM_{2.5}$ and $PM_{10-2.5}$), major $PM_{2.5}$ components [daily mean elemental carbon (EC), organic carbon (OC), nitrate ($NO_3^-$), and sulfate ($SO_4^{2-}$)], and major gaseous pollutants [daily 8-h maximum ozone ($O_3$), 1-h maximum oxides of nitrogen ($NO_x$), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), and CO]. $PM_{10-2.5}$ concentrations were generated by subtracting $PM_{2.5}$ from $PM_{10}$ concentrations. Negative $PM_{10-2.5}$ concentrations that accounted for 3% of all $PM_{10-2.5}$ data, resulting from uncertainty in the CMAQ-fused data at very low coarse particle pollution conditions, were converted to 0. We analyzed $PM_{2.5}$ components individually instead of combinations of multiple components to avoid introducing large uncertainty to exposure estimates resulting from collinearity among components. We used Pearson correlation coefficients to describe the correlations among the CMAQ-fused air pollutants. The main advantage of using the CMAQ-fused data for this analysis was that the data provided temporally continuous estimates of exposure for all pollutants of interest, which allowed for estimating cumulative health associations over multiple lagged days. This exposure dataset was especially advantageous for assessment of $PM_{2.5}$ components that were not measured temporal continuously in the AQS network.

We also acquired available daily ground observations of criteria air pollutants ($PM_{2.5}$, $O_3$, $NO_2$, $SO_2$, and CO) at the AQS sites as our secondary exposure data. In sensitivity analyses, we compared the robustness of health associations estimated based on the CMAQ-fused and AQS data to evaluate the reliability of the CMAQ-fused data.

Meteorological factors, especially air temperature and humidity, are critical confounders of the associations between short-term exposure to air pollution and respiratory outcomes.[38,39] We obtained hourly meteorological parameters—ground-level air temperature (T) and dew-point temperature (DPT)—from the Meteorological Assimilation Data Ingest System (MADIS) Aviation Routine Weather Report (METAR) database (https://madis.ncep.noaa.gov/). Because the METAR sites did not overlap the AQS sites, we used ordinary kriging on the hourly scale to obtain temporally continuous T and DPT at the AQS sites. We then calculated daily 1-h maximum T and 24-h mean DPT based on the hourly values. Finally, we converted the continuous daily maximum T to discrete integers (in degrees Kelvin).

### *Time-Series and Bayesian Hierarchical Modeling*

We adopted a two-stage modeling approach to estimate relative risks of short-term exposure to air pollution on ED visits for asthma. In the first stage, we built AQS site-specific quasi-Poisson log-linear models to estimate associations at single-day lags (lag 0 to lag 7; lag 0 is the same day, lag 1 is the previous day, etc.) and cumulative associations with unconstrained distributed lags 0–2 (3-d immediate cumulative exposure), 3–6 (4-d delayed cumulative exposure), and 0–7 (8-d prolonged cumulative exposure). Our models assumed linear air pollution effects due to the relatively small ranges of short-term exposure levels in the United States as well as limited evidence of deviation from

linearity found in prior studies.[10] The distributed lag model is expressed as[40]:

$$\log\left[E\left(Y_t\right)\right] = \alpha + \sum_{q=d}^{D} \beta_{t-q} AP_{t-q} + (\text{confounders}), \quad (1)$$

where $E(Y_t)$ is the mean ED visit count on day $t$; $AP_{t-q}$ is an air pollutant's concentration $q$ days before day $t$; and the sum of $\beta_{t-q}$ is the main parameter of interest for distributed lagged associations (i.e., lags 0–2, 3–6, or 0–7). The use of distributed lags was motivated by the evidence showing that the adverse respiratory effects of air pollution exposure can occur over multiple days.[41,42] The single-day lag model had a similar structure with only one pollution term on a specific day and a corresponding $\beta$ coefficient.

The site-specific models included nonlinear meteorology effects (moving averages of daily maximum T and mean DPT over the lag periods for the distributed lag models; single-day mean DPT at the same lags for the single-day lag models) specified as natural cubic splines with 4 degrees of freedom (df). Discrete integers of daily maximum T (in degrees Kelvin) were included as an additional ordinal covariate. The models also included daily indicator variables for day-of-week (Monday through Sunday), holidays (0 = nonholidays, 1 = federal and Federal Reserve Board holidays), and for each hospital in the 30-mi area surrounding each AQS site, indicating whether or not it contributed visits (to account for changes to ED visit totals attributable to hospital data availability). Long-term time trends were controlled using natural cubic splines with 12 knots per year (i.e., monthly knots). In addition, the models were controlled for ED visit counts for influenza to adjust for viral-induced asthma in flu seasons.[43]

The time-series design treats individuals within the same geographical area (in our case, the 30-mi area surrounding each AQS site) as the "at-risk population." This "population" serves as its own control over the multiday exposure windows. Individual-level characteristics averaged across the entire population (e.g., socioeconomic status, diet, and physical activity) are expected to change minimally over the course of several days and thus are not considered to be potential confounders.[44]

In the second stage, we built a Bayesian hierarchical model (BHM) to pool site-specific log relative risks [RRs, per interquartile range (IQR) increase in pollution concentration] derived from the first stage to estimate a pooled RR and its 95% CI. The BHM is given by:

$$\widehat{\beta}_i = \theta_i + \epsilon_i \quad \theta_i \sim N(\mu, \tau^2) \quad \epsilon_i \sim N(0, \widehat{\sigma}_i^{\,2}), \quad (2)$$

where $\theta_i$ is the unobserved true log RR at site $i$ and $\epsilon_i$ is the random deviation of the risk that is independent across sites. Site-specific log RR is denoted by $\widehat{\beta}_i$ with standard error $\widehat{\sigma}_i$. We assumed $\theta_i$ follows a normal distribution with mean $\mu$, the pooled risk, and variance $\tau^2$, the between-site heterogeneity. We also assumed the priors of $\mu$ and $\tau^2$ follow noninformative normal and inverse-gamma distributions, respectively. The 95% CI was calculated based on the posterior mean and standard deviation (SD) of the pooled log RR. The pooled log RR and 95% CI were then exponentiated. Our statistical analyses were conducted based on the R (version 4.0.2; R Development Core Team) packages "dlnm" (version 2.4.6)[45] and "R2jags" (version 0.6-1).

We conducted the 2-stage modeling process for all 11 air pollutants ($PM_{2.5}$, $PM_{10-2.5}$, EC, OC, nitrate, sulfate, $O_3$, $NO_2$, $NO_x$, $SO_2$, and CO) to estimate their single-day lag and distributed-lag effects. We also conducted stratification analyses by age group (1–4, 5–17, 18–49, 50–64, and 65+ y) and by region (east and west; Figure S1).

