Short-Term Exposure to Ambient Air Pollution and Asthma Mortality

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Author Contributions:

YL planned the study, analyzed the data, contributed to data collection and interpretation, and drafted the manuscript. LZ contributed to the conception, acquired the data, and revised the manuscript. JP, CS and JM participated in data collection and validation, and helped revise the manuscript. HZ, GL, ZP and YZ contributed to data analysis and interpretation, and revised the manuscript. All authors gave final approval of the work to be published and agreed to be accountable for all aspects of the work.

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At a Glance Commentary:

Scientific Knowledge on the Subject: Short-term exposure to air pollution has been associated with increased risk of mortality from a variety of causes including respiratory diseases. As a common chronic respiratory disease, asthma affects 339 million people worldwide. Substantial evidence suggests that short-term exposure to air pollution causes asthma symptoms and leads to exacerbation and increased health-care use of asthma, but its effect on asthma mortality remains largely unknown.

What This Study Adds to the Field: In this large case-crossover study, we found that short-term exposures to $PM_{2.5}$, NO_2 and O_3 were positively associated with asthma mortality. For each IQR increase of exposures to $PM_{2.5}$, NO_2 and O_3, the odds of asthma mortality significantly increased by 7%, 11% and 9%, respectively. Our findings suggest that air pollution increase the risk of asthma mortality and highlight the needs to take effect measures to protect asthmatic individuals by reducing exposure to air pollution.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract

Rationale: Short-term exposure to air pollution has been associated with asthma exacerbation and increased health-care use due to asthma, but its effect on asthma mortality remains largely unknown.

Objectives: To quantitatively assess the association between short-term exposure to air pollution and asthma mortality.

Methods: We investigated 4,454 individuals who lived in Hubei province, China and died from asthma between 2013 and 2018. A case-crossover design and conditional logistic regression models were applied for data analyses. Exposures to particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$), PM_{10}, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone (O_3) were estimated by inverse distance weighted averages of all monitoring stations within 50 km from each case's home address.

Measurements and Main Results: Each interquartile range (IQR) increase of $PM_{2.5}$ (lag 3; IQR: 47.1 $\mu g/m^3$), NO_2 (lag 03; IQR: 26.3 $\mu g/m^3$) and O_3 (lag 3; IQR: 52.9 $\mu g/m^3$) were positively associated with asthma mortality, with odds ratios (ORs) of 1.07 (95% confidence interval [CI]: 1.01-1.12), 1.11 (95% CI: 1.01-1.22) and 1.09 (95% CI: 1.01-1.18), respectively. There was no evidence of departure from linearity for these associations. Further adjustment for other pollutants did not change the associations materially. We did not observe significant associations between PM_{10}, SO_2, CO exposures and asthma mortality. Overall, the estimates remained consistent in various sensitivity analyses.

Conclusions: Our results provide new evidence that short-term exposures to $PM_{2.5}$, NO_2 and O_3 may increase asthma mortality risk. Further studies are needed to confirm our findings in other populations.

Word Count: 249

Keywords: air pollutants; particulate matter; nitrogen dioxide; carbon monoxide

Introduction

As a common chronic respiratory disease, asthma was estimated to affect over 339 million people worldwide in 2016, and its age-standardized prevalence increased by 3.5% compared with that in 2006 (1). Asthma continues to cause substantial burden of disease. In 2016, it contributed 13.2 million years of life lived with disability (YLDs) and 10.5 million year of life lost due to premature death (YLLs) across all ages, ranking 16th and 23rd among the leading causes of YLD and YLL, respectively (1, 2). It is believed that asthma is caused by a combination of complex and incompletely understood environmental and genetic interactions (3, 4), and that the increased prevalence of asthma is related to a changing living environment such as air pollution (5).

Previous studies have linked short-term exposure to air pollution with increased risk of asthma symptoms (6-8), asthma exacerbation (9-11), as well as increased health-care use due to asthma including hospital admission (10-13) and emergency department visits (14). Emerging studies suggest that long-term exposure to air pollution may cause new-onset asthma as well (15-18), though the results remain somewhat inconsistent (19). Given that air pollution has been well documented to increase risk of mortality from respiratory diseases including chronic obstructive pulmonary disease and pneumonia (20-23), it is of great interest whether air pollution can also increase the risk of asthma mortality. However, the association between air pollution and asthma mortality has been rarely investigated due to presence of missing data and small number of asthma deaths (24), as asthma is a rare cause of death (2). To our knowledge, only one study specifically investigated the effect of short-term exposure to air pollution on asthma mortality to date (Supplemental Table E1). This study was conducted early in 1999 and reported that nitrogen dioxide (NO_2) increased risk of death from asthma in Barcelona, Spain between 1986 and 1989, but interpretation of the results were limited by a small

sample size (at most 1 asthma death per day) (24).

We therefore conducted a large case-crossover study to quantitatively assess the exposure-response association between short-term exposure to air pollution and asthma mortality, taking advantage of sufficient monitoring data for analyses in Hubei province, China between 2013 and 2018. We hypothesized that short-term exposures to certain air pollutants including particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), PM_{10}, sulfur dioxide (SO_2), NO_2, carbon monoxide (CO) and ozone (O_3) could increase the risk of asthma mortality. None of the results in this study were previously reported in an abstract form.

Methods

Study Population and Outcome Definition

From the Hubei provincial cause of death surveillance system, we identified 7,358 death cases from a total of ~1.7 million death cases who lived in Hubei province, China before death and died from asthma (ICD-10 codes: J45, J46) as the underlying cause between February 1, 2013 and November 30, 2018. The asthma mortality was defined as our study outcome. For each asthma death case, we extracted information on sex, age at death, race, home address before death, and the date of death. The Hubei province is located in the Central China region, and has an area of 185,900 km^2, covering ~740 km from east to west and ~470 km from south to north; the population was 58,850,000 (about 4.3% of China population) in 2016, yielding an estimated population density of 317 people/km^2 (25). This study was approved by the Ethical Committee of Hubei Provincial Center for Disease Control and Prevention with a waiver of informed consent.

Study Design

We assessed the association between short-term exposure to air pollution and asthma mortality using a time-stratified case-crossover design, which has been widely used for investigating acute effects of air pollution on various health outcomes (26). For each asthma death, the case day was defined as the date of death, and the same asthma death case served as his or her own control by assessing referent exposures on 3 or 4 control days (see Supplement Methods). The control days were defined as the days in the same year and month that shared the same day of week to control for potential confounding effects by day of week, long-term trend and seasonality (27, 28).

Exposure Assessment

We obtained daily mean concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO, and daily 8-hour maximum concentrations of O_3 measured at all state-controlled air quality monitoring stations between 2013 and 2018 from the National Urban Air Quality Real-Time Publishing Platform in China. In Hubei province, there were 55 state-controlled monitoring stations at the end of 2017, which were added the platform in a staged manner. We also collected daily air pollution data from 2 province-controlled monitoring stations in Shennongjia Forestry District (Figure 1).

We used the inverse distance weighting (IDW) method to assess air pollutant exposures. Specifically, locations of all monitoring stations and asthma death cases' home addresses were geocoded using the Baidu Maps API (http://lbsyun.baidu.com/). For each asthma death, we estimated air pollutant exposure on the same day of death (lag 0) by calculating inverse distance ($1/d^2$) weighted average of concentrations at all monitoring stations within 50 km of the corresponding home address on each of the case and control days (Figure 1) (29, 30). We also estimated single-day lag exposures (lag 1 to lag 4) and moving average day exposures (lag 01 to lag 04). For example, lag 1-day exposure refers to the daily exposure at 1 day prior to death, while lag 01-day exposure refers to the mean of

daily exposure on the same day of death and 1 day prior. Cases living over 50 km from any monitoring station before the date of death were excluded in the analyses.

For each air pollutant, validation of the exposure assessment was implemented using a 10-fold cross validation technique. We randomly split the 57 monitoring stations in Hubei province into 10 subsets. The IDW method was then applied to predict exposures for each subset using data from the remaining 9 subsets. The same process was repeated until all subsets were predicted. Finally, the predicted and measured daily air pollutant concentrations at all monitoring stations were used to calculate statistical indicators including coefficient of determination (R^2) to evaluate the prediction accuracy of the exposure assessment (see Supplemental Methods).

Covariates

We obtained data on meteorological conditions from the National Meteorological Information Center. Based on the asthma death cases' home addresses, temperature and relative humidity were estimated for each asthma death case on each of the case and control days, and included in all models to account for their potential confounding effects (see Supplemental Methods). We considered lag periods for both temperature and relative humidity as for the air pollution exposure. By virtue of the case-crossover design, individual-level covariates (including sex, age) that did not vary day to day were not considered as confounders, because they remained constant for the case at both case and control days.

