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ORIGINAL ARTICLE

Short-term effects of ambient air pollutants on asthma-related emergency department visits in Indianapolis, Indiana, 2007–2011Nathan Byers, BA^{1*}, Matthew Ritchey, PT, DPT, OCS, MPH², Ambarish Vaidyanathan, PhD, MScEnvE³, Amy J. Brandt, MPH⁴, and Fuyuen Yip, PhD, MPH³¹Indiana Department of Environmental Management, Indianapolis, IN, USA, ²National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA, ³National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA, and ⁴Indiana State Department of Health, Indianapolis, IN, USA**Abstract**

Objective: We estimate the short-term associations between daily changes in ambient air pollutants and daily asthma-related emergency department (ED) visits in Indianapolis, IN. **Methods:** We identified asthma-related ED visits among Indianapolis residents aged ≥ 5 years. We used Poisson regression in a time-series framework to estimate the increased risk for asthma-related ED visits from exposure to ambient SO₂, PM_{2.5} and ozone during the warm season (April–September) and SO₂ and PM_{2.5} during the cold (October–March) season, from 2007 to 2011. Our models controlled for measured confounders, including weather and respiratory infections, as well as unmeasured confounders using a natural cubic spline to account for long-term seasonal trends. **Results:** During 2007–2011 in Indianapolis, 165 056 asthma-related ED visits occurred. We found statistically significant positive associations ($p < 0.05$) between ambient air pollutants and ED visits during the warm season for persons aged 5–44 years. Interquartile range increases in daily ozone concentrations with same day, 2-day lagged, and 3-day moving average were associated with increased risks for ED visits of 3.2% (95% CI: 0.2%, 6.3%), 4.4% (0.1%, 8.9%) and 4.8% (0.2%, 9.6%), respectively. Interquartile range increases in 3-day moving averages for SO₂ were associated with an increased risk of 3.3% (95% CI: 0.2%, 6.5%). We identified statistically significant associations ($p < 0.05$) between increased SO₂ and PM_{2.5} levels and decreased ED visits among some age groups, primarily during the cold season, and no significant positive associations between changes in PM_{2.5} concentration and asthma-related ED visits. **Conclusions:** During the warm season, increases in ozone and SO₂ concentrations were associated with increased asthma morbidity in children and young adults in Indianapolis. These results will enable reliable estimation of the health impacts of increases in these pollutants on asthma-related ED visits in Indianapolis and similar communities.

Keywords

Lagged effects, ozone, particulate matter, sulfur dioxide, time-series

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Published online 21 October 2015**Introduction**

In 2011, approximately 8.8% of adults and 8.7% of children in the United States, and approximately 9.6% of adults and 9.5% of children in Indiana, had medically diagnosed asthma [1]. Ambient air pollution is known to adversely affect persons with asthma, especially children, and exposure to high pollution concentrations elevates the risk for asthma exacerbation [2–4]. The U.S. Environmental Protection Agency (EPA), in response to health concerns related to air pollution,

has conducted several extensive national assessments to determine the potential health benefits of lowering the National Ambient Air Quality Standards (NAAQS) for six criteria pollutants, including ozone, fine particulate matter (PM_{2.5}) and sulfur dioxide (SO₂) [5–7]. To standardize these national assessments, EPA developed a freely available computer program called the Environmental Benefits Mapping and Analysis Program (BenMAP).

Many state and local regulatory agencies are also interested in quantifying the health impacts of air pollutants in their jurisdictions. A local air quality health impact assessment (HIA) can be performed with BenMAP using methods very similar to the larger national air quality HIAs [8,9]. However, local air quality HIAs require an appropriate concentration-response (C–R) function for the specific locality. C–R functions describe the association between ambient pollution concentrations and health endpoints and are derived

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from epidemiologic studies. To perform a reliable air quality HIA at the state or community level, a C–R function should be selected from a peer-reviewed study that was conducted using an appropriate study design, among a population and geography with comparable characteristics, and measuring the impact of the pollutant of interest on similar health outcomes [10]. C-R functions that pool information from studies across localities with similar characteristics can potentially improve the reliability of air quality HIA estimates [11].

Indiana state environmental and health agencies, with assistance from the Centers for Disease Control and Prevention (CDC), have collaborated on a study that investigates the short-term associations between three ambient air pollutants (ozone, PM_{2.5} and SO₂) and asthma exacerbations in Indianapolis. To our knowledge, Ritchie and Lehnen [12] are the only researchers to have published estimates of the short-term association between criteria pollutants and acute respiratory morbidity in Indianapolis. They used a logistic regression model and found that, during the years 1997–1999, there were statistically significant positive associations between two pollutants (SO₂ and NO₂) and hospital admissions for asthma among children. They also found a statistically significant negative association between ozone and hospital admissions for asthma among children. We investigate a more recent time period (2007–2011), use a different measure of morbidity (emergency department [ED] visits rather than hospitalizations, which likely improves our ability to identify a broader range of asthma exacerbation acuity), consider different age groups (ages 5–17 years, 18–44 years, 45 years and older, and all ages), and use different statistical methods (Poisson regression which includes smooth functions of minimum temperature and time) to measure the association between air pollution concentrations and adverse health outcomes. The results of our study will enable Indiana state agencies to reliably estimate the impact of criteria pollutants on asthma ED visits in Indianapolis.

