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Exposure to hourly ambient air pollutants and risk of emergency department visits for asthma: A multicenter time-stratified case-crossover analysis

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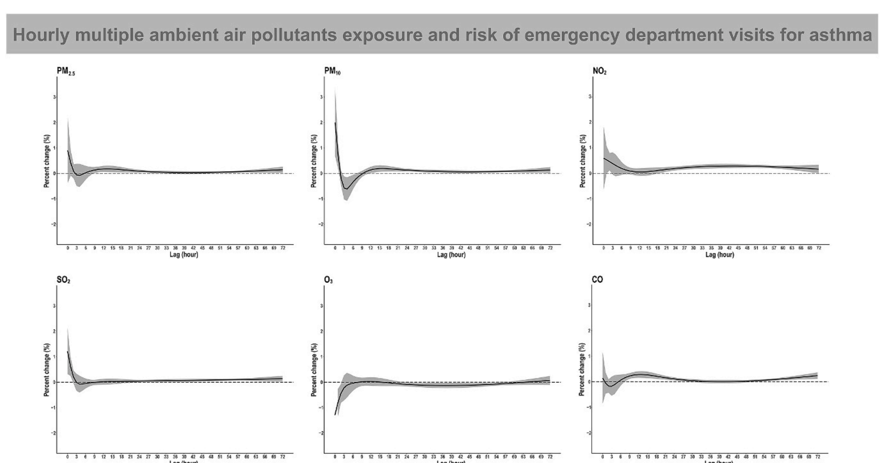
HIGHLIGHTS

- We examined hourly air pollutants exposure and risk of ED visits for asthma.
- $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO was associated with the increased risk of asthma ED visits.
- The association was most pronounced at the lag 0 h, gradually attenuated and diminished after 12 h of exposure.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Exposure to daily ambient air pollutants has been linked with increased risk of asthma morbidity and mortality. However, the association between exposure to air pollution and risk of emergency department (ED) visits for asthma on an hourly level remains unclear.

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Hourly exposure
Time-stratified case-crossover

Methods: We conducted a time-stratified case-crossover design and included a total of 121,112 asthma ED visits from 11 hospitals in three cities located in Zhejiang province, China, between January 1, 2016 and September 30, 2021. We used conditional logistic regressions combined with a distributed lag linear model to estimate the association between risk of asthma ED visits and hourly exposure to fine particulate matter ($PM_{2.5}$), respirable particulate matter (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) after adjusted for meteorological factors and public holiday.
Results: Hourly exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO was associated with an increased risk of asthma ED visits. This association was most pronounced in the concurrent hour of exposure (lag 0 h), rapidly attenuated over a period of 3–12 h, and diminished thereafter. Each interquartile range increase in air pollutant over 0–72 h was associated with increased risk of asthma ED visits by 7.0% (95% confidence interval [CI]: 5.4%, 8.6%) for $PM_{2.5}$, 6.7% (95% CI: 5.1%, 8.2%) for PM_{10}, 18.1% (95% CI: 15.4%, 21.0%) for NO_2, 6.5% (95% CI: 4.8%, 8.2%) for SO_2, and 7.4% (95% CI: 5.6%, 9.1%) for CO.
Conclusion: Our findings suggest that hourly exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO, but not O_3, is associated with increased risk of ED visits for asthma shortly after exposure.

1. Introduction

Asthma is a complex respiratory condition characterized by various symptoms, such as wheezing and breathlessness. It is a global public health challenge, affecting approximately 334 million individuals around the world, and its prevalence has been growing, particularly in low- and middle-income countries (Papi et al., 2018). In China, asthma has posed a significant threat, with an incidence rate of 4.2% in 2019 (Huang et al., 2019). Individuals with asthma often experience persistent and recurrent symptoms, significantly impacting their quality of life and imposing a substantial burden on both individuals and communities (Kirby, 2022). Therefore, it is crucial to identify modifiable risk factors and develop effective strategies to alleviate the burden associated with asthma.

In addition to well-known asthma triggers, such as allergens and viral infections (Lemanske and Busse, 1997), there is a growing body of evidence suggesting that air pollution may contribute to either triggering or exacerbating asthma. However, the findings from these studies have been mixed, with some reporting an association between exposure to air pollution and risk of asthma (Anenberg et al., 2018; Chatkin et al., 2022; Liu et al., 2019; McConnell et al., 2010; Song et al., 2022), while others do not find an association (Anderson et al., 2012, 2013). Additionally, most previous studies have examined the association between exposure to air pollution and the risk of asthma on a daily level (Liu et al., 2019; Song et al., 2022; Zhao et al., 2021), which has been challenged by concerns about potential underestimation of the effects resulting from misclassification of the time of event onset (Chen et al., 2021; Lokken et al., 2009).