Statistical Analysis

Spearman's correlation coefficient was used to measure the correlation between levels of air pollutant exposures and meteorological conditions. By matching data on the case day with that on the control days, we used conditional logistic regression models to assess exposure-response associations between short-term air pollutant exposures with different lag periods and asthma mortality. The

association between O_3 and asthma mortality was examined specifically in warm season, which was defined as April to September (28). Daily average temperature and relative humidity were included as natural cubic spline functions (with degrees of freedom of 6 and 3, respectively) in all models to account for potential confounding by meteorological conditions (21). We first included each air pollutant exposure in a separate model as a continuous variable, and estimated odds ratios (ORs) and their 95% confidence intervals (CIs) for asthma mortality associated with each interquartile range (IQR) increase of exposure. We also included the air pollution exposure as a natural cubic spline function with 3 degrees of freedom in the model to test nonlinearity of the association and visualize the exposure-response relationship between air pollution and asthma mortality.

To identify potentially susceptible population, we conducted stratified analyses by sex (male, female), age (<80, ≥80 years) and season (warm, cool) to examine their potential effect modifications. After fitting separate models by each stratification variable, the effect modification was tested by comparing stratification-specific estimates of ORs, in which a two-sample test was performed using the point estimate and standard error (see Supplemental Methods) (28, 31).

Sensitivity analyses were conducted to examine the robustness of our results. First, if a significant association was observed between a given air pollutant and asthma mortality, we further fitted two-pollutant models to adjust for potential residual confounding by other pollutants and compared them using the likelihood ratio test. However, we did not include two pollutants with a correlation coefficient higher than 0.5 in the same model to avoid collinearity (30). Second, we restricted the analyses among those who died in 2014-2018 and 2015-2018, because the small number of monitoring stations in 2013 and 2014 might lead to extra misclassification in exposure assessment. Third, we examined the association using 25 km as the buffer distance in the exposure assessment.

Finally, we restricted the analyses to Han race cases only. All analyses were performed using R version 3.5.0. All *P* values were two-sided, and a *P* value < 0.05 was considered as statistically significant.

Results

We identified 7,358 asthma death cases during the study period. With exclusion of 2 cases with incomplete home address information and 2,902 cases who lived beyond 50 km from any air quality monitoring station, 4,454 (60.5%) cases were included in the main data analyses (Table 1, Figure 1). Of the 4,454 cases, 57.8% were male, and 98.6% were Han race. The mean age at death was 77.6 years, ranging from 1.2 to 104.3 years, and 30.2% of the cases died before 75 years old.

Supplemental Figure E1 summaries the asthma death case coverage at varying buffer distances in exposure assessment. The median number of stations within 50 km from each asthma case's home address was 4, 3, 4, 4, 4, and 4 for $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3, respectively. The performance of IDW method in assessing air pollutant exposures were relatively high for $PM_{2.5}$, PM_{10}, NO_2 and O_3, and moderate for SO_2 and CO, with R^2 ranging from 0.47 to 0.93 (Supplemental Table E2). Table 2 gives the distributions of air pollutants and meteorological conditions during 4,454 case days and 15,104 control days. The mean exposures to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 were 65.0 $\mu g/m^3$, 103.2 $\mu g/m^3$, 20.3 $\mu g/m^3$, 37.1 $\mu g/m^3$, 1.20 mg/m^3 and 92.0 $\mu g/m^3$, respectively. As shown in Table 3, $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO were positively and moderately or strongly correlated. O_3 exposure was negatively and weakly associated with other air pollutant exposures. Temperature was positively associated with O_3, and negatively associated other air pollutants, while relative humidity was negatively associated with all air pollutants.

Figure 2 shows that exposures to $PM_{2.5}$ (lag 3), NO_2 (lag 2, lag 02 to lag 04) and O_3 (lag 3) were significantly associated with asthma mortality, and the lag 03-day exposure for NO_2 pronounced the strongest. The ORs for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$ (lag 3; IQR: 47.1 $\mu g/m^3$), NO_2 (lag 03; IQR: 26.3 $\mu g/m^3$) and O_3 (lag 3; IQR: 52.9 $\mu g/m^3$) were 1.07 (95% CI: 1.01-1.12), 1.11 (95% CI: 1.01-1.22) and 1.09 (95% CI: 1.01-1.18), respectively. The ORs (95% CI) for asthma mortality associated each 10 $\mu g/m^3$ increase of exposures to $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and 1 mg/m^3 increase of exposure to CO are summarized in Supplemental Table E3. The models including air pollutant exposure as a natural cubic spline function did not suggest significant nonlinear associations (all *P* for nonlinear trend > 0.05; Figure 3).

Table 4 presents the associations between air pollutant exposures and asthma mortality stratified by sex, age and season. For $PM_{2.5}$ and NO_2, though the ORs were somewhat different and some of them were insignificant, we did not observe any significant effect modification by sex, age or season (all *P* for effect modification > 0.05). For O_3, the associations were not significantly different across sex, but we only observed significantly association among cases who died before 80 years old and in warm season (all *P* for effect modification < 0.05).

In the sensitivity analysis, further adjustment for other pollutant exposures in the 2-pollutant models did not significantly change the associations between $PM_{2.5}$, NO_2, O_3 exposures and asthma mortality (all *P* for likelihood ratio test > 0.05; Supplemental Table E4), though some of the association for O_3 exposure became insignificant. Restricting the asthma death cases to those who died in 2014-2018 (Supplemental Figure E2) and 2015-2018 (Supplemental Figure E3) yielded similar results, except that in 2015-2018 the OR associated with NO_2 exposure (lag 03) remained close (1.11 vs 1.10) but became insignificant. Using a buffer distance of 25 km in the exposure

assessment gave similar results for $PM_{2.5}$ and NO_2; for O_3, the OR was 1.10 (95% CI: 0.99-1.23), which was slightly higher than that estimated in the main analysis (OR: 1.09) but became insignificant possibly due to smaller sample size (Supplemental Figure E4). Supplemental Figure E5 shows the associations when restricted to Han race cases, and the results were similar.

Discussion

In this large case-crossover study, we found that short-term exposures to $PM_{2.5}$, NO_2 and O_3 were significantly associated with asthma mortality. For each IQR increase of $PM_{2.5}$ (lag 3), NO_2 (lag 03) and O_3 (lag 3), the odds of asthma mortality increased by 7%, 11% and 9%, respectively. These findings did not change materially after adjustment for other pollutants in two-pollutant models. Sex, age and season did not appear to significantly modify the associations between short-term exposure to air pollution and asthma mortality, except that the association for O_3 was only identified among cases who died before 80 years old and in warm season. We did not observe any significant association of PM_{10}, SO_2 or CO exposure with asthma mortality.

To our knowledge, only one study specifically investigated the relationship between short-term exposure to air pollution and asthma mortality to date (24). In the study, Saez et al. used the generalized estimating equations method to assess the acute effects of black smoke, SO_2, NO_2 and O_3 exposures on daily count of asthma mortality in Barcelona, Spain from 1986 to 1989, and found that lag 02-day exposure to NO_2 was significantly associated with increased risk of asthma death (RR: 1.037 per 1 $\mu g/m^3$ increase). Our results were consistent with this study that short-term exposure to SO_2 did not significantly contribute increased risk of asthma mortality, and we also found significant association between lag 02-day exposure to NO_2 and asthma mortality, though the strength of

association was much lower (OR: 1.0033 per 1 μg/m^3 increase) possibly due to different study design, strategy for data analyses and variations in air pollution levels.

The effect of long-term exposure to air pollution on asthma mortality was investigated in only a limited number of studies. In 1986, Imai et al. reported that asthma mortality increased with worsening air pollution, and decreased in response to improvement of air quality in Yokkaichi, Japan (32). Likewise, Kravchenko et al. found decline of asthma deaths with lower NO_2, SO_2, CO and PM_{10} levels in North Carolina (33). Though there were significant difference in study design and region, these results are comparable with ours that air pollution may lead to increased risk of death from asthma. In 2002, Sunyer et al. investigated 1078 patients who had visited emergency department in Barcelona for asthma and died between 1985 and 1989, and concluded that NO_2 and O_3 might exacerbate severe asthma and even cause death among asthmatic subjects (34). Note that in this study subjects with asthma as the underlying cause of death only accounted for 12.0% of all study subjects, while our study subjects all died from an underlying cause of asthma. Nonetheless, this study is in line with our study that NO_2 and O_3 may increase risk of asthma death.