**Table 1.** Summary statistics for daily emergency department visit counts with primary asthma diagnosis and visit counts for influenza in 10 U.S. states (within 30-mi areas around 53 AQS sites) over the study period 2005–2014.

| Parameter | Mean | SD | Minimum | Maximum | IQR |
|---|---|---|---|---|---|
| ED visits for asthma | | | | | |
| All ages, daily visit counts | 874 | 210 | 402 | 1,762 | 284 |
| Ages 1–4 y, daily visit counts | 130 | 44 | 35 | 287 | 61 |
| Ages 5–17 y, daily visit counts | 204 | 83 | 49 | 627 | 111 |
| Ages 18–49 y, daily visit counts | 341 | 70 | 173 | 760 | 91 |
| Ages 50–64 y, daily visit counts | 119 | 30 | 49 | 260 | 41 |
| Ages 65+ y, daily visit counts | 63 | 17 | 21 | 166 | 22 |
| ED visits for influenza | | | | | |
| All ages, daily visit counts | 139 | 251 | 0 | 1,949 | 129 |
| Ages 1–4 y, daily visit counts | 17 | 34 | 0 | 334 | 16 |
| Ages 5–17 y, daily visit counts | 29 | 67 | 0 | 780 | 27 |
| Ages 18–49 y, daily visit counts | 59 | 99 | 0 | 768 | 55 |
| Ages 50–64 y, daily visit counts | 13 | 25 | 0 | 208 | 12 |
| Ages 65+ y, daily visit counts | 12 | 29 | 0 | 361 | 10 |

Note: AQS, Air Quality System; ED, emergency department; IQR, interquartile range; SD, standard deviation.

To examine robustness of the single-pollutant effect estimates, we built several two-pollutant models using single-day lags (lag 0 to lag 7). The first two-pollutant model included $PM_{2.5}$ and $O_3$, which estimates the effects of both pollutants after adjusting for each other. The second type of two-pollutant models targeted traffic-related pollutants—EC, $NO_2$, $NO_x$, and CO—to derive their effect estimates individually, while controlling for $PM_{2.5}$ or $O_3$ (i.e., treating $PM_{2.5}$ or $O_3$ as the second pollution term).

### *Sensitivity Analyses*

We performed several sensitivity analyses to further examine robustness of our findings. For meteorological adjustment, we tested different degrees of freedom (from 2 to 6) of the natural cubic splines based on 8-d cumulative exposure. For long-term time trends, we tested natural cubic splines with varying knots (from 0.7 to 1.3 knots per month) based on 8-d cumulative exposure. Additionally, we adopted the negative outcome control approach to detect unmeasured confounding.[46,47] In our case, the negative outcome control was tomorrow's (lag −1) air pollution concentrations as an indicator in the single-day lag modeling framework. Furthermore, we examined the use of different definitions of influenza ED visits by the Armed Forces Health Surveillance Center (AFHSC) in adjusting for viral-induced asthma in flu seasons based on 8-d cumulative exposure.[48] Finally, we built single-day lag models using the AQS observations for several criteria air pollutants—$PM_{2.5}$, $O_3$, $NO_2$, $SO_2$, and CO—and compared the effect estimates with those estimated based on the CMAQ-fused data at the same time points (i.e., for days when there were no AQS data, the corresponding CMAQ-fused data were excluded as well).

## Results

### *Summary Statistics*

There were 3,190,333 ED visits for asthma over our study period 2005–2014. The mean daily ED visit count with primary asthma diagnosis was 874 (SD = 210) across all locations (Table 1). The five age groups (1–4, 5–17, 18–49, 50–64, and 65+ y) accounted for, respectively, 14.9%, 23.4%, 39.0%, 13.6%, and 7.3% of the total ED visits. The remaining 1.8% were ED visits made by patients with an age below 1 y or unknown age.

According to the CMAQ-fused air pollution concentrations (Table 2), the average of site-specific daily $PM_{2.5}$ concentration was 10.5 $\mu g/m^3$ (SD = 5.5 $\mu g/m^3$) with a maximum (of site-specific daily concentrations) of 53.5 $\mu g/m^3$ [25th, 75th

**Table 2.** Summary statistics for daily, site-specific air pollution and meteorological parameters at 53 AQS sites over the study period 2005–2014. An overall summary statistic (mean, SD, minimum, or maximum) of a parameter is a summary of 53 site-specific statistics. The 25th and 75th percentiles correspond to the percentiles of 53 site-specific statistics.

| Parameter | Overall mean (25th, 75th percentile) | Overall SD (25th, 75th percentile) | Overall minimum (25th, 75th percentile) | Overall maximum (25th, 75th percentile) |
|---|---|---|---|---|
| PM | | | | |
| 24-h avg $PM_{2.5}$ ($\mu g/m^3$) | 10.5 (9.6, 11.2) | 5.5 (4.3, 6.1) | 1.6 (1.2, 2.1) | 53.5 (36.1, 63.1) |
| 24-h avg $PM_{10-2.5}$ ($\mu g/m^3$) | 12.0 (7.0, 14.4) | 7.0 (4.2, 8.3) | 0.1 (0.0, 0.0) | 76.8 (34.7, 77.0) |
| 24-h avg EC ($\mu g/m^3$) | 0.7 (0.5, 0.8) | 0.4 (0.3, 0.6) | 0.0 (0.0, 0.1) | 5.4 (2.7, 6.7) |
| 24-h avg OC ($\mu g/m^3$) | 3.1 (2.5, 3.7) | 2.3 (1.6, 2.9) | 0.3 (0.1, 0.4) | 34.1 (14.3, 45.7) |
| 24-h avg nitrate ($\mu g/m^3$) | 1.9 (1.0, 2.0) | 2.4 (1.1, 2.8) | 0.0 (0.0, 0.0) | 37.0 (12.4, 47.1) |
| 24-h avg sulfate ($\mu g/m^3$) | 2.0 (1.3, 2.7) | 1.8 (0.9, 2.5) | 0.1 (0.0, 0.1) | 24.3 (9.8, 27.8) |
| Gaseous pollutants | | | | |
| 8-h max $O_3$ (ppm) | 0.04 (0.04, 0.04) | 0.01 (0.01, 0.01) | 0.01 (0.00, 0.01) | 0.10 (0.09, 0.10) |
| 1-h max $NO_2$ (ppb) | 22.6 (17.0, 27.5) | 9.6 (7.9, 11.4) | 2.9 (1.3, 4.3) | 70.8 (55.0, 84.5) |
| 1-h max $NO_x$ (ppb) | 48.7 (32.7, 60.2) | 38.1 (21.6, 50.3) | 3.4 (1.6, 4.6) | 323.7 (179.6, 442.1) |
| 1-h max $SO_2$ (ppb) | 3.9 (1.8, 5.5) | 3.8 (1.6, 4.8) | 0.1 (0.0, 0.1) | 42.8 (19.0, 50.9) |
| 1-h max CO (ppm) | 0.6 (0.5, 0.8) | 0.4 (0.2, 0.5) | 0.1 (0.1, 0.1) | 3.1 (2.1, 3.7) |
| Meteorology | | | | |
| 1-h max temperature (K) | 294.1 (291.2, 296.7) | 8.7 (7.9, 10.2) | 269.7 (263.3, 278.0) | 317.8 (314.2, 319.6) |
| 24-h avg dew point temperature (K) | 279.3 (278.1, 281.3) | 7.9 (5.6, 10.0) | 253.3 (249.3, 257.0) | 294.7 (292.1, 297.0) |