Methods

The ED data were obtained from the Indiana Hospital Association Outpatient Discharge Database for 2007–2011. Approval for using the ED visit data in this study was obtained from the Indiana State Department of Health Data Release Committee. We used daily counts of de-identified ED patients, whose home address and ZIP codes were in the Indianapolis metropolitan statistical area (MSA). The Indianapolis MSA includes Marion and the eight surrounding counties (including Madison), which had a total population of 1 798 516 in 2010 according to the US Census. Asthma-related ED visits were defined as having an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code of asthma (493) or wheeze (786.07) in the first three diagnosis fields. Daily counts of respiratory-related cases (ICD-9-CM codes 460–466, 487 and 488) in the first three diagnosis fields, without an asthma or wheeze code, were also identified as a marker for viral infections. Individual patients could have multiple ED encounters during the period, including multiple encounters that are potentially the result of a continued exacerbation.

Age-specific ED visit rates were calculated using 2010 ZIP code-level population data obtained from the US Census.

We obtained daily ambient air pollutant concentrations for 1-hour maximum ozone and SO₂, 8-hour maximum ozone, and 24-hour average PM_{2.5} from the EPA’s Air Quality System (AQS) database for 2007–2011. We used data from 11 ambient air monitors in the Indianapolis MSA to calculate a daily average of ozone concentrations, and data from three ambient monitors and two ambient monitors to calculate daily averages of PM_{2.5} and SO₂ concentrations, respectively. We also obtained daily temperature, humidity and barometric pressure data from a centrally located monitor.

Daily pollutant concentrations were estimated by taking a distance and population weighted average of the monitor values [13].

We also evaluated ambient monitor data for the study period in reference to the NAAQS (Figure 1). We determined the total number of days that an Indianapolis MSA monitor measured pollutant concentrations higher than the NAAQS for 8-hour maximum ozone (75 ppb), 24-hour mean PM_{2.5} (35 µg/m³), and 1-hour maximum SO₂ (75 ppb); and we calculated the percentage of active monitoring days that were above the NAAQS for each pollutant (the active monitoring season was April through September for ozone and all year for PM_{2.5} and SO₂).

We used Poisson generalized linear regression models [14] that accounted for over-dispersion to estimate the association between ambient pollutant concentrations and asthma-related ED visits during the warm season (April–September) for 1-hour and 8-hour maximum ozone, 24-hour mean PM_{2.5}, and 1-hour maximum SO₂, and during the cold season (October–March) and all seasons for 24-hour mean PM_{2.5}, and 1-hour maximum SO₂. Within a time-series framework, the daily counts of asthma-related ED visits were regressed against daily estimated ambient pollutant concentrations, daily counts

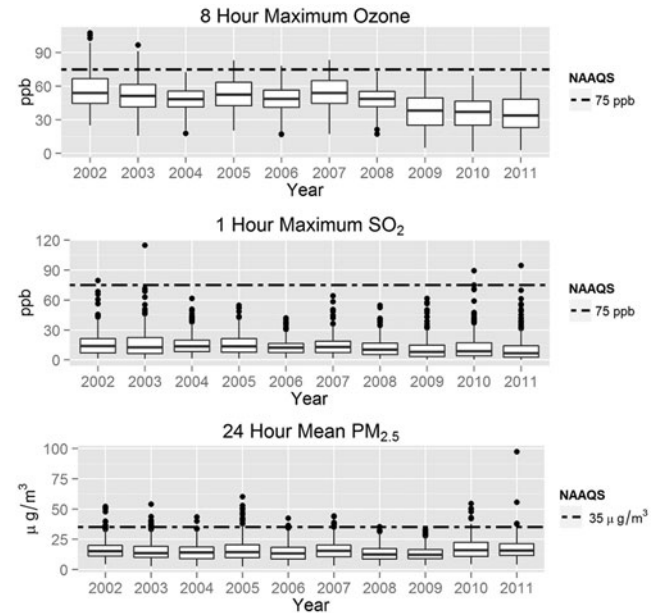


Figure 1. Air pollutant trends in the Indianapolis MSA, 2002–2011, in relation to the National Ambient Air Quality Standards (NAAQS)^a. SO₂ = sulfur dioxide, PM_{2.5} = particulate matter, ppb = parts per billion. ^aCurrent NAAQS as of September 2014.

of ED visits for respiratory infections, and daily values of weather variables. ED counts for respiratory infections were included as a marker to control for viral infections. Potential unmeasured confounders were controlled for by including indicator variables for year, month, day-of-week and holidays; and by including a smoothing function of time.