The biological plausibility that $PM_{2.5}$, NO_2 and O_3 exposures increase the odds of asthma mortality is generally supported by animal studies and controlled exposure experiments in healthy and asthmatic patients, though the underlying mechanisms are not fully understood. High level air pollutant exposures (e.g. in China and India) may have direct irritant and inflammatory effects on airway neuroreceptors and epithelium (35). At lower level exposures, $PM_{2.5}$, NO_2 and O_3 exposures can induce airway inflammation (36-38), which is thought to be an important characteristic of asthma. It has been suggested that NO_2 and O_3 exposures can also enhance airway hyper-responsiveness (39, 40), another characteristic of asthma. In addition, the $PM_{2.5}$, NO_2 and O_3 exposures have been linked

with oxidative stress (41-43), which contributed significantly to severe asthma.

Our study has several strengths. First, this is the first study with a considerably large sample size to explore whether air pollution can increase the risk of asthma mortality. The asthma death cases included in this study covered a general population of ~59 million individuals between 2013 and 2018, and provided sufficient statistical power for exposure-response analyses. Second, we assessed exposure to each air pollutant based on the home address for each asthma death case, which provided accurate estimates of individual level exposures and helped reduce misclassifications. Third, we conducted this study using a time-stratified case-crossover design that accounted for long-term and season trends, and controlled the influence of individual level confounding factors including sex, age, lifestyle, genetics, and even time-varying variables (e.g. daily temperature and relative humidity). Finally, we considered as many as 6 common air pollutants, and used multi-pollutant models to assess the robustness of estimated association between each pollutant and asthma mortality.

Our study also has some potential limitations. First, we assessed air pollutant exposures using inverse distance weighted mean concentrations at all nearest monitoring stations within 50 km of each case's home address. Although this individual-level based method is believed to provide more accurate estimates compared with that using an average concentration for a city, there was a tradeoff to choose a buffer distance. A relatively short buffer distance may better represent the exposure estimate, while a relatively large buffer distance can increase the number of subjects in data analyses. In this study, we chose a buffer distance of 50 km to include 60.5% of all asthma death cases during the study period, which was also used in several previous case-crossover studies (29, 30). In our study, the performance of exposure assessments for all air pollutants was generally high or moderate, and analyses with a buffer distance of 25 km yielded generally similar results. Nonetheless, the

exposure assessment for SO_2 and CO was less accurate, which might lead to less certain results. Second, though time-invariant confounding factors were well considered in the case-crossover design and we further adjusted for daily temperature and relative humidity, there is still possibility that residual or unmeasured time-varying confounding partly contributed to the associations (e.g. temporary exposure to allergens, medication use), which might induce inaccurate estimates. Third, the high correlations between $PM_{2.5}$ and NO_2 exposures made it difficult to distinguish their respective effects on asthma mortality, and limited interpretation of the present findings. Finally, the generalization of our results is limited due to the specific study area, though it is considerably large. Cautions should be paid to apply our findings to other populations, especially those with much lower air pollution exposures.

In conclusion, we found that short-term exposures to $PM_{2.5}$, NO_2 and O_3 were significantly associated with asthma mortality. Our findings add new evidence that air pollution may increase the risk of asthma mortality and highlight the needs for asthmatic individuals to take effective measures to reduce air pollutant exposures especially in highly polluted areas. Further research is needed to confirm our results in other populations.

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Figure Legends

Figure 1. Spatial distributions of air quality monitoring stations (triangles) and 4,454 asthma death cases' home addresses (periods) in Hubei province, China.

Figure 2. ORs (95% CIs) for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$ (IQR: 47.1 μg/m^3), PM_{10} (65.0 μg/m^3), SO_2 (16.6 μg/m^3), NO_2 (26.3 μg/m^3), CO (0.50 mg/m^3) and O_3 (52.9 μg/m^3) with different lag periods. ORs (95% CIs) were estimated using conditional logistic regression models, adjusting for temperature and relative humidity. Definition of abbreviations: OR = odds ratio; CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

Figure 3. Exposure-response curves between exposures to $PM_{2.5}$ (lag 3), PM_{10} (lag 03), SO_2 (lag 2), NO_2 (lag 03), CO (lag 03), O_3 (lag 3) and asthma mortality. The solid and dashed lines represent ORs and the 95% CIs, respectively. The three vertical lines in each panel indicate the 5th, 50th, and 95th percentile of corresponding air pollution exposure. ORs (95% CIs) were estimated for continuous exposures (relative to the median exposure) using conditional logistic regression models, adjusting for temperature and relative humidity. Definition of abbreviations: OR = odds ratio; CI = confidence interval; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

Table 1. Baseline characteristics of study population, 2013-2018

Baseline characteristic	Value
Asthma deaths, No.	4,454
J45 Asthma, No. (%)	4,300 (96.5)
J46 Status asthmaticus, No. (%)	154 (3.5)
Case days, No.	4,454
Control days, No.	15,104
Sex, No. (%)	
Male	2,575 (57.8)
Female	1,879 (42.2)
Age, yr	
Mean (SD)	77.6 (11.8)
Median (IQR)	80.2 (11.8)
No. (%)	
< 75	1,343 (30.2)
75-79	848 (19.0)
80-84	1,145 (25.7)
≥ 85	1,118 (25.1)
Race, No. (%)	
Han	4,392 (98.6)
Other	62 (1.4)

Definition of abbreviations: SD = standardized deviation; IQR = interquartile range.

Table 2. Distributions of air pollutants and meteorological conditions during case and control days in Hubei province, China, 2013-2018

Variable	Mean	SD	Min	P_{25}	Median	P_{75}	Max
Air pollutant							
$PM_{2.5}$, μg/m^3	65.0	43.3	4.1	34.8	53.8	83.2	376.3
PM_{10}, μg/m^3	103.2	56.8	7.6	62.6	91.5	129.5	608.5
SO_2, μg/m^3	20.3	17.5	1.0	8.9	14.7	25.5	186.6
NO_2, μg/m^3	37.1	20.8	1.6	21.8	32.8	48.0	155.3
CO, mg/m^3	1.20	0.49	0.03	0.88	1.10	1.42	6.67
O_3, μg/m^3	92.0	43.8	1.9	58.2	86.8	120.4	323.0
Meteorological condition							
Temperature, °C	16.1	9.0	-5.2	8.2	15.9	24.0	35.1
Relative humidity, %	72.4	14.1	18.0	63.3	74.3	83.5	100.0

Definition of abbreviations: SD = standardized deviation; P_{25} = the 25th percentile; P_{75}, the 75th percentile; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

Table 3. Spearman's correlation coefficients between air pollutants and meteorological conditions during case and control days in Hubei province, China, 2013-2018[a]

	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3	Temperature
PM_{10}	0.91						
SO_2	0.57	0.61					
NO_2	0.63	0.68	0.61				
CO	0.67	0.60	0.37	0.48			
O_3	-0.20	-0.13	-0.05	-0.18	-0.26		
Temperature	-0.51	-0.44	-0.26	-0.36	-0.38	0.62	
Relative humidity	-0.27	-0.37	-0.38	-0.37	-0.07	-0.26	0.13

Definition of abbreviations: $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

[a]All pairwise correlation coefficients were statistically significant ($P < 0.05$).

Table 4. Odds ratios (95% CIs) for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$, NO_2 and O_3 stratified by sex, age and season[a]

Variable	$PM_{2.5}$		NO_2		O_3	
	OR (%95 CI)	*P* value[d]	OR (%95 CI)	*P* value[d]	OR (%95 CI)	*P* value[d]
Sex[b]						
Male	1.06 (0.99, 1.14)	0.81	1.10 (0.98, 1.24)	0.85	1.06 (0.95, 1.17)	0.35
Female	1.07 (0.99, 1.16)		1.12 (0.98, 1.29)		1.14 (1.01, 1.29)	
Age[b]						
< 80	1.11 (1.03, 1.19)	0.18	1.12 (0.97, 1.28)	0.91	1.20 (1.07, 1.34)	0.014
≥ 80	1.03 (0.96, 1.11)		1.10 (0.98, 1.25)		0.98 (0.88, 1.10)	
Season[c]						
Warm	1.08 (0.95, 1.23)	0.76	1.14 (0.95, 1.37)	0.77	1.09 (1.01, 1.18)	0.018
Cool	1.06 (1.00, 1.12)		1.10 (0.99, 1.22)		0.93 (0.85, 1.03)	

Definition of abbreviations: OR = odds ratio; CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; NO_2 = nitrogen dioxide; O_3 = ozone.

[a]The IQR of $PM_{2.5}$, NO_2 and O_3 was 47.1 μg/m^3, 26.3 μg/m^3 and 52.9 μg/m^3, respectively. ORs (95% CIs) were estimated using conditional logistic regression models, adjusting for temperature and relative humidity.

[b]Analyses for O_3 were restricted to asthma death cases who died in warm season.

[c]Warm season was defined as April to September, while cool season was defined as January to March, and October to December.

[d]*P* value < 0.05 indicates significant effect modification.