Note: AQS, Air Quality System; avg, average; CO, carbon monoxide; EC, elemental carbon; max, maximum; OC, organic carbon; PM, particulate matter; SD, standard deviation.

percentile = ($36.1\ \mu g/m^3$,$63.1\ \mu g/m^3$)]. $O_3$ had an average of 0.04 ppm (SD = 0.01 ppm) with a maximum of 0.10 ppm [25th, 75th percentile = (0.09 ppm, 0.10 ppm, respectively)]. $NO_2$, $NO_x$, $SO_2$, and CO had averages of site-specific daily concentrations of 22.6 ppb, 48.7 ppb, 3.9 ppb, and 0.6 ppm, respectively.

Figure S2 shows the mean site-specific Pearson correlation coefficients of daily concentrations among the CMAQ-fused air pollutants. Most correlation coefficients among air pollutants were below 0.5. $NO_2$ and $NO_x$ had a correlation coefficient of 0.78 because $NO_2$ is the most prevalent form of $NO_x$. Traffic-related air pollutants had high correlations, especially between $NO_x$ and CO (correlation coefficient = 0.75); EC was moderately correlated with other traffic-related pollutants ($NO_x$, $NO_2$, and CO; correlation coefficients around 0.5).

### *Relative Risks for All Ages*

Table 3 shows the 10-state pooled RRs and 95% CIs for associations between IQR increases in 3-d immediate (distributed lags 0–3), 4-d delayed (distributed lags 3–6), and 8-d prolonged (distributed lags 0–7) cumulative exposure to individual air pollutants and asthma ED visits for the entire study population across all age groups. We observed that, in general, increases in cumulative exposure to air pollutants were positively associated with increased rates of asthma ED visits [e.g., 8-d prolonged exposure to $PM_{2.5}$: 1.016 (95% CI: 1.008, 1.025) per $6.3\ \mu g/m^3$ increase, $PM_{10-2.5}$: 1.014 (95% CI: 1.007, 1.020) per $9.6\ \mu g/m^3$ increase, OC: 1.016 (95% CI: 1.009, 1.024) per $2.8\ \mu g/m^3$ increase, $NO_2$: 1.025 (95% CI: 1.012, 1.039) per 18.9 ppb increase, and $O_3$: 1.008 (95% CI: 0.995, 1.022) per 0.02 ppm increase]. For most of the pollutants, as expected, 8-d prolonged exposure had stronger effects than 3-d immediate exposure. $PM_{10-2.5}$ and nitrate had similar effects for three cumulative exposure windows. $PM_{2.5}$ and sulfate had the weakest effects for the 4-d delayed exposure. $O_3$ had the strongest effect for the 3-d immediate exposure.

Figure 1 and Table S1 show the pooled RRs and 95% CIs for associations between increases in single-day exposure (from lag 0 to lag 7) to individual air pollutants and increased rates of asthma ED visits for the entire study population across all age groups. OC, traffic-related pollutants (EC, $NO_x$, $NO_2$, and CO), and $SO_2$ (the latter mostly from the burning of fossil fuels in power plants and other industrial facilities) had a similar single-day lag pattern in that the effects were generally weaker for exposure at shorter lags (lag 1 to lag 2) than at longer lags (lag 4 to lag 6) before the ED visit. The same-day (lag 0) exposure had similar effects as exposure at lag 4 to lag 6 for these pollutants. $O_3$, $PM_{2.5}$, and sulfate, on the other hand, had stronger effects at shorter lags. The effects of exposure to $PM_{10-2.5}$ and nitrate had relatively uniform distributions across lags.

**Table 3.** Pooled effects of cumulative air pollution exposure on asthma emergency department visits across all age groups ($n = 3{,}190{,}333$).