Below is the general model used for all analyses that did not use a moving average of the pollutant:

$$Y_t \sim \text{Poisson}(\mu_t)$$
$$\log(\mu_t) = \alpha + \beta \text{pollutant}_{t-l} + \delta \log(\text{respiratory infections}_t) + \sum_{j=0}^l \sum_k \zeta_{kj} \text{weather}_{k, t-j} + f(\gamma_1, \gamma_2, \gamma_3; \text{minimum temp}_t) + g\left(\vartheta_1, \vartheta_2, \vartheta_3; \left(\frac{1}{2} \sum_{i=0}^1 \text{minimum temp}_{t-i}\right)\right) + \sum_d \xi_d \text{week day}_d + \sum_m \zeta_m \text{month}_m + \sum_y \psi_y \text{year}_y + \sum_h \varphi_h \text{holiday}_h + g(\lambda_1 \dots \lambda_N; \text{time}),$$

(1)

where μ_t is the expected count of asthma-related ED visits on day t . The same day effect of the pollutant variable was estimated ($l=0$). Lagged effects were also estimated in separate models, up to a lag of 3 days ($l=3$). The effect of a three-day moving average of pollutant concentration estimates (an average of lag 0, lag 1 and lag 2) was also estimated. Models that have a pollutant variable of non-zero lag l also included weather variables with lags up to and including lag l . The weather variables not specified in the general model were mean temperature, mean humidity and mean barometric pressure. All models included a third-order orthogonal polynomial $f(\cdot)$ of minimum temperature. A natural cubic spline $g(\cdot)$ of the moving average of the minimum temperature at lags 0 and 1, with three degrees of freedom, was included in all models that included a non-zero lag l pollutant variable. A natural cubic spline $g(\cdot)$ of time was included in all models. All explanatory variables were chosen *a priori*, and all models were examined for their sensitivity to the change in the degrees of freedom for the spline on time. Sensitivity analyses were also conducted on the removal of respiratory counts and the removal of month and year indicator variables from the models.

The effects of unmeasured confounders were minimized by choosing the degrees of freedom in the spline on time that best predicted the pollutant series in a linear model. Generalized cross validation was used to estimate which linear model yielded the best prediction [15,16]. The degrees of freedom used in the ozone models were consistent across monitoring averaging period (1 h and 8 h), age group and season (61 degrees of freedom). The PM_{2.5} models were consistent across age group with very little variation across season (from 95 degrees of freedom in the warm season to 97 in the cold season); SO₂ models were consistent across age groups with large variation across season (from 5 degrees of freedom in the cold season to 83 in the all-year models). Residual confounding was investigated by including a pollutant variable of future values in the models and assessing what effect this had on the linear relationship between the exposure variable of interest and the response variable [17]. Sensitivity to population change over time was also investigated. A population offset was used in alternative models, and no difference was observed in the results.

The estimation of risk was calculated as a rate ratio (RR) using the interquartile range in single pollutant models, accounting for age group and season. RRs for multi-pollutant models were calculated using a 10 unit increase in pollutant concentrations. *p* Values for the RRs were calculated without adjusting for multiple comparisons. We found no multiple comparison adjustments in the literature, and we assume that conditioning our regressions on lag, age and season is an appropriate study design to account for effect modification. All analyses were performed using R 3.0.0 (Vienna, Austria).

Results

During 2007–2011, there were 165 056 asthma-related ED visits among persons aged 5 years and older in the Indianapolis MSA. The mean number of asthma-related ED visits per day among people of all ages was 87.2 during the warm season (April–September) and 93.6 during the cold season (October–March) (Table 1). The overall rate was 1.8 ED visits per 1000 population. Among children aged 5–17 years, the annual rate was 2.0 per 1000 and accounted for 20.6% of all cases. Their average number of ED visits ranged from 17.4 per day during the warm season to 19.9 per day during the cold season. Adults aged 18–44 years accounted for 40.2% of ED visits with an annual rate of 2.0 per 1000

Table 1. Descriptions of mean daily counts of asthma-related^a emergency department encounters, by age group and season, Indianapolis MSA, 2007–2011.

Ages (yrs.)	All seasons			Warm season (Apr–Sept)			Cold season (Oct–Mar)		
	Mean (SD)	Percentile		Mean (SD)	Percentile		Mean (SD)	Percentile	
		10%	90%		10%	90%		10%	90%
All ages	90.4 (18.9)	68	114	87.2 (17.9)	66	109	93.6 (19.2)	71	118
5–17	18.6 (7.6)	10	28	17.4 (7.4)	9	27	19.9 (7.6)	12	29
18–44	36.3 (8.8)	26	48	36.2 (8.6)	26	47	36.5 (9.0)	26	48
45 and older	22.8 (6.1)	15	31	22.6 (5.8)	16	31	23.0 (6.3)	15	31

SD = standard deviation.
^aICD-9 Codes 493 or 786.07 in the first three diagnosis fields.

Table 2. Descriptions of weighted^a ambient air pollutant concentrations, atmospheric variables and the number of days when an Indianapolis MSA monitor was above the National Ambient Air Quality Standards (NAAQS), 2007–2011.