Figure 1

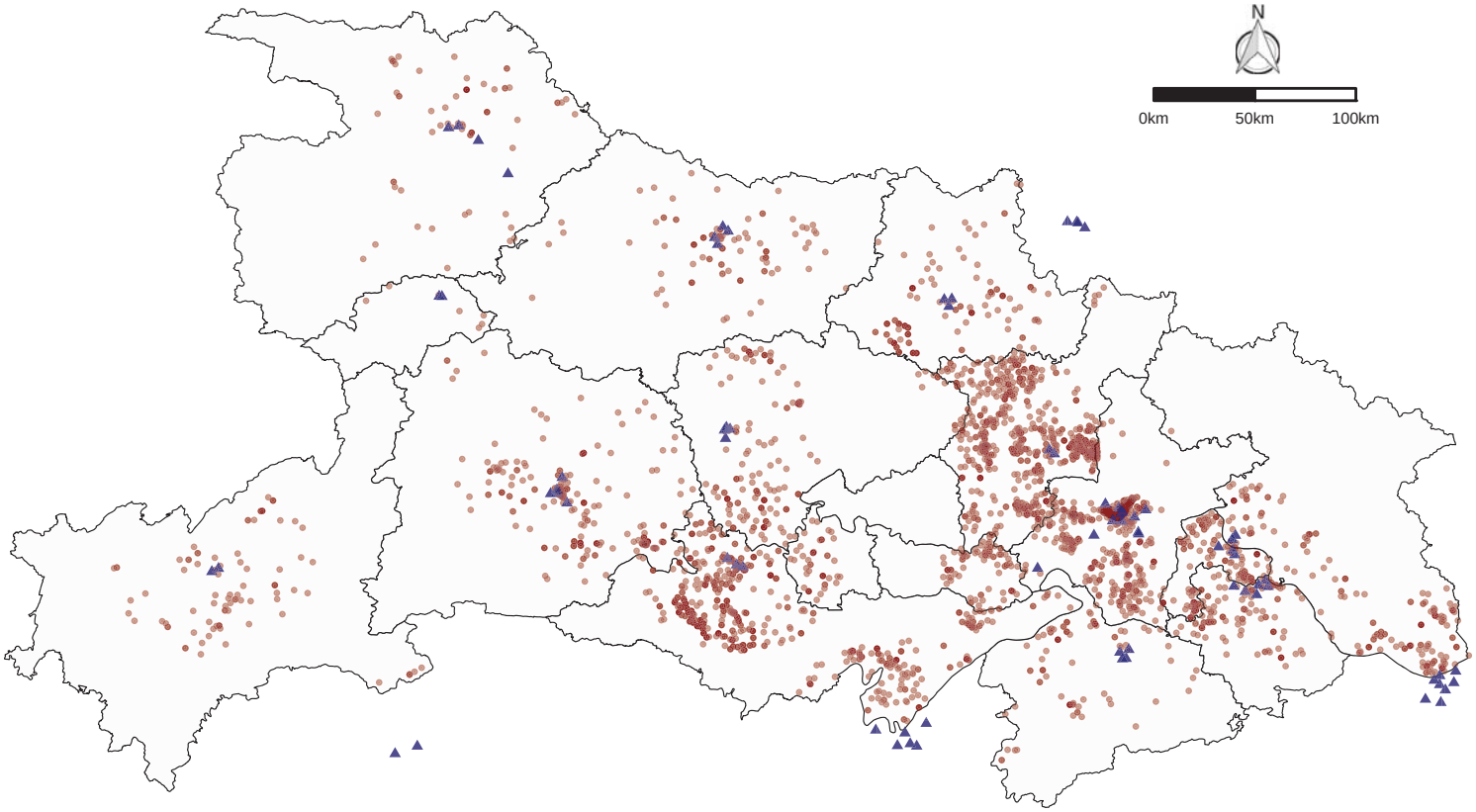


Figure 2

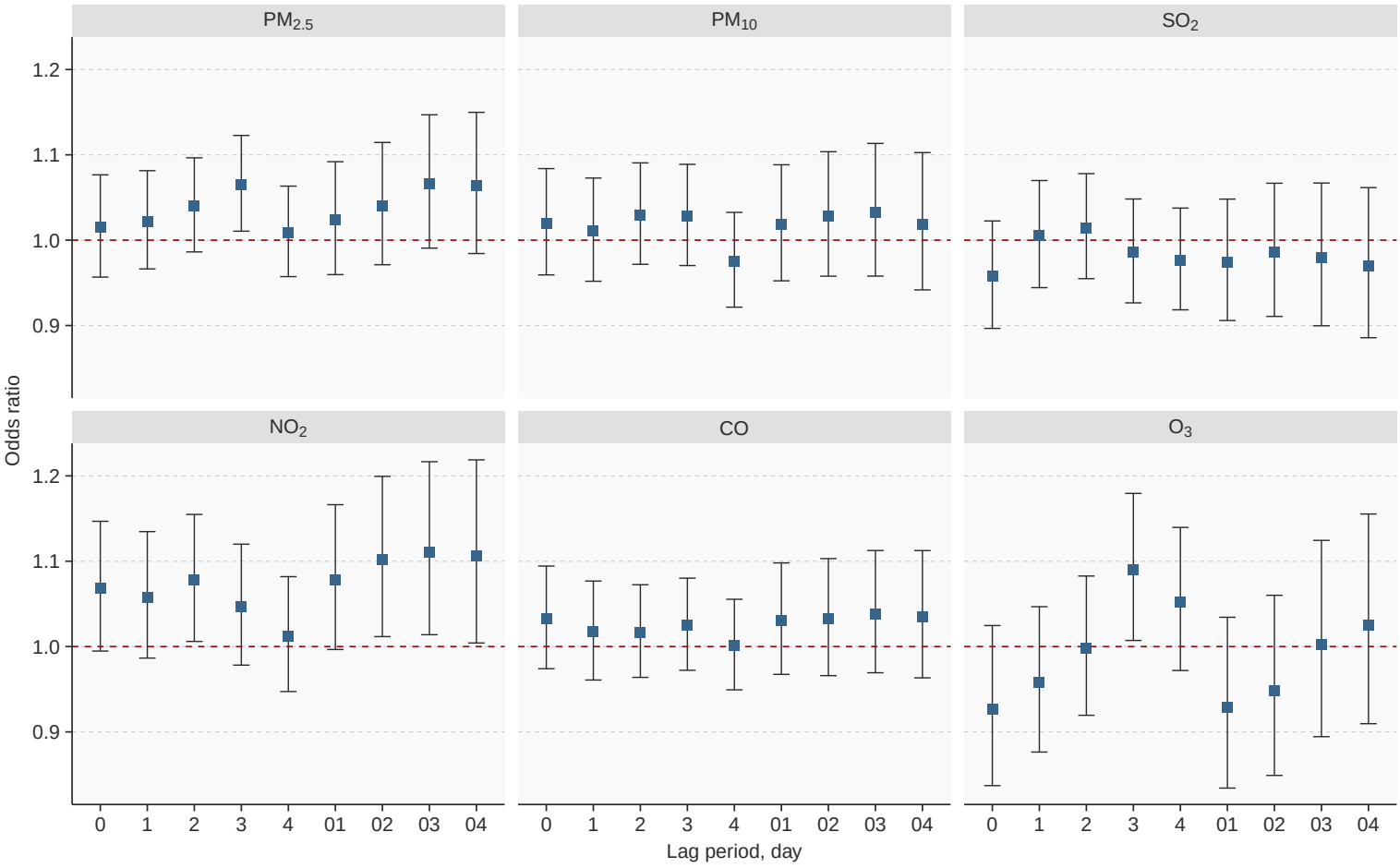
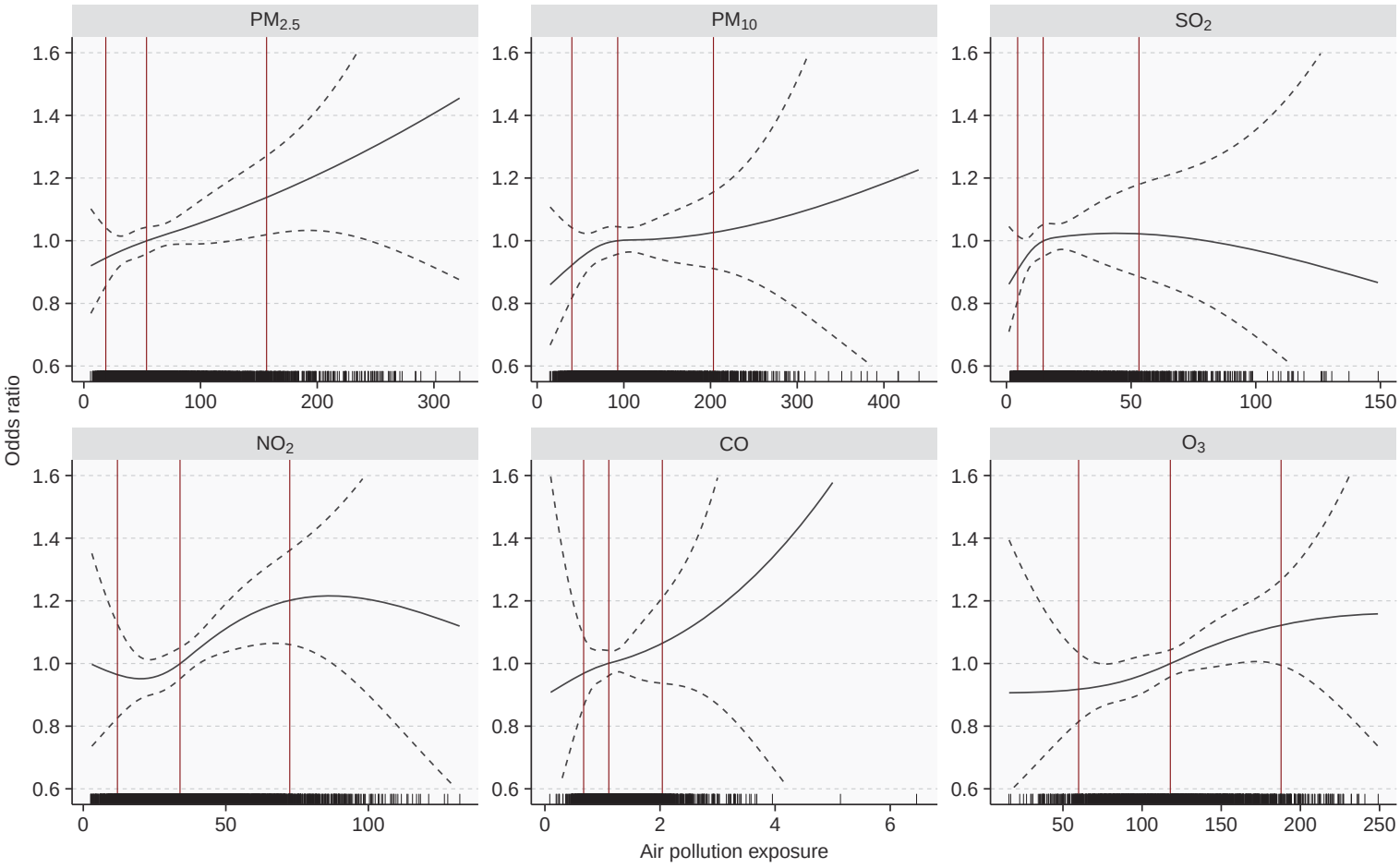