| | Pollutant | IQR | Pooled RR (95% CI) |
|---|---|---|---|
| Distributed lags 0–2 | | | |
| PM | $PM_{2.5}$ | $6.3\ \mu g/m^3$ | 1.013 (1.007, 1.020) |
| | $PM_{10-2.5}$ | $9.6\ \mu g/m^3$ | 1.011 (1.007, 1.016) |
| Major $PM_{2.5}$ components | EC | $0.5\ \mu g/m^3$ | 1.005 (1.001, 1.008) |
| | OC | $2.8\ \mu g/m^3$ | 1.009 (1.005, 1.012) |
| | Nitrate | $1.7\ \mu g/m^3$ | 1.002 (0.999, 1.005) |
| | Sulfate | $1.8\ \mu g/m^3$ | 1.008 (1.005, 1.012) |
| Gaseous pollutants | $O_3$ | 0.02 ppm | 1.022 (1.014, 1.030) |
| | $NO_x$ | 47.6 ppb | 0.996 (0.991, 1.002) |
| | $NO_2$ | 18.9 ppb | 1.004 (0.995, 1.012) |
| | CO | 0.5 ppm | 1.003 (0.998, 1.009) |
| | $SO_2$ | 4.2 ppb | 1.001 (0.997, 1.005) |
| Distributed lags 3–6 | | | |
| PM | $PM_{2.5}$ | $6.3\ \mu g/m^3$ | 1.007 (1.002, 1.011) |
| | $PM_{10-2.5}$ | $9.6\ \mu g/m^3$ | 1.014 (1.008, 1.021) |
| Major $PM_{2.5}$ components | EC | $0.5\ \mu g/m^3$ | 1.006 (1.000, 1.012) |
| | OC | $2.8\ \mu g/m^3$ | 1.010 (1.005, 1.016) |
| | Nitrate | $1.7\ \mu g/m^3$ | 1.001 (0.998, 1.005) |
| | Sulfate | $1.8\ \mu g/m^3$ | 1.001 (0.996, 1.006) |
| Gaseous pollutants | $O_3$ | 0.02 ppm | 1.002 (0.991, 1.012) |
| | $NO_x$ | 47.6 ppb | 1.010 (1.005, 1.016) |
| | $NO_2$ | 18.9 ppb | 1.019 (1.011, 1.027) |
| | CO | 0.5 ppm | 1.007 (0.999, 1.016) |
| | $SO_2$ | 4.2 ppb | 1.004 (0.999, 1.009) |
| Distributed lags 0–7 | | | |
| PM | $PM_{2.5}$ | $6.3\ \mu g/m^3$ | 1.016 (1.008, 1.025) |
| | $PM_{10-2.5}$ | $9.6\ \mu g/m^3$ | 1.014 (1.007, 1.020) |
| Major $PM_{2.5}$ components | EC | $0.5\ \mu g/m^3$ | 1.010 (1.002, 1.018) |
| | OC | $2.8\ \mu g/m^3$ | 1.016 (1.009, 1.024) |
| | Nitrate | $1.7\ \mu g/m^3$ | 1.004 (0.999, 1.009) |
| | Sulfate | $1.8\ \mu g/m^3$ | 1.008 (1.001, 1.015) |
| Gaseous pollutants | $O_3$ | 0.02 ppm | 1.008 (0.995, 1.022) |
| | $NO_x$ | 47.6 ppb | 1.013 (1.005, 1.020) |
| | $NO_2$ | 18.9 ppb | 1.025 (1.012, 1.039) |
| | CO | 0.5 ppm | 1.013 (1.001, 1.026) |
| | $SO_2$ | 4.2 ppb | 1.007 (0.999, 1.014) |

Note: CI, credible interval; CO, carbon monoxide; EC, elemental carbon; IQR, interquartile range; OC, organic carbon; PM, particulate matter; RR, rate ratio.

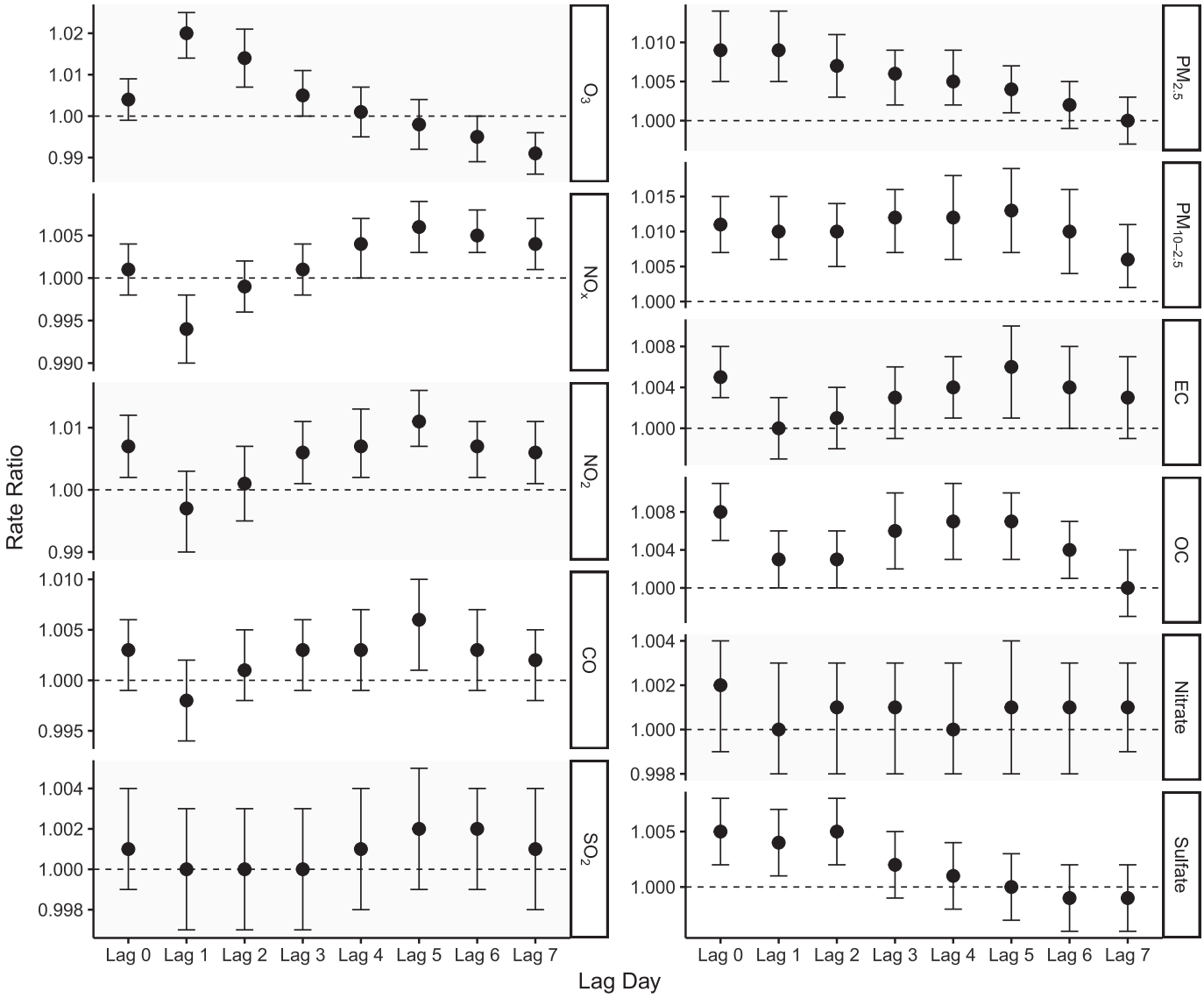


**Figure 1.** Pooled effects of single-day air pollution exposure (lag 0 to lag 7) on asthma emergency department visits across all age groups ($n = 3{,}190{,}333$); units: per 6.3-μg/m$^3$ increase in $PM_{2.5}$, per 9.6-μg/m$^3$ increase in $PM_{10–2.5}$, per 0.5-μg/m$^3$ increase in EC, per 2.8-μg/m$^3$ increase in OC, per 1.7-μg/m$^3$ increase in nitrate, per 1.8-μg/m$^3$ increase in sulfate, per 0.02-ppm increase in $O_3$, per 47.6-ppb increase in $NO_x$, per 18.9-ppb increase in $NO_2$, per 0.5-ppm increase in CO, and per 4.2-ppb increase in $SO_2$; corresponding numeric data is located in Table S1. Note: CO, carbon monoxide; EC, elemental carbon; OC, organic carbon; PM, particulate matter.