	Number of monitors	All seasons		Warm season		Cold season		NAAQS ^b	Days above NAAQS (% of days)
		Mean (SD)	IQR	Mean (SD)	IQR	Mean (SD)	IQR		
1-h Maximum ozone ^c (ppb)	11	NA	NA	53.9 (12.5)	16.7	NA	NA	NA	NA
8-h Maximum ozone ^c (ppb)	11	NA	NA	48.5 (11.9)	15.8	NA	NA	75	67 (7.3 ^d)
24-h Mean PM _{2.5} (µg/m ³)	3	13.6 (7.1)	9.4	13.8 (7.5)	9.8	13.4 (6.6)	9.0	35	37 (2.0)
1-h Maximum sulfur dioxide (ppb)	2	10.1 (11.4)	9.9	10.5 (11.6)	10.6	9.8 (11.2)	9.3	75	36 (2.1)
Mean temperature (°C)	1	12.8 (11.0)	19.2	21.2 (5.8)	7.3	4.3 (8.2)	11.9	NA	NA
Mean relative humidity (%)	1	66.3 (13.7)	20.2	63.2 (13.1)	19.0	69.5 (13.5)	21.2	NA	NA
Mean barometric pressure (mbar)	1	991.8 (6.1)	7.3	990.4 (4.9)	6.1	996.7 (6.5)	8.8	NA	NA

SD = standard, IQR = interquartile range, NA = not available.

^aConcentrations described in this table were weighted by distances from monitors to zip codes and by the population of all ages in each zip code.

^bNAAQS as of September 2014. There are currently no standards for 1-hour ozone.

^cOzone data were only available for the warm season (April–September).

^dPercentage is based on the warm season (April–September) for ozone data.

persons. Adults aged 45 years and older accounted for 25.2% of ED visits with an annual rate of 1.3 per 1000.

Table 2 shows the descriptive statistics for the weighted ambient air-pollutant concentrations and atmospheric variables during the 5-year study period (2007–2011). Overall, the Indianapolis MSA was above the NAAQS on 67 days (7.3% of the monitored days) for 8-hour maximum ozone, 37 days (2.0% of monitored days) for 24-hour mean PM_{2.5} and 96 days (5.3% of monitored days) for 1-hour maximum SO₂ during the study period. No current NAAQS exist for 1-hour maximum ozone. The interquartile ranges (≥) for 1-hour maximum ozone, 8-hour maximum ozone, 24-hour PM_{2.5}; and 1-hour maximum SO₂ are 16.7 ppb, 15.8 ppb, 9.8 µg/m³, and 10.6 ppb, respectively. These values were used to calculate associations between pollutant concentration changes and asthma-related ED visits. The Pearson correlation coefficient values for inverse-distance and population weighted pollutant concentrations for the warm season were 0.983 for 1-hour and 8-hour maximum ozone, 0.578 and 0.454 for 1-hour maximum ozone and 0.538 and 0.421 for 8-hour maximum ozone when paired with 24-hour PM_{2.5} and 1-hour maximum SO₂, respectively, and 0.381 for 24-hour PM_{2.5} and 1-hour maximum SO₂. The correlations between 24-hour PM_{2.5} and 1-hour maximum SO₂ were 0.286 and 0.338 for the cold season and both seasons combined, respectively.

We provide RR estimates and 95% confidence intervals (CIs) summarizing the relationship between asthma ED visits and ambient air pollutant concentrations for all seasons (Table 3, Figure 2), the warm season (Table 3, Figure 3) and the cold season (Table 3, Figure 4). RRs were calculated assuming a change in pollutant exposure equal to the pollutant's concentration IQR (Table 2). Overall, few RRs greater than 1.0 were statistically significant with IQR-level increases in pollutant concentrations. However, increases in 1-hour and 8-hour maximum ozone concentrations for all ages during the warm season appeared to increase risk gradually for asthma-related ED encounters from 0-day to 2-day lag, with a drop in risk for the 3-day lag (Table 3, Figure 3). Children aged 5–17 years had a statistically significant RR of 1.044 (95% CI: 1.001–1.089) associated with IQR increases in

1-hour maximum ozone concentrations at a 2-day lag. This association attenuated with age as adults aged 18–44 years had a 2-day lag RR of 1.026 (95% CI: 0.996–1.057) and adults aged 45 years and older had a RR of 0.992 (95% CI: 0.960–1.026). Statistically significant RRs were also associated with IQR increases in 1-hour maximum ozone concentrations for adults aged 18–44 years: 1.032 (95% CI: 1.002–1.063) for same day and 1.048 (95% CI: 1.002–1.096) for 3-day moving average.

Changes in 24-hour mean PM_{2.5} among all ages during the warm season (Table 3, Figure 3) increased gradually in the point estimation of risk for lags 2 and 3, although the RRs were not statistically significant. The point estimation of risk for lag 2 increased among children, but the RR was also not statistically significant. Changes in 1-hour maximum SO₂ concentrations showed elevated associations with risk on the same day and the first two lags for asthma-related ED encounters among children during the warm season. This cumulative effect resulted in a statistically significant RR for IQR increases in a 3-day moving average (average concentration of the same day, lag 1 and lag 2) of 1-hour maximum SO₂ (1.033, 95% CI: 1.002–1.065). This relationship was not found among the two adult age groups.

There were also statistically significant associations between increased SO₂ and PM_{2.5} levels and decreased ED visits among some age groups (Table 3). This finding was primarily during the cold season and was mostly driven by the association of 1-hour SO₂ concentrations with risk among children and adults aged 18 to 44 years.