PM2.5
PM10
SO2
NO2
CO
O3
Odds ratio
1.2
1.1
1.0
0.9
0
1
2
3
4
01
02
03
04
Lag period, day

Figure 3



Online Data Supplement

Short-Term Exposure to Ambient Air Pollution and Asthma Mortality

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Supplemental Methods

Literature review

We initially identified 336 unique citations by searching PubMed for articles published in any language up to January 20, 2019 using the search terms "(Air pollution OR particulate matter OR sulfur dioxide OR nitrogen dioxide OR carbon monoxide OR ozone) AND (mortality OR death) AND asthma" in the publication title or abstract. By excluding citations that were not relevant (animal studies, or did not study air pollution and asthma mortality), 12 potential relevant articles were selected for further full text review and were summarized in Table E1.

Study design

This is a time-stratified case-crossover study. Proposed by Lumley and Levy in 2000, the time-stratified case-crossover design consists of taking as control 1 or more days falling within the same time stratum (e.g. month) as that in which the event occurred (1, 2). As implemented in a variety of previous case-crossover studies, for each asthma death we defined its case day as the day of death, and defined its control days as the days in the same year and month that shared the same day of week to control for potential confounding effects by day of week, long-term trend and seasonality (1, 3). Based on this design, there are 1 case day and 3-4 control days for each asthma death. For example, if an asthma death occurred on May 2, 2015 (Tuesday), its case day was May 2, 2015, while its control days were May 9, May 16, May 23, and May 30 in 2015; if an asthma death occurred on May 10, 2015 (Sunday), the case day was May 10, 2015, while its control days were May 3, May 17, and May 24, and May 31 in 2015.

Validation of exposure assessment

We employed a 10-fold cross validation (CV) technique to validate the use of inverse distance

weighting (IDW) method in exposure assessment. Specifically, the 57 air quality monitoring stations in Hubei province, China were randomly split into 10 subsets. For each subset, we applied the IDW method using data on the other 9 subsets to predict concentration for each monitoring station on each date. The process was repeated 10 times until all subsets were predicted. For each air pollutant, prediction accuracy was assessed by calculating coefficient of determination (R^2), mean absolute error (MAE) and bias between predicted and measured concentrations using the following equations.

$$R^2 = 1 - \frac{\sum_{i=1}^{N}(M_i - P_i)^2}{\sum_{i=1}^{N}(M_i - \overline{M}_i)^2}$$

$$MAE = \frac{1}{N}\sum_{i=1}^{N}|P_i - M_i|$$

$$Bias = \frac{1}{N}\sum_{i=1}^{N}P_i - M_i$$

Where M = measured concentration; $\overline{M}$ = mean of measured concentrations; P = predicted concentration.

Meteorological condition data

Grid data on daily mean temperature at 2 m above the ground, specific humidity at 2 m above the ground and surface pressure between 2013 and 2018 were extracted from the CMA Land Data Assimilation System (CLDAS version 2.0) with a spatial resolution of 0.0625° × 0.0625°. Based on each subject's home address, the daily average temperature, specific humidity and surface pressure values at each case and control day were extracted from the grid data using a bilinear interpolation method. Using daily average temperature, specific humidity and surface pressure, relative humidity was estimated using the following formulas (4):

$$\text{Saturation vapor pressure} = 6.112 \times e^{17.67 \times \frac{\text{temperature}}{\text{temperature} + 243.5}}$$

$$\text{Actual vapor pressure} = \frac{\text{specific humidity} \times \text{surface pressure}}{0.378 \times \text{specific humdity} + 0.622}$$

$$\text{Relative humidity} = \frac{\text{actual vapor pressure}}{\text{saturation vapor pressure}} \times 100$$

Test for effect modification

Effect modifications by sex, age and season were examined based on the point estimates (E = ln OR) and their standard errors (SE) in stratified models using a two-sample test (3, 5). For example (male vs female):

$$Z = \frac{E_{male} - E_{female}}{\sqrt{SE_{male}{}^2 + SE_{female}{}^2}}$$

Table E1. Characteristics and main relevant findings of the studies that investigated both air pollution and asthma mortality

Study	Country	Population/Health data	Pollutants	Exposure	Outcome	Main relevant findings	Comment
Sinharoy et al., 2018 (6)	Ausralia, Bangladesh, Belgium, Brazil, China, France, Germany, India, Israel, Malaysia, Mali, Mexico, Namibia, Nepal, Nigeria, Norway, Saudi, UK, Uruguay, USA, Vietnam, Zimbabwe	Asthma-related mortality data in each country obtained from WHO 2014 report	PM_{10}	Annual mean concentration in each country obtained from WHO 2014 report	Asthma-related mortality	No significant association was observed between annual mean PM_{10} concentration and annual asthma-related mortality rate.	This study did not investigate short-term exposure to air pollution.
Yorifuji et al., 2018 (7)	Japan	29,839 individuals who lived in Yokkaichi and a neighboring town, Kusu, of the Mie Prefecture, Japan and died from any causes (excluding external causes) between 1972 and 1991	SO_2	City-wide daily mean SO_2 concentration using daily concentrations at 4 monitoring stations in Yokkaichi	Mortality from all causes (excluding external causes), cardiovascular diseases, and respiratory diseases	SO_2 exposure (lag 0 day) was significantly associated with increased odds of COPD and asthma mortality (OR for each 6.9 ppb increase of SO_2 between 1982 and 1991: 1.610 [1.165-2.225]; ORs for SO_2 quartiles between 1972 and 1991: 1 [ref], 1.352 [1.039-1.760], 1.481 [1.109-1.978], and 1.450 [0.991-2.120]).	This case-crossover study did not investigate the association between short-term exposure to SO_2 and mortality from asthma separately.
Kravchenko et al., 2014 (8)	USA	Mortality data in North Carolina between 1993 and 2010	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3	City-wide averaged month-specific concentrations in North Carolina	Mortality from respiratory diseases (emphysema, asthma, pneumonia)	Decreasing levels of ambient PM_{10}, SO_2, NO_2 and O_3 were significantly associated with decline in asthma death.	This study did not investigate short-term exposure to air pollution.
Guaita et al., 2011 (9)	Spain	10,351 deaths due to respiratory diseases (78 due to asthma) in Madrid between 2003 and 2005	$PM_{2.5}$	Daily concentrations in Madrid	Mortality from all respiratory diseases, pneumonia, respiratory failure, chronic diseases of the air ways, and asthma	Short-term exposure to $PM_{2.5}$ was significantly associated with mortality from all respiratory diseases, pneumonia and respiratory failure. No association was found for mortality from chronic diseases of the air ways or asthma.	The daily number of asthma deaths in this time series study was too small (mean: 0.1; range: 0-2) to provide sufficient statistical power in qualifying the association between $PM_{2.5}$ exposure and asthma mortality.
Sicard et al., 2010 (10)	France	Mortality data in Alpes Maritimes between 1990 and 2005	$PM_{2.5}$, O_3	Annual concentrations in Alpes Maritimes	Mortality from ischemic heart diseases, other heart diseases, asthma, and airway diseases	Between 1997 and 2005, the annual mean and median values of ozone in urban areas increased by 3.0% $year^{-1}$ and 3.9% $year^{-1}$, respectively. PM10	The association between air pollution exposure and asthma mortality was not investigated. Also, this study did not investigate short-term exposure