To quantify heterogeneity in risk estimates across sites, Table S2 shows the estimated SDs of the site-specific log RRs ($\tau$ in Equation 2) associated with each air pollutant; $\tau$ is a measure reflecting how site-specific log RRs varied around the pooled estimate per IQR increase in pollution concentration. It is notable that the values for CO, $PM_{2.5}$, $NO_2$, $O_3$, and EC were relatively high, potentially indicating larger heterogeneity in their effects on asthma ED visits across sites in comparison with other pollutants. The observed heterogeneity across sites may be associated with differences in exposure, population susceptibility, access to health care, etc.

### *Age Group–Specific Relative Risks*

Figure 2 and Table S3 show the pooled RRs and 95% CIs for associations between IQR increases in 3-d immediate (distributed lags 0–3), 4-d delayed (distributed lags 3–6), and 8-d prolonged (distributed lags 0–7) cumulative exposure to individual air pollutants and increased rates of asthma ED visits for subpopulations by age group. We observed that for $NO_x$, $NO_2$, CO, $SO_2$, $PM_{10–2.5}$, nitrate, and sulfate, the effects on younger individuals age 17 y and under were more pronounced than adult age groups. As expected, 8-d prolonged exposure to these pollutants generally had stronger effects than shorter-term exposure. For $PM_{2.5}$, EC, and OC, the effects were stronger on both young and old populations than on other adults. For $O_3$, the effects were generally stronger on adults age 18 y and above, whereas the effects of 3-d immediate exposure were at a similar level across age groups.

### *Region-Specific Relative Risks*

Figure 3 and Table S4 show the pooled RRs and 95% CIs for associations between IQR increases in 3-d immediate (distributed lags 0–3), 4-d delayed (distributed lags 3–6), and 8-d prolonged (distributed lags 0–7) cumulative exposure to individual air pollutants and increased rates of asthma ED visits for subpopulations by region (east and west). We observed that for EC, nitrate, $O_3$ (except

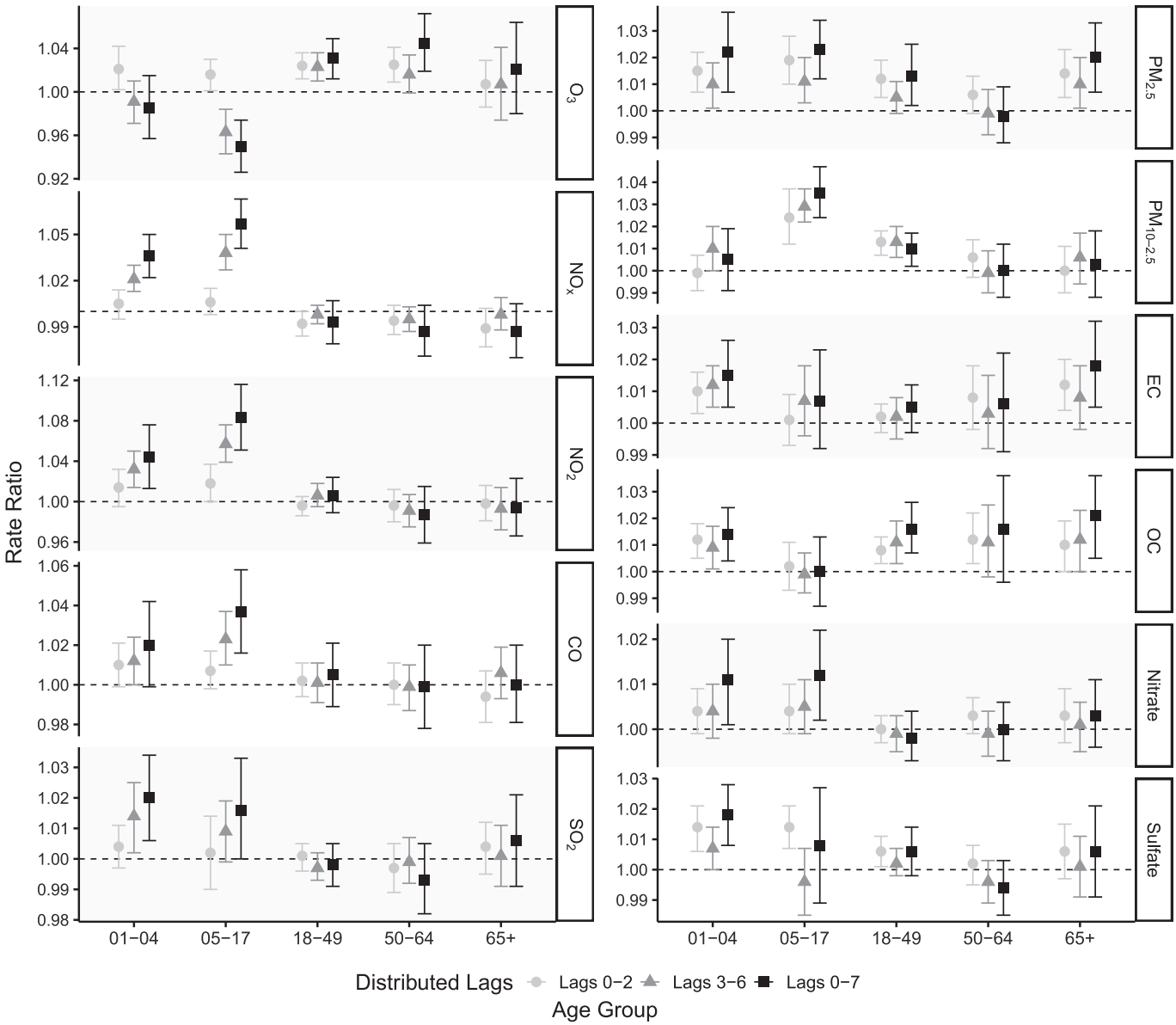


**Figure 2.** Pooled effects of cumulative air pollution exposure on asthma emergency department visits for individual age groups ($n$ for age group 1–4 y = 473,890, $n$ for age group 5–17 y = 746,797, $n$ for age group 18–49 y = 1,246,191, $n$ for age group 50–64 y = 433,997, $n$ for age group 65+y = 231,384); units: per 6.3-$\mu g/m^3$ increase in $PM_{2.5}$, per 9.6-$\mu g/m^3$ increase in $PM_{10-2.5}$, per 0.5-$\mu g/m^3$ increase in EC, per 2.8-$\mu g/m^3$ increase in OC, per 1.7-$\mu g/m^3$ increase in nitrate, per 1.8-$\mu g/m^3$ increase in sulfate, per 0.02-ppm increase in $O_3$, per 47.6-ppb increase in $NO_x$, per 18.9-ppb increase in $NO_2$, per 0.5-ppm increase in CO, and per 4.2-ppb increase in $SO_2$; corresponding numeric data is located in Table S3. Note: CO, carbon monoxide; EC, elemental carbon; OC, organic carbon; PM, particulate matter.