The inclusion of a variable of future pollution values in the Poisson regressions suggested that residual confounding occurred in two PM_{2.5} models (patients aged 45 years or older with 1 day lag during all seasons, and patients aged 45 years or older with no lag during the cold season). We identified no other discernible residual confounding.

The sensitivity analyses revealed that the RR estimates would have been very similar to the results we report had we used a pre-determined range of degrees of freedom per year (4 to 12 internal knots, corresponding to 5 to 13 degrees of freedom per year) instead of our chosen method of using the degrees of freedom that best predicted the pollutant series in

Table 3. Rate ratios (RR)^a for asthma-related emergency department visits during all seasons, by age and season.

Pollutants	Age group (years)			
	All	5–17	18–44	≥45
All seasons				
24-h PM _{2.5}				
Same day	0.990 (0.980–1.000)	1.007 (0.986–1.029)	0.991 (0.975–1.006)	0.974 (0.957–0.992)
1-day lag	0.994 (0.983–1.004)	0.997 (0.976–1.019)	0.991 (0.975–1.007)	0.993 (0.975–1.012) ^c
2-day lag	1.003 (0.993–1.014)	1.013 (0.992–1.036)	0.996 (0.981–1.012)	1.008 (0.990–1.026)
3-day lag	1.005 (0.995–1.016)	0.996 (0.975–1.018)	1.001 (0.985–1.016)	1.004 (0.986–1.022)
Moving average ^b	0.993 (0.979–1.008)	1.011 (0.980–1.043)	0.988 (0.966–1.011)	0.990 (0.964–1.016)
1-h SO ₂				
Same day	0.999 (0.993–1.005)	1.006 (0.993–1.018)	1.002 (0.994–1.011)	0.991 (0.981–1.002)
1-day lag	1.000 (0.994–1.006)	1.006 (0.993–1.018)	0.999 (0.990–1.008)	0.997 (0.986–1.008)
2-day lag	1.001 (0.995–1.007)	1.003 (0.991–1.016)	0.998 (0.989–1.007)	1.002 (0.992–1.013)
3-day lag	0.996 (0.990–1.002)	0.994 (0.982–1.006)	0.992 (0.983–1.000)	1.002 (0.992–1.012)
Moving average ^b	1.001 (0.991–1.011)	1.013 (0.992–1.034)	1.000 (0.986–1.015)	0.994 (0.977–1.012)
Warm season (Apr–Sept)				
1-h Ozone				
Same day	1.013 (0.993–1.034)	1.004 (0.962–1.047)	1.032 (1.002–1.063)	0.992 (0.959–1.026)
1-day lag	1.015 (0.994–1.036)	1.022 (0.978–1.067)	1.009 (0.978–1.040)	1.008 (0.974–1.043)
2-day lag	1.019 (0.998–1.040)	1.044 (1.001–1.089)	1.026 (0.996–1.057)	0.992 (0.960–1.026)
3-day lag	1.004 (0.984–1.024)	0.994 (0.953–1.036)	1.000 (0.971–1.029)	1.009 (0.977–1.043)
Moving average ^b	1.028 (0.997–1.060)	1.032 (0.969–1.099)	1.048 (1.002–1.096)	0.989 (0.940–1.040)
8-h Ozone				
Same day	1.008 (0.987–1.030)	1.014 (0.970–1.060)	1.023 (0.992–1.055)	0.984 (0.950–1.019)
1-day lag	1.012 (0.990–1.034)	1.022 (0.977–1.070)	1.009 (0.977–1.041)	0.999 (0.963–1.035)
2-day lag	1.021 (1.000–1.043)	1.043 (0.998–1.090)	1.030 (0.999–1.063)	0.994 (0.959–1.029)
3-day lag	1.005 (0.985–1.026)	0.988 (0.946–1.032)	1.002 (0.972–1.033)	1.010 (0.976–1.045)
Moving average ^b	1.024 (0.993–1.057)	1.040 (0.974–1.110)	1.044 (0.997–1.094)	0.979 (0.929–1.031)
24-h PM _{2.5}				
Same day	0.987 (0.971–1.004)	0.995 (0.960–1.032)	0.990 (0.966–1.014)	0.982 (0.956–1.009)
1-day lag	0.995 (0.979–1.012)	0.993 (0.957–1.029)	0.996 (0.971–1.021)	1.008 (0.981–1.035)
2-day lag	1.009 (0.992–1.025)	1.015 (0.980–1.051)	1.014 (0.990–1.039)	1.015 (0.981–1.043)
3-day lag	1.013 (0.996–1.030)	0.989 (0.953–1.026)	1.019 (0.995–1.044)	1.003 (0.976–1.031)
Moving average ^b	0.989 (0.964–1.014)	0.985 (0.934–1.040)	0.999 (0.962–1.037)	1.004 (0.964–1.046)
1-h SO ₂				
Same day	0.999 (0.990–1.007)	1.009 (0.991–1.028)	1.002 (0.990–1.015)	0.988 (0.974–1.003)
1-day lag	1.005 (0.996–1.014)	1.016 (0.997–1.036)	1.000 (0.988–1.013)	1.001 (0.987–1.016)
2-day lag	1.006 (0.997–1.015)	1.015 (0.996–1.035)	0.998 (0.985–1.011)	1.006 (0.992–1.020)
3-day lag	0.996 (0.987–1.005)	0.998 (0.979–1.018)	0.996 (0.983–1.009)	0.988 (0.974–1.003)
Moving average ^b	1.008 (0.993–1.022)	1.033 (1.002–1.065)	1.000 (0.980–1.021)	0.996 (0.973–1.019)
Cold season (Oct–March)				
24-h PM _{2.5}				
Same day	0.989 (0.974–1.004)	0.997 (0.965–1.030)	0.994 (0.971–1.018)	0.977 (0.950–1.006) ^c
1-day lag	0.989 (0.973–1.006)	0.978 (0.945–1.012)	0.995 (0.970–1.019)	0.990 (0.961–1.021)
2-day lag	0.989 (0.973–1.005)	0.983 (0.951–1.017)	0.982 (0.958–1.006)	1.011 (0.981–1.041)
3-day lag	0.984 (0.969–1.000)	0.962 (0.930–0.995)	0.978 (0.955–1.002)	1.011 (0.982–1.042)
Moving average ^b	0.984 (0.962–1.007)	0.976 (0.930–1.025)	0.983 (0.949–1.018)	0.999 (0.957–1.043)
1-h SO ₂				
Same day	0.994 (0.986–1.002)	0.988 (0.972–1.005)	0.997 (0.985–1.009)	0.997 (0.983–1.011)
1-day lag	0.990 (0.982–0.998)	0.986 (0.970–1.003)	0.993 (0.981–1.005)	0.991 (0.977–1.006)
2-day lag	0.994 (0.987–1.002)	0.986 (0.970–1.002)	0.998 (0.986–1.010)	0.999 (0.985–1.013)
3-day lag	0.993 (0.985–1.001)	0.983 (0.967–0.999)	0.987 (0.975–0.999)	1.012 (0.998–1.026)
Moving average ^b	0.986 (0.974–0.998)	0.970 (0.946–0.994)	0.993 (0.975–1.012)	0.994 (0.973–1.016)