						concentration showed a significant decreasing trend. Asthma significantly decreased during the study period (-4.03% $year^{-1}$).	to air pollution.
Iwai et al., 2005 (11)	Japan	525,903 deaths in 47 prefectures and 13 big cities in 2000	$PM_{2.5}$ (converted from PM_{10})	Annual mean concentration	Cause-specific mortality (including asthma)	$PM_{2.5}$ was significantly associated with asthma mortality only in females (RR: 1.21 [1.06-1.36] for each 10 $\mu g/m^3$ increase of $PM_{2.5}$ exposure).	This study did not investigate short-term exposure to air pollution.
Sunyer et al., 2002 (12)	Spain	467 male and 611 female patients aged over 14 years who had visited the emergency department of one of the four largest hospitals in Barcelona for asthma in 1985-1989 and died in 1985-1995	PM_{10}, SO_2, NO_2, CO, O_3	City-wide daily concentrations in Barcelona	Mortality from cardiovascular diseases, myocardial infraction, respiratory diseases, COPD, and asthma	Short-term exposure (lag 02) to NO_2 was significantly associated with increased risk of death for patients with severe asthma. The authors concluded that NO_2 and O_3 may exacerbate severe asthma and even cause death among asthmatic subjects.	This study investigated short-term exposure to air pollution and mortality among asthmatic patients. Of these asthmatic patients, only about 12% died from asthma.
Saez et al., 1999 (13)	Spain	Deaths (aged 2-45 years at death) from asthma in Barcelona between 1986 and 1989	SO_2, NO_2, O_3	Daily 24-hour mean concentrations of SO_2 and NO_2, and 1-hour maximum concentration of O_3 in Barcelona.	Asthma mortality	NO_2 (RR: 1.0374 for 1 $\mu g/m^3$ increase of exposure; $p = 0.013$) and O_3 (RR: 1.0215 for 1 $\mu g/m^3$ increase of exposure; $p = 0.054$) increased the probability of dying from asthma in Barcelona during the period 1986-1989. However, these associations disappeared in multi-pollutant models.	This study specifically investigated the association between short-term exposure to air pollution and asthma mortality using the generalized estimating equations method. Note that the sample size was small, as there was at most 1 death due to asthma per day during the study period.
Andersson et al., 1998 (14)	Sweden	780 male sulfite mill workers aged 40-75 years at death between 1960 and 1989	Occupational air pollutants in sulfite mills	Subjects were classified as exposed and unexposed based on their job titles	Mortality from asthma, COPD, lung cancer, stomach cancer, and brain cancer	There was an increased mortality from asthma and brain tumor among the sulfite workers. The mortality due to lung cancer was not significantly increased, and there was a reduced mortality from stomach cancer.	This case-control study concluded that the increased asthma mortality might be due to accidental exposure to irritating gases, including sulfur dioxide. However, there was no sufficient exposure assessment and exposure-response analyses.

Salinas et al., 1995 (15)	Chile	Mortality data in Greater Santiago from 1988 to 1991	$PM_{2.5}$, $PM_{2.5-10}$, SO_2, CO, O_3	City-wide daily concentrations averaged from 5 monitoring stations in Greater Santiago	Mortality from pneumonia, COPD, and asthma	The authors concluded that a clear pattern in the geographical distribution of risk of death, both for general mortality and specific respiratory causes (pneumonia, COPD and asthma) was found using SMR, with higher values in the most polluted areas regardless of socioeconomic and living conditions.	This study did not investigate short-term exposure to air pollution.
Lang et al., 1994 (16)	USA	Mortality data in Philadelphia residents between 1969 and 1991	PM_{10}, SO_2, NO_2, CO, O_3	Annual concentrations; Annual numbers of unhealthy days based on Pollution-Standards Index.	Asthma mortality	The rate of death from asthma have increased in Philadelphia, whereas concentrations of major air pollutants have declined.	This study did not investigate short-term exposure to air pollution and did not investigate if the increasing trend of asthma mortality and declining air pollutants was correlated.
Imai et al., 1986 (17)	Japan	215 deaths from bronchial asthma in Yokkaichi between 1963 and 1983	SO_2	Polluted area defined as 1.5 mg/100 cm^2*day or more; non-polluted area was within Yokkaichi city and at least 5 km away from the factories of the complex, where SO_2 had never exceeded the national ambient air quality standards.	Asthma mortality	(1) In response to worsening air pollution, mortality for bronchial asthma and chronic bronchitis began to increase. (2) Mortality due to bronchial asthma decreased immediately in response to improvement of pollution, whereas mortality due to chronic bronchitis decreased to the level in the control area 4 to 5 years after the concentration of sulfur dioxide (SO_2) began to satisfy the ambient air quality standard. (3) In the polluted area, mortality due to bronchial asthma in subjects who were 20 years of age was higher during the period in which higher concentrations of sulfur oxides were prevalent.	This study did not investigate short-term exposure to air pollution.

Table E2. Performance of IDW method in exposure assessment for daily exposures to air pollutants

Air pollutant	R^2	MAE	Bias
$PM_{2.5}$, $\mu g/m^3$	0.93	7.18	-0.07
PM_{10}, $\mu g/m^3$	0.84	13.73	0.14
SO_2, $\mu g/m^3$	0.56	6.31	-0.04
NO_2, $\mu g/m^3$	0.65	8.52	-1.51
CO, mg/m^3	0.47	0.23	-0.01
O_3, $\mu g/m^3$	0.75	15.64	1.47

Definition of abbreviations: IDW = inverse distance weighting; R^2 = coefficient of determination; MAE = mean absolute error; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

Table E3. OR (95% CI) for asthma mortality associated with each 10 μg/m^3 increase of exposures to $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and 1 mg/m^3 increase of exposure to CO

Lag period, day	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3
0	1.003 (0.991-1.016)	1.003 (0.994-1.012)	0.974 (0.936-1.013)	1.025 (0.998-1.053)	1.066 (0.949-1.198)	0.986 (0.967-1.005)
1	1.005 (0.993-1.017)	1.002 (0.992-1.011)	1.003 (0.966-1.042)	1.022 (0.995-1.049)	1.035 (0.923-1.159)	0.992 (0.975-1.009)
2	1.008 (0.997-1.020)	1.004 (0.996-1.013)	1.009 (0.973-1.046)	1.029 (1.002-1.056)	1.034 (0.929-1.150)	1.000 (0.984-1.015)
3	1.013 (1.002-1.025)	1.004 (0.995-1.013)	0.991 (0.955-1.029)	1.018 (0.992-1.044)	1.050 (0.945-1.167)	1.016 (1.001-1.032)
4	1.002 (0.991-1.013)	0.996 (0.988-1.005)	0.986 (0.950-1.022)	1.005 (0.980-1.030)	1.002 (0.901-1.114)	1.010 (0.995-1.025)
01	1.005 (0.991-1.019)	1.003 (0.993-1.013)	0.984 (0.942-1.029)	1.029 (0.999-1.060)	1.062 (0.936-1.206)	0.986 (0.966-1.006)
02	1.008 (0.994-1.023)	1.004 (0.993-1.015)	0.991 (0.945-1.040)	1.037 (1.004-1.072)	1.065 (0.933-1.217)	0.990 (0.970-1.011)
03	1.014 (0.998-1.030)	1.005 (0.993-1.017)	0.988 (0.938-1.040)	1.041 (1.005-1.077)	1.078 (0.940-1.238)	1.001 (0.979-1.022)
04	1.013 (0.997-1.030)	1.003 (0.991-1.015)	0.982 (0.929-1.037)	1.039 (1.002-1.078)	1.072 (0.928-1.238)	1.005 (0.982-1.028)