To our knowledge, only few studies have assessed the association between air pollution exposure and risk of asthma at the hourly level (Cheng et al., 2022; Lei et al., 2022). Additionally, limited evidence exists regarding the relationship between hourly exposure to air pollution and the risk of asthma emergency department (ED) visits in China, particularly in areas with moderate to severe air pollution.

Accordingly, we sought to conduct a large-scale case-crossover study to examine the association between hourly exposure to air pollutants and the risk of asthma ED visits from 11 hospitals in 3 cities located in southeast China from 2016 to 2021. Additionally, we aimed to examine whether the association was varied by subgroups defined by age, sex, season, city, and time of day exposure.

2. Methods

2.1. Study participants

This study was conducted in three cities in Zhejiang province, specifically Hangzhou, Zhoushan, and Jinhua. These cities are situated in the southeastern region of China and experience a subtropical monsoon climate, characterized by distinct seasons, ample sunshine, and rainfall. Hourly data on asthma ED visits were obtained from a total of 11 hospitals across the three cities from January 1, 2016 to December 31, 2021. The patients were coded according to the International Classification of Disease, 10th version (ICD-10 codes J45-J46). For each asthma case, information on the date and time of ED visits, diagnosis reports, corresponding ICD-10 codes, and demographic characteristic were extracted. The study protocol was reviewed and approved by the Institutional Review Board at the Zhejiang Provincial Center for Disease Control and Prevention (AF/SC-06/01.0) prior to data collection.

2.2. Air pollution exposure assessment

We obtained hourly concentrations of six criteria air pollutants from the National Urban Air Quality Real-time Publishing Platform (http://106.37.208.233:20035), including fine particulate matter ($PM_{2.5}$), particulate matter with an aerodynamic diameter $\leq$10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO). To match each patient's hospital address with the nearest air monitoring station, we geocoded the longitude and latitude coordinates of the hospitals. In cases where data were missing for the nearest station, simple linear regression was used to predict the missing value based on the available measurements between the nearest and the second nearest station, both of which were within a 10 km radius of the hospital. The median distance between the hospitals and the selected monitoring stations was 4.1 km. To minimize the potential influence of outliers in the concentrations of air pollutants, we excluded the highest and lowest 0.1% of hourly concentrations for the analysis.

2.3. Covariates

We collected hourly meteorological data covering the same study period from China Meteorological Data Service Center (http://data.cma.cn). The median distance between the selected meteorological monitoring stations and hospitals was 12.1 km. Meteorological variables (i.e., ambient temperature, relative humidity, air pressure, wind speed, precipitation) and public holiday are included in all models to account for their potential confounding effects.

2.4. Study design

We conducted a case-crossover design and used a conditional logistic regression model at the individual level to examine the relationship between hourly changes in concentrations of air pollutants and the risk of asthma ED visits (Huang and Lai, 2023; Levy et al., 2001). The case-crossover study design is commonly used for the assessment of acute effects of air pollution on various health outcomes (Chen et al., 2022a; Lei et al., 2022). By utilizing this self-matched design, we effectively controlled for the effects of long-term trends, seasonality, and potential individual-level confounders, such as age and sex (Bateson and Schwartz, 1999; Bhaskaran et al., 2011; J. Cheng et al., 2022).

For each participant, we compared the exposure level during the hour when asthma occurred (i.e., the case period) with the exposure level during the same hour on other days when asthma did not occur (i.e., the control period) (Di et al., 2017). To select control periods, we used a time-stratified approach. Specifically, we selected the same hour of the day on the same weekday within the same month and year as the case period. For example, if an individual admitted to ED visits for asthma at 10 a.m. on Friday, March 22, 2019 (the case period), the control periods would include 10 a.m. on all other Fridays in March 2019 (March 1, 8, 15, and 29).

2.5. Statistical analysis

We used conditional logistic regression to estimate the association between hourly exposure to air pollution and the risk of asthma ED visits. In the models, we adjusted for hourly ambient temperature using a natural cubic spline with 6 degrees of freedom (*df*), hourly relative humidity using a natural cubic spline with 3 *df*, hourly air pressure using a natural cubic spline with 3 *df* (Chen et al., 2022b; Lv et al., 2023; Xue et al., 2023), precipitation (dummy variable), and public holiday (dummy variable).

We initially assumed a linear exposure-response relationship between air pollution and the risk of asthma ED visits. We used a distributed lag linear modelling framework to capture both the linear exposure-response function and nonlinear lag-response function for air pollution.

Based on our preliminary analysis, we selected a maximum lag of 72 h. We modeled the lag response function using a natural cubic spline function with 3 internal knots placed at equal intervals on the log scale of lags up to 72 h. To evaluate potential nonlinear exposure–response relationships, we used a natural cubic spline with 3 *df* for each air pollutant and included the same covariates as the main analysis (Liu et al., 2019).