Bold type indicates statistical significance ($p < 0.05$).

^aRate ratios were calculated using the interquartile range of the exposure estimations for each pollutant.

^bA three-day moving average of lag 0, lag 1 and lag 2.

^cResidual confounding detected for this model.

a linear model (results not shown) [15,16]. Moreover, based on the Akaike information criterion values we calculated, the majority of our models were not overparameterized by including month and year indicator variables and respiratory infection-related encounter counts (results not shown). For the models which may have been overparameterized by including the month and year indicator variables, their inclusion did not substantially affect the results (i.e. RR point estimates generated during the sensitivity analyses

were within the confidence intervals of the reported RR values).

We also estimated RRs from selected multi-pollutant models, using 10-unit increases in moving average concentrations of pollutants for 5- to 17-year olds during the warm season. RRs for 1-hour SO₂ were attenuated when 1-hour ozone and 24-hour PM_{2.5} were introduced into the model. Point estimates for the 1-hour ozone RRs increased in models that included 24-hour PM_{2.5} (results not shown).

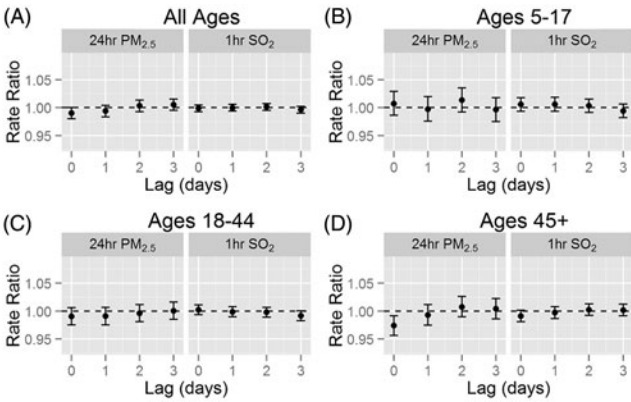


Figure 2. Rate ratios with 95% CI for asthma-related emergency department visits, by days of lag, all seasons. PM = fine particulate matter (PM_{2.5}), SO₂ = sulfur dioxide.