Definition of abbreviations: OR = odds ratio; CI = confidence interval; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

Table E4. ORs (95% CIs) for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$ (lag 3), NO_2 (lag 03) and O_3 (lag 3) estimated by single- and two-pollutant models[a]

Air pollutant	Model	OR (95% CI)	*P* value[b]
$PM_{2.5}$	$PM_{2.5}$	1.07 (1.01-1.12)	
	$PM_{2.5}$ + O_3	1.06 (1.01-1.12)	0.69
NO_2	NO_2	1.11 (1.01-1.22)	
	NO_2 + CO	1.11 (1.00-1.22)	0.74
	NO_2 + O_3	1.12 (1.02-1.23)	0.58
O_3	O_3	1.09 (1.01-1.18)	
	O_3 + $PM_{2.5}$	1.08 (0.99-1.18)	0.62
	O_3 + PM_{10}	1.07 (0.99-1.17)	0.50
	O_3 + SO_2	1.11 (1.02-1.20)	0.27
	O_3 + NO_2	1.07 (0.98-1.16)	0.12
	O_3 + CO	1.08 (1.00-1.17)	0.25

Definition of abbreviations: OR = odds ratio; CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

[a]The IQR of $PM_{2.5}$, NO_2 and O_3 was 47.1 μg/m^3, 26.3 μg/m^3, and 52.9 μg/m^3, respectively. ORs (95% CIs) were estimated using conditional logistic regression models, adjusting for temperature and relative humidity.

[b]Estimated using likelihood ratio test by comparing the single-pollutant model and each nested two-pollutant model.

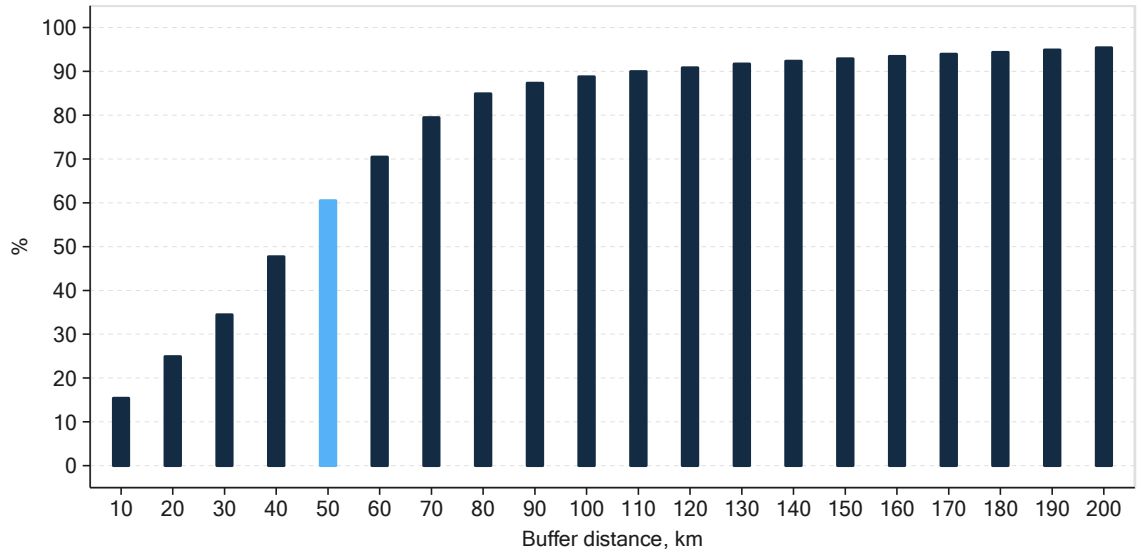

Figure E1. Asthma death case coverage at varying fixed buffer distances in Hubei province, China. The light blue column indicates a 50 km buffer distance used in the exposure assessment.

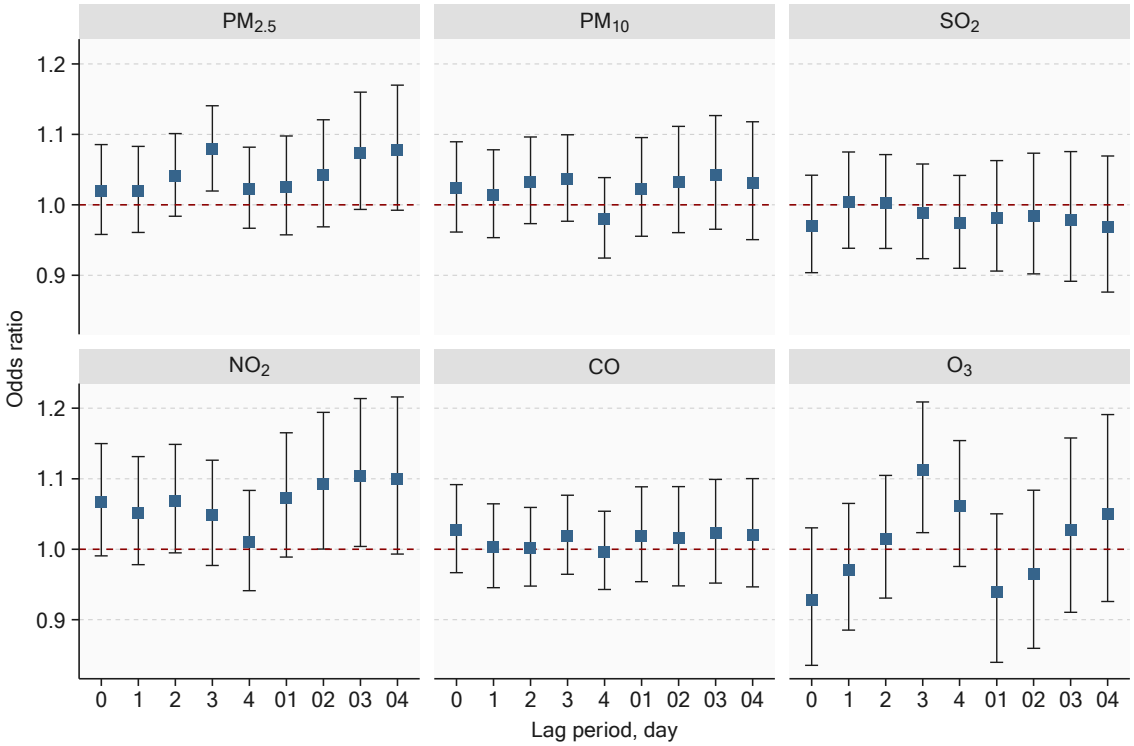

Figure E2. ORs (95% CIs) for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$ (IQR: 47.1 μg/m^3), PM_{10} (IQR: 65.0 μg/m^3), SO_2 (IQR: 16.6 μg/m^3), NO_2 (IQR: 26.3 μg/m^3), CO (IQR: 0.50 mg/m^3) and O_3 (IQR: 52.9 μg/m^3) with different lag periods, restricted to asthma death cases who died between 2014 and 2018. ORs (95% CIs) were estimated using conditional logistic regression models, adjusting for temperature and relative humidity. Definition of abbreviations: OR = odds ratio; CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