To identify vulnerable subgroups, we performed stratified analyses by age (preschool children [0–5 years], school children [6–18 years], adult [19–64 years], and older [≥65 years]) (Cheng et al., 2023; Sapkota et al., 2020; Zhang et al., 2019), sex (male versus female), season (spring [Mar–Jun], summer [Jun–Sep], autumn [Sep–Dec], and winter [Dec–Mar]) (Janssen et al., 2017), city (Hangzhou, Jinhua, and Zhoushan), and time of day (daytime [8 am to 8 pm] versus nighttime [8 pm to 8 am in the next day]) (Chen et al., 2022a; Lv et al., 2023). A two-sample Z test was used to evaluate the significance of differences in effect estimates between subgroups. For example, effect differences between sex could be tested using the formula as follows:

$$z = \frac{\beta_{female} - \beta_{male}}{\sqrt{SE_{female}^2 + SE_{male}^2}}$$

where β were the stratum-specific regression coefficients and SE were the corresponding standard errors.

2.6. Sensitivity analysis

We performed several sensitivity analyses to confirm the robustness of our findings. First, we varied the number of knots for the natural cubic spline in the lag-response function for air pollutants. We tested models with 2, 4, or 5 internal knots placed at equal intervals on the log scale of lags up to 72 h. Second, to explore longer delayed effects of air pollution, we fitted the models with maximum lags up to 96 h, 120 h, 144 h, or 168 h. Third, to control for potential confounding of co-pollutant, we constructed two-pollutant models and included co-pollutant one at a time. Due to high correlation between

$PM_{2.5}$ and PM_{10} ($r > 0.9$), both pollutants were not simultaneously included in the same model to prevent potential issues with collinearity.

All analyses were conducted in R software (version 4.2.1). We expressed results as percentage excess risk (ER%) increase in risk of asthma ED visits associated with an interquartile range (IQR) increase in $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO. All tests were two-sided, and effects of $p < 0.05$ were considered statistically significant.

Table 1
Characteristics of the studied population.

Characteristics	N or N (%)
Case days	121,112
Control days	411,631
Age, years	
0-5	41,560 (34.3)
6-18	21,689 (17.9)
19-64	36,045 (29.8)
≥ 65	14,551 (12.0)
Missing	7267 (6.0)
Sex	
Male	69,005 (57.0)
Female	51,872 (42.8)
Missing	235 (0.2)
Season	
Winter (Dec–Mar)	33,723 (27.8)
Spring (Mar–Jun)	32,277 (26.7)
Summer (Jun–Sep)	28,129 (23.2)
Autumn (Sep–Dec)	26,983 (22.3)
City	
Hangzhou	81,807 (67.5)
Jinhua	5871 (4.9)
Zhoushan	33,434 (27.6)
Time of day†	
Daytime	111,031 (91.7)
Nighttime	10,081 (8.3)

Notes: †Daytime was from 8 a.m. to 8 p.m. during 1 day; nighttime was the rest of the day.

Table 2
Percentage excess risk of asthma associated with an interquartile range increase in air pollutant over lags 0–72 h.

Air pollutants	IQR	Percentage excess risk (95% CI)
$PM_{2.5}$	29	7.0 (5.4, 8.6)
PM_{10}	43	6.7 (5.1, 8.2)
NO_2	30	18.1 (15.4, 20.9)
SO_2	5	6.5 (4.8, 8.2)
O_3	63	−6.6 (−9.2, −3.9)
CO	0.4	7.4 (5.6, 9.1)

Abbreviations: IQR, interquartile range; CI, confidence interval; $PM_{2.5}$, fine particulate matter; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; CO, carbon monoxide.

3. Results

3.1. Descriptive statistics

We included a total of 121,112 asthma ED visits from 2016 to 2021 in this analysis, of which 52.2% were under the age of 18 years, 57.0% were male, 67.5% resided in Hangzhou city, 26.7% of cases occurred during the spring season, and 91.7% occurred during daytime (Table 1).

The concentration of air pollutants and the values of meteorological variables during the "case periods" was similar to those during the "control periods" (**Table S2**). The correlations between air pollutants and meteorological variables generally ranged from low to moderate (Table S8). $PM_{2.5}$ was strongly correlated with PM_{10} and thus we did not include $PM_{2.5}$ and PM_{10} simultaneously in the two-pollutant models.