for 3-d immediate exposure), $NO_x$, $NO_2$, and CO, the effects were stronger in the east. $SO_2$ had stronger effects in the west. Other pollutants generally had similar effects across regions.

### *Two-Pollutant Models*

$PM_{2.5}$ and $O_3$ had consistent effects with similar single-day lag patterns in both single- and two-pollutant model settings (Figure S3). A similar lag structure, in which the effects were stronger at shorter lags (except for lag 0), was observed in both model settings for $O_3$.

After adjusting for $PM_{2.5}$, the effects of all traffic-related air pollutants (EC, $NO_2$, $NO_x$, and CO) at lag 0 to lag 4 became smaller or negative (RRs < 1.0), whereas the effects at longer lags (lag 5 to lag 7) were more consistent with those in the single-pollutant setting (Figure S4). In contrast, after adjusting for $O_3$, the effects of these pollutants were consistent with those in the single-pollutant setting across lags. A possible reason for the shift of effects is that the traffic-related pollutants had higher correlations with $PM_{2.5}$ than with $O_3$.

### *Sensitivity Analyses*

The sensitivity analyses did not alter the overall conclusions. The relative risk estimates of asthma ED visits associated with short-term exposure to air pollution were consistent with different degrees of freedom (df = 2–6) of natural cubic splines of daily maximum T and mean DPT (Figures S5 and S6). The relative risk estimates were also consistent with different monthly knots (df = 0.7–1.3) (Figure S7). Our models generated similar relative risk estimates when controlling for different definitions of influenza activity (Figure S8). Except for $O_3$, all other pollutants

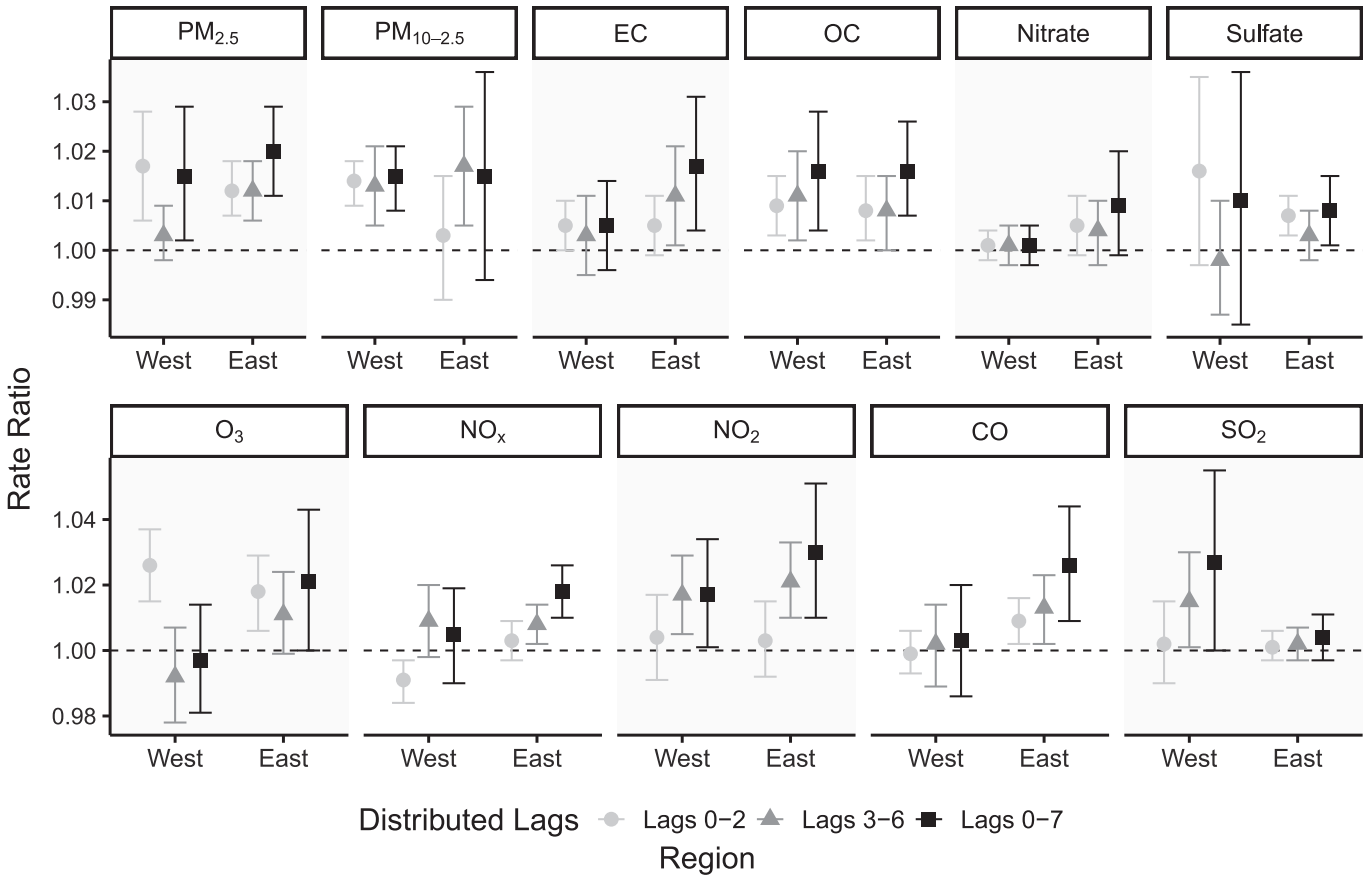


**Figure 3.** Pooled effects of cumulative air pollution exposure on asthma emergency department visits in different regions ($n$ for west = 1,036,115, $n$ for east = 2,154,218); units: per 6.3-μg/m$^3$ increase in $PM_{2.5}$, per 9.6-μg/m$^3$ increase in $PM_{10–2.5}$, per 0.5-μg/m$^3$ increase in EC, per 2.8-μg/m$^3$ increase in OC, per 1.7-μg/m$^3$ increase in nitrate, per 1.8-μg/m$^3$ increase in sulfate, per 0.02-ppm increase in $O_3$, per 47.6-ppb increase in $NO_x$, per 18.9-ppb increase in $NO_2$, per 0.5-ppm increase in CO, and per 4.2-ppb increase in $SO_2$; corresponding numeric data is located in Table S4. Note: CO, carbon monoxide; EC, elemental carbon; OC, organic carbon; PM, particulate matter.