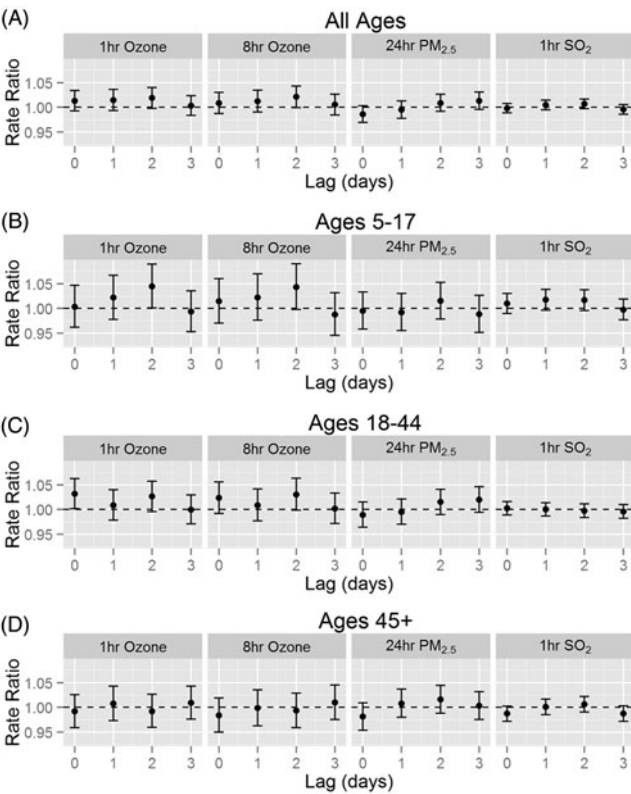


Figure 3. Rate ratios with 95% CI for asthma-related emergency department visits, by days of lag, warm season (April–September). PM = fine particulate matter (PM_{2.5}), SO₂ = sulfur dioxide.

Discussion

This study found that, annually, approximately 30 000 asthma-related ED visits occurred among residents aged 5 years and older in the Indianapolis MSA during 2007–2011. Children aged 5–17 years had the highest asthma-related ED visit rate – 2.0 visits per 1000 population per year. We also identified associations between ozone concentrations and asthma-related ED visits among children and young adults (aged 5–44 years) during the warm season, with statistically significant positive associations for exposures on the same day (aged 18–44 years), lagged by 2 days (aged 5–17 years),

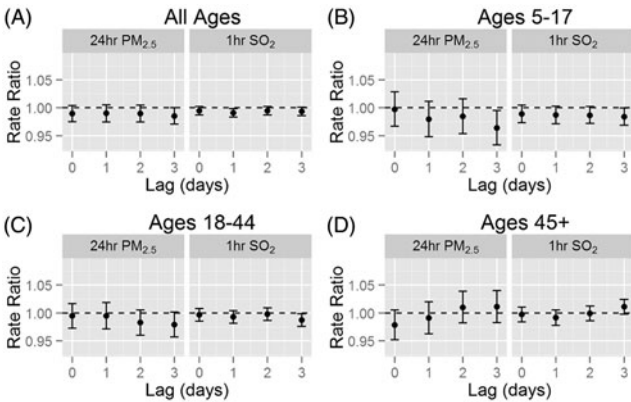


Figure 4. Rate ratios with 95% CI for asthma-related emergency department visits, by days of lag, cold season (October–March). PM = fine particulate matter (PM_{2.5}), SO₂ = sulfur dioxide.

and lagged using a 3-day moving average (aged 18–44 years). Moreover, we identified a statistically significant positive RR for the moving average exposure estimate of SO₂ (aged 5–17 years). Positive associations between PM_{2.5} and ED visits were most pronounced among all ages for lagged exposures, although no statistically significant positive RRs were identified. These findings during the warm season are in agreement with other published findings [4]. In particular, the associations found in the younger cohorts are expected, as children with asthma are particularly at risk for air pollution-induced asthma exacerbation. Compared with adults, children have relatively weak lung function and immature immune systems; are often more physically active with increased ventilation, breath more air volume per body weight and have smaller airways that are more apt to be negatively affected by inflammation [18].

In contrast, there were multiple statistically significant negative associations for PM_{2.5} and SO₂ during the cold season. We were unable to identify evidence in the literature supporting association between higher levels of these contaminants and lower occurrences of asthma-related ED visits during the winter months. The negative findings during the cold season might be due to the decreased exposure to such pollutants during the winter months when the ambient outdoor temperatures in Indianapolis would be low, limiting the amount of time people spent outdoors. Moreover, these inconsistent and negative findings for PM_{2.5} and SO₂ may be the result of our model not controlling for a confounder present during the cold months (e.g. higher prevalence of a co-morbid condition impacting asthma exacerbation). The inconsistent findings for PM_{2.5} and SO₂ may primarily be the effect of low ambient concentrations of these pollutants in Indianapolis during the study period. During 2007–2011, only 7.3% of measured days for ozone (warm season only) were above the NAAQS, with only 2.0% for PM_{2.5} (both seasons) and 5.3% for SO₂ (both seasons). Because there were a limited number of days with high pollutant concentrations, it might be more difficult to identify statistical associations between ambient concentrations and asthma exacerbations.

Decreases in exposure to these air pollutants also coincided with an overall increase in asthma prevalence and exacerbation in Indiana (Figure 5). This is an indication that other factors, including non-ambient-pollutant triggers for

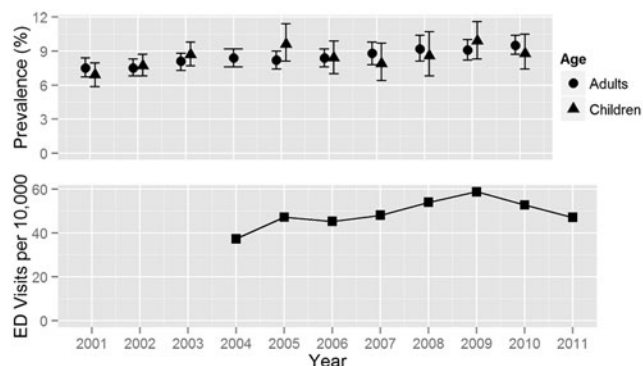


Figure 5. Indiana asthma trends: self-reported asthma prevalence^a among children and adults, 2001–2010, and the age-standardized asthma-related ED visit rate^b, 2004–2011.