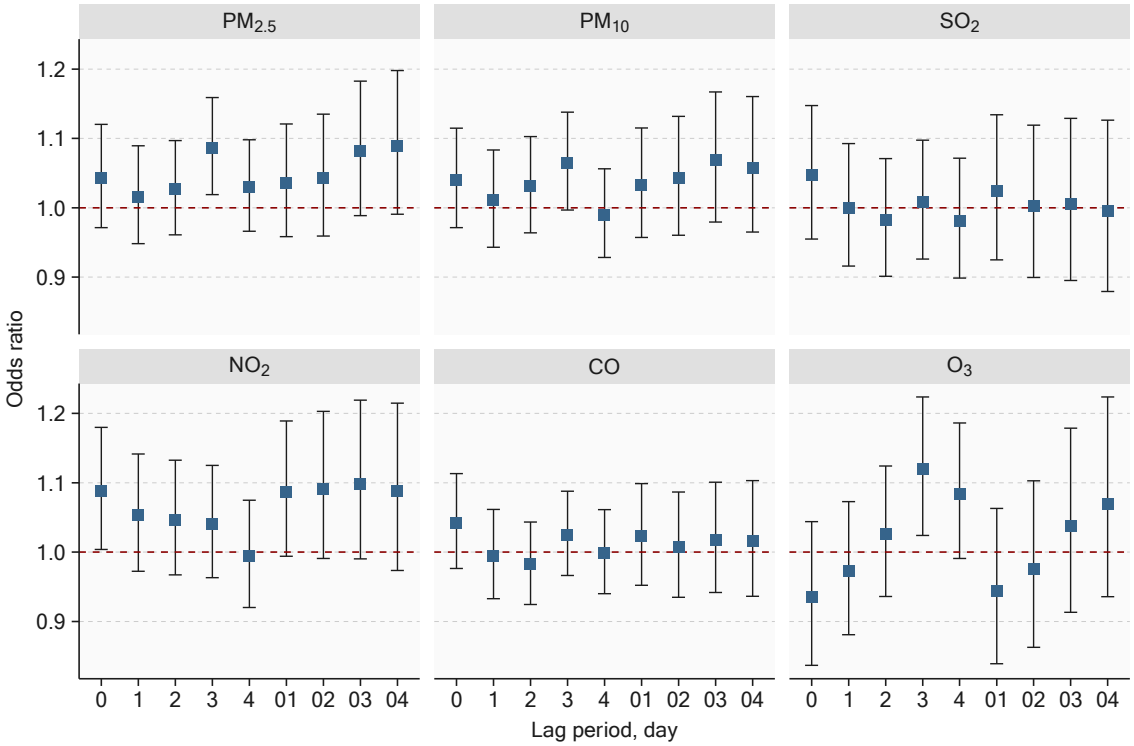

Figure E3. ORs (95% CIs) for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$ (IQR: 47.1 μg/m^3), PM_{10} (IQR: 65.0 μg/m^3), SO_2 (IQR: 16.6 μg/m^3), NO_2 (IQR: 26.3 μg/m^3), CO (IQR: 0.50 mg/m^3) and O_3 (IQR: 52.9 μg/m^3) with different lag periods, restricted to asthma death cases who died between 2015 and 2018. ORs (95% CIs) were estimated using conditional logistic regression models, adjusting for temperature and relative humidity. Definition of abbreviations: OR = odds ratio; CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

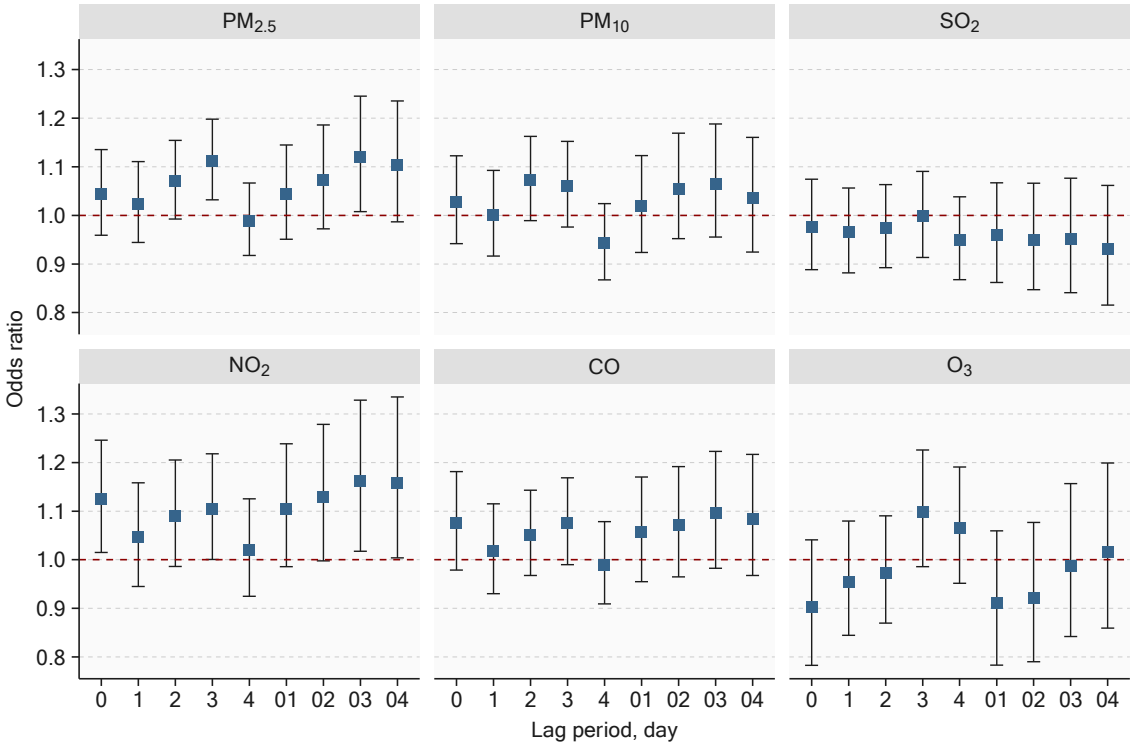

Figure E4. ORs (95% CIs) for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$ (IQR: 47.1 μg/m^3), PM_{10} (IQR: 65.0 μg/m^3), SO_2 (IQR: 16.6 μg/m^3), NO_2 (IQR: 26.3 μg/m^3), CO (IQR: 0.50 mg/m^3) and O_3 (IQR: 52.9 μg/m^3) with different lag periods, with exposure assessed using all monitoring stations within 25 km from the home address. ORs (95% CIs) were estimated using conditional logistic regression models, adjusting for temperature and relative humidity. Definition of abbreviations: OR = odds ratio; CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

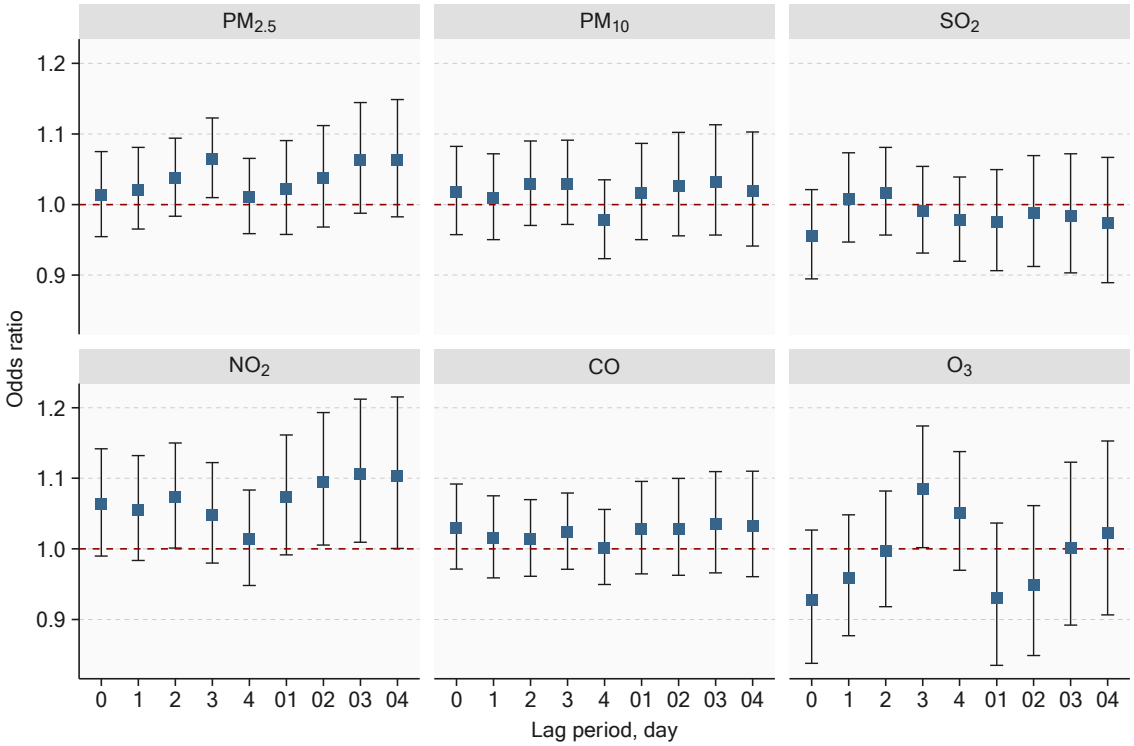

Figure E5. ORs (95% CIs) for asthma mortality associated with each IQR increase of exposures to $PM_{2.5}$ (IQR: 47.1 μg/m^3), PM_{10} (IQR: 65.0 μg/m^3), SO_2 (IQR: 16.6 μg/m^3), NO_2 (IQR: 26.3 μg/m^3), CO (IQR: 0.50 mg/m^3) and O_3 (IQR: 52.9 μg/m^3) with different lag periods, restricted to Han race asthma death cases. ORs (95% CIs) were estimated using conditional logistic regression models, adjusting for temperature and relative humidity. Definition of abbreviations: OR = odds ratio; CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2 = sulfur dioxide; NO_2 = nitrogen dioxide; CO = carbon monoxide; O_3 = ozone.

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