showed no significant associations between tomorrow's (lag −1) pollution concentrations and today's (lag 0) ED visits when controlling for today's pollution concentrations, and the lag 0 RRs and 95% CIs remained about the same before and after controlling for tomorrow's pollution concentrations (Figure S9). Last, the estimated single-day effects of air pollution exposure on asthma ED visits were consistent between using the CMAQ-fused and AQS data as exposure estimates (Figure S10 and Table S5).

## Discussion

Using a multisite time-series design spanning 10 U.S. states, this analysis observed positive associations between increases in short-term exposure to multiple ambient air pollutants, including $PM_{2.5}$, $PM_{10–2.5}$, major $PM_{2.5}$ components (EC, OC, sulfate, and nitrate), and gaseous pollutants ($O_3$, $NO_x$, $NO_2$, $SO_2$, and CO), and increased rates of ED visits for asthma. We observed differential effects of air pollution on asthma across age groups, in that $NO_x$, $NO_2$, CO, $SO_2$, $PM_{10–2.5}$, nitrate, and sulfate had stronger effects on children and adolescents than adult age groups; $PM_{2.5}$, EC, and OC had strong effects on both the young and older populations; and $O_3$ had stronger effects on adult age groups than children and adolescents in general. This analysis provides robust evidence with regard to adverse effects of short-term air pollution exposure on asthma-related outcomes.

This analysis improves on prior short-term air pollution-asthma morbidity studies in four ways. First, our study domain covers multiple U.S. states with a large number of asthma ED visits, and thus our study population may be more representative of the U.S. population than prior studies. Second, we assessed associations across age groups from children age 1–4 y to the elderly population age 65+ y. Third, we examined a wide spectrum of air pollutants that included criteria air pollutants and $PM_{2.5}$ components. Finally, our use of temporally continuous exposure estimates allowed both single-day and multiday cumulative effect analyses. This analysis has thus provided a comprehensive and systematic view of the effects of air pollution on asthma morbidity across various regions of the United States, allowing for rigorous assessment of pooled effects and effect heterogeneity.

The air pollutants this analysis focused on are major ambient pollutants mostly from anthropogenic sources, with extensive epidemiological evidence regarding their adverse effects on acute cardiovascular and other respiratory disease outcomes.[49–51] The anthropogenic sources of PM, a mixture of solid particles and liquid droplets, include motorized vehicles, industrial processes, power generation, agriculture, road dust, and residential wood burning.[52] Wildland fires, as a natural source, also have played an increasing role in heavy, episodic PM pollution in recent decades.[53,54] $O_3$ is a secondary pollutant formed by photochemical reactions between $NO_x$ and volatile organic compounds (VOCs) as major precursors.[55] The two precursors are mainly from mobile sources and industrial processes in urban areas, whereas wildland fires and biogenic emissions are important natural sources of VOCs.[56] In regard to other gases, $SO_2$ is primarily produced by the burning of fossil fuels that contain sulfur during energy production and industrial processes, and CO is principally emitted from fossil fuel combustion.[57]

Our findings are generally consistent with previous work demonstrating acute asthmatic effects of short-term exposure to air pollution across all age groups, with a similar magnitude of effect.[9,10,12,17,25,30,58] For example, based on ED data from 17 U.S. states, Strosnider et al.[25] estimated that an increase of 0.02 ppm in daily 8-h maximum $O_3$ was associated with 1.055-fold higher rate of asthma ED visits (95% CI: 1.048, 1.063); and an increase of 10 $\mu g/m^3$ in daily mean $PM_{2.5}$ was associated with 1.038-fold higher rate of asthma ED visits (95% CI: 1.030, 1.045). A meta-analysis with effect estimates mostly from countries in North America and Europe reported pooled relative risks (per 10 $\mu g/m^3$ increase) of 1.008 (95% CI: 1.005, 1.011; number of effect sizes = 27) for daily 8-h maximum or 24-h mean $O_3$, 1.014 (95% CI: 1.008, 1.020; $n = 22$) for daily mean $NO_2$, and 1.010 (95% CI: 1.001, 1.020; $n = 23$) for daily mean $SO_2$ associated with asthma-related ED visits.[10] However, the pooled associations between asthma ED visits and daily 1-h maximum $NO_2$ and $SO_2$ reported by Zheng et al.[10] were close to the null (0.999 for $NO_2$ and 1.003 for $SO_2$). In contrast, we observed positive associations (RRs > 1.0) for both pollutants, possibly due to the higher statistical power and a more consistent quality of our exposure and health data. Additionally, the single-day lag patterns of certain air pollutants observed in our analysis, especially $PM_{2.5}$ and $O_3$, are consistent with a previous finding: Strickland et al.[30] found a tendency that warm-season $PM_{2.5}$ and $O_3$ concentrations were associated with higher rates of pediatric asthma ED visits at shorter lags in Atlanta, Georgia. Our analysis also revealed a unique lag-specific pattern that the effects of traffic-related air pollutants ($NO_2$, $NO_x$, and CO in particular) tended to peak at lag 0 followed by protective effects at lag 1, with another peak at lag 4 to lag 6. This pattern may reflect two different types of asthma-related outcomes in which lag 0 was associated with more acute outcomes. The lack of detailed diagnosis information in electronic hospital billing records limited our ability to fully interpret the observed pattern, and this pattern is worth further explorations in studies with more detailed asthma-related health data.

Our age group–stratified analysis adds to the evidence that children may be more susceptible to air pollution (especially $NO_x$, $NO_2$, CO, $SO_2$, $PM_{10-2.5}$, nitrate, and sulfate) with higher risks of acute asthma-related outcomes.[9,10,11,58] Possible explanations of childhood vulnerability to air pollution include: *a*) immature growth of airways and underdeveloped host defense capacity,[10] *b*) a higher ratio of inhaled air volume to body weight than that found in adults,[9] and *c*) higher physical activity levels that may potentially be associated with increased time spent outdoors and increased exposure to ambient air pollution than adults.[59] Children age 1–4 y may experience transient wheeze, and asthma diagnoses can be challenging.[30] ED visits for asthma selected based on the ICD-9 code may actually identify a mix of asthma and wheeze for this young population. However, it is still valuable to report their effects of air pollution exposure because this age range accounted for 15% of total ED visits in our study population and ED visits indicate severe symptoms that require emergency care. Our results can help identify and prevent potential asthma triggers and benefit long-term control of the disease among children.