^aSurvey results from the Behavioral Risk Factor Surveillance System Prevalence Data [1]. ^bPrimary diagnosis of asthma (ICD-9 Code 493), Indiana Hospital Association Outpatient Discharge Database.

asthma, are likely more significant drivers of asthma morbidity in Indiana. One important non-ambient pollutant asthma trigger in Indianapolis may be pollen [19,20]. Pollen counts for Indianapolis were not available for this study, which may have contributed to misspecification in our Poisson regression models. The smooth function of time was included in our models to account for unmeasured confounders, such as pollen. Based on our investigation of residual confounding using the method described by Flanders et al. [17], the seasonal and long-term trends of pollen counts appear to be sufficiently accounted for in all but two models ($PM_{2.5}$ ages 45 and older with 1-day lag during all seasons, and $PM_{2.5}$ ages 45 and older with no lag during the cold season).

In this study, we chose covariates *a priori* to minimize bias in model selection. We controlled for viral infections and weather (minimum temperature, mean temperature, mean humidity and mean barometric pressure), as well as for periodic unmeasured confounders (dummy variables for day, month, year, and holiday). We also controlled for seasonal unmeasured confounders by including a natural cubic spline on time. The method for choosing the number of degrees of freedom for this term is inconsistent in the literature (methods include minimizing autocorrelation, minimizing the dispersion parameter, AIC, BIC, expert opinion, etc.). We used the results of a simulation study to select a method for choosing the number of degrees of freedom [13]. We also took the extra step of investigating residual confounding by implementing a method that, as of this writing, has not been widely used in published studies [17].

One limitation for this study was the method used to calculate the exposure estimates. We used a double-weighted average (weighted by distance from monitor to ZIP-code centroid and weighted by age-specific census population) for pollutants with only a few ambient monitors. Over an area of 3541 square miles, a maximum of 10 ozone monitors contributed values to the daily exposure estimates compared to just two monitors for $PM_{2.5}$ and SO_2 . Non-regional pollutants from point sources, especially SO_2 , are highly variable and two monitors may not have provided adequate coverage to accurately characterize the spatial heterogeneity

in ambient concentration. Therefore, associations related to increases in SO_2 concentration should be interpreted with caution. Another limitation was the use of static 2010 census data to describe the ZIP-code level population density during the entire study period, which may have contributed to exposure estimate error. However, we explored Poisson models with a population offset using interpolated population values and the results did not differ substantially.

The practical purpose of this study was to estimate the short-term association between ambient air pollutants and asthma exacerbations in Indianapolis, so that future local air quality HIAs can use the results as C-R functions. Analysts at state or local government agencies have published relatively few studies of this kind. This may be due, in large part, to the technical difficulty of the analysis, but it also may be due to the historical division between environmental and public health agencies at the state government level. This study provided an opportunity to establish a working relationship between separate agencies in Indiana. Our collaboration among Indiana environmental and public health agencies and CDC enabled us to obtain the necessary data and build the appropriate statistical models to effectively assess these associations.

Regarding the application of the results of this study in an HIA, Hubbell et al. [10] note that RRs from a single local epidemiological study may not provide “adequate statistical power to allow the global literature to be ignored” when determining an appropriate C-R function. As a result, single city studies may be problematic because of the relatively small effect size compared to the variability, as measured by the confidence intervals [21]. For example, a review of the short-term association between ozone and respiratory hospitalizations by Ji et al. [22] indicates that our estimated RRs for ED visits associated with 8-hour maximum ozone concentrations are lower than single city meta-analysis estimates. However, it is also reasonable to conclude that health effects differ between cities, and results from various study locations may not be transferable to Indianapolis. Ideally, an appropriate C-R function for an HIA of Indianapolis would include results from this local study as well as results from peer-reviewed studies of locations similar in characteristics affecting ambient pollutant exposure and population vulnerability to asthma triggers. “[A]ir conditioning prevalence and utilization... [as well as] prevalence of heart disease, education, income/poverty... and asthma prevalence” are some examples of characteristics that should be considered when selecting study results from a location similar to Indianapolis [10]. If another suitable study location is found (or multiple locations are found), then a C-R function can be developed by pooling the results from more than one study as described by Fuentes [11].

Conclusion

This study found that ozone and SO_2 have a statistically significant positive association with asthma morbidity in children and young adults in Indianapolis during the warm season. Future HIAs of Indianapolis will be able to use the results of this study to help quantify the burden of asthma exacerbations attributable to criteria air pollutants. This

collaborative study also demonstrates that state agencies, with the appropriate guidance from federal agencies and other subject matter experts, are capable of performing the statistical analysis necessary to estimate associations between ambient air pollutants and health outcomes in the presence of confounding variables.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Indiana Department of Environmental Management, or the Indiana State Department of Health.

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