Our analysis also shows that exposure to some air pollutants ($PM_{2.5}$, EC, OC, and $O_3$) were associated with strong adverse effects on the elderly population. Despite asthma being usually considered a disease of young people, older people suffer disproportionately from asthma; people age 65+ y have the highest rate of asthma mortality in the United States.[60] There are at least two phenotypes among older patients with asthma: asthma of early onset that has persisted into older adulthood ("longstanding") and asthma that starts in middle age or older ("late-onset").[61] A plausible mechanism of the effects of air pollution is that short-term exposure to air pollution may amplify inflammatory responses of remodeled airways in the elderly.[11,58] Asthma in the elderly is underdiagnosed and undertreated[61]; with an ever-increasing elderly population worldwide, identifying risk factors of asthma may benefit detection and proper management of the disease in old age, with a great impact from the public health perspective.

Our analysis showed evidence of differential effects of air pollution on asthma across regions, where EC, nitrate, $O_3$, $NO_x$, $NO_2$, and CO had stronger effects in the eastern states, and $SO_2$ had stronger effects in the western states. Differential air pollution characteristics (e.g., pollution concentration, composition, and exposure), population susceptibility, and access to health care may play a role in the observed differences. The regional difference in the health effects of air pollution exposure is an important topic that is worth additional research with spatially more complete health data (e.g., ZIP code–level ED visits and hospitalization data covering the entire state, as opposed to our current data surrounding AQS sites).

There are several plausible biological mechanisms that air pollution triggers asthma exacerbations: oxidative stress from reactive oxygen species, airway remodeling and inflammation, and sensitization to aeroallergens.[62–64] Pulmonary inflammation may also serve as an indirect cause of asthma exacerbations through its impacts on host defenses and respiratory viral infections.[65,66] Specifically, PM, a mixture of various chemical species, imposes more complex impacts on asthmatic airways and may cause oxidative stress and airway remodeling and hyper-responsiveness.[67] $O_3$ and $NO_2$ have been demonstrated in generating free radicals that impair the function and structure of airways and releasing inflammatory mediators.[68] $SO_2$ has been found to promote airway inflammation and eosinophilia.[69] CO may serve as a proxy of air pollutants from incomplete combustion, whereas its biological mechanisms associated with asthma exacerbations are less certain.[11,70] Although the CO concentrations observed in this analysis were low in comparison with the current regulatory standards, no known safe threshold has been found for CO exposure.[57] Our recent exposure modeling study demonstrated substantial CO concentration variations at a finer, intracity scale in the United States.[71] This current analysis further provided evidence of the adverse effects of CO, either as a primary pollutant or a proxy of other pollutants, at low exposure levels.

Our analysis has several strengths. The analysis was based on a multistate electronic hospital billing records data set in which ED diagnosis data were subject to standardized preprocessing and quality assurance procedures that aimed to provide a consistent quality across states. This large-scale ED data set allowed sufficient statistical power to estimate robust effect estimates for both all-age and age group–stratified analyses. In contrast, the vast majority of prior studies on this topic confined to much smaller study areas.[72,73] In addition, we used temporally continuous exposure estimates available for major PM components and multiple criteria gaseous pollutants.[37] The temporal continuity improved the comparability of single-day effect estimates and allowed the analysis of multiday (distributed-lag) exposure. Also, the use of continuous exposure time series minimized the potential bias being introduced due to dropping missing/incomplete records.[74] Because the improved exposure estimates produced by Senthilkumar et al.[37] are also spatially complete, future analyses may be expanded spatially by linking ED data at locations not represented by the AQS monitoring network, particularly in nonurban environments. Last, our analysis rigorously controlled for potential confounders of the air pollution–asthma association through the adjustment for meteorology (air temperature and

humidity), influenza activity, long-term time trend, and other important indictors. It is worth mentioning that our analysis is among the first to account for influenza-related confounding for respiratory disease outcomes. Future analyses may further consider temporal activities of other respiratory viruses, including respiratory syncytial virus and SARS-CoV-2.

We acknowledge several limitations to this analysis. First, although we adopted improved air pollution exposure estimates by bias-correcting chemical transport model simulations using ground-level air pollution observations, exposure misclassification was still expected to exist, and the levels of misclassification might differ among different air pollutants.[37] The potential exposure misclassification, if nondifferential, may result in bias toward the null and thus underestimated asthma-related effect estimates.[75–77] Second, our use of hospital billing records may be subject to ascertainment bias.[78] However, the potential ascertainment bias is less likely to be correlated with air pollution concentrations and to bias the magnitude of the observed asthma-related effect estimates. Third, as we assessed associations between asthma ED visits and multiple air pollutants, some statistically significant associations may have been observed by chance. Further, the statistically significant negative association observed in the negative outcome control analysis for $O_3$, which was not expected, may indicate the potential residual confounding specifically for the pollutant. However, this association may also be due to the large number of pollutants investigated. Last, we assumed the effects of air pollution exposure on asthma-related outcomes to be linear in this analysis. The assumption of nonlinear exposure–response relationships is worth additional investigations, which is beyond the scope of this study.

In summary, this analysis assessed the risk of ED visits for asthma associated with short-term exposure to $PM_{2.5}$, $PM_{10-2.5}$, major $PM_{2.5}$ components, and gaseous pollutants in 10 U.S. states over a 10-y period. We reported adverse effects of all air pollutants investigated on asthma-related outcomes and differential effects of air pollution that posed a higher risk to children and older populations. This analysis is among the first to investigate acute effects of air pollution on asthma across the entire age range at the U.S. national scale with a comprehensive set of pollutants, emphasizing the urgent need of further reduction of air pollution to avert increase in asthma morbidity.

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The contents of this publication, including data analysis, interpretation, conclusions derived, and the views expressed herein are solely those of the authors and do not represent the conclusions or official views of data sources listed above. Authorization to release this information does not imply endorsement of this study or its findings by any of these data sources. The data sources, their employees, officers, and agents make no representation, warranty, or guarantee as to the accuracy, completeness, currency, or suitability of the information provided here.

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