3.2. Regression results

Generally, exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO was associated with an increased risk of asthma ED visits over 0–72 h (Table 2). For example, after adjusting for potential confounders, each IQR increase in the concentrations of $PM_{2.5}$ (29 μg/m^3), PM_{10} (43 μg/m^3), NO_2 (30 μg/

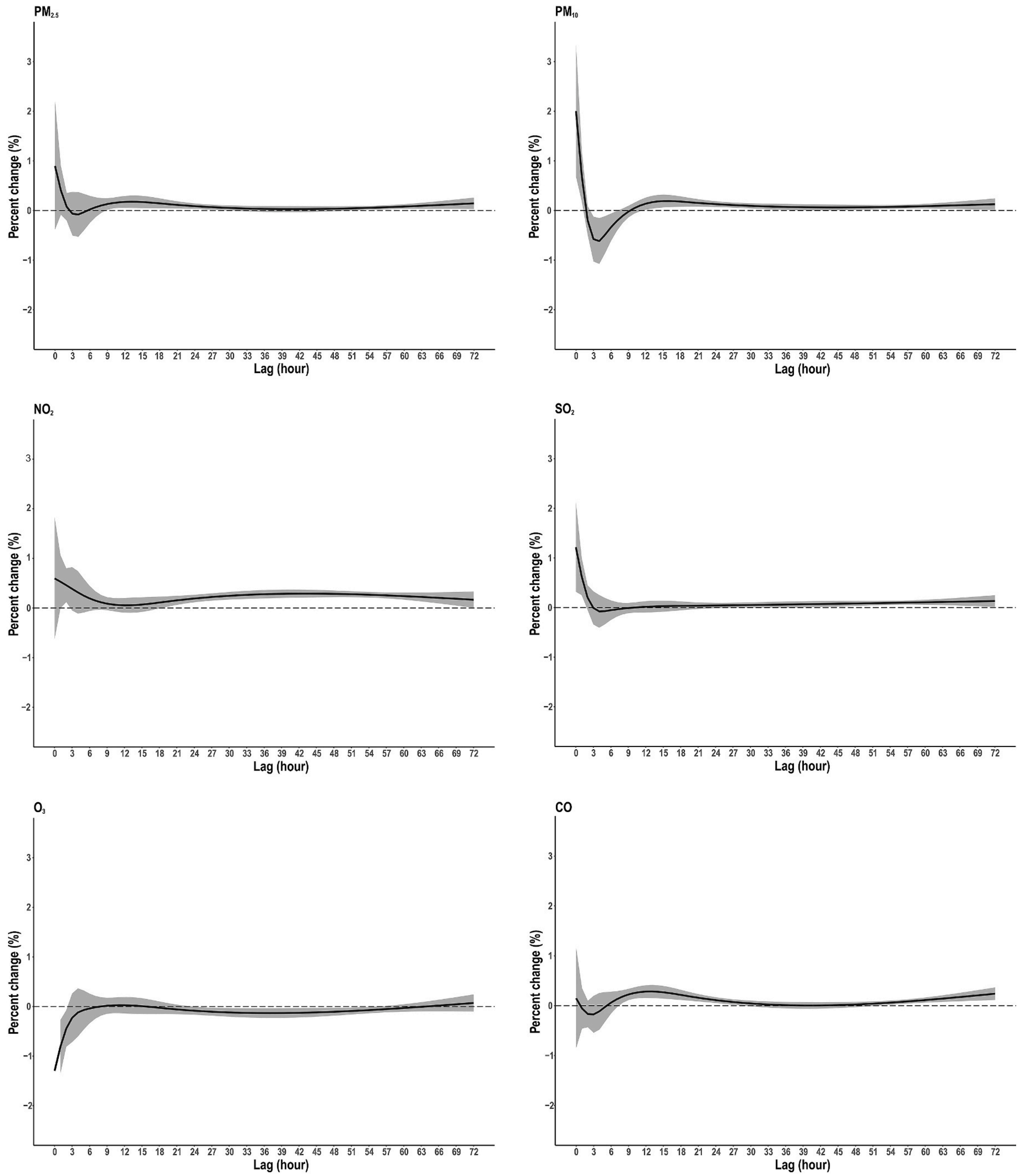


Fig. 1. Lag structures for the associations between exposure to hourly air pollutants and risk of emergency department visits for asthma.
Note: A, Fine particulate matter ($PM_{2.5}$); B, particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}); C, nitrogen dioxide (NO_2); D, sulfur dioxide (SO_2); E, ozone (O_3); F, carbon monoxide (CO). The black solid lines are the average odds ratio in the risk of asthma admission associated with each interquartile range increase of pollutants ($PM_{2.5}$, 29.0 μg/m^3; PM_{10}, 43 μg/m^3; NO_2, 30.0 μg/m^3; SO_2, 5.0 μg/m^3; O_3, 63.0 μg/m^3; and CO, 0.6 mg/m^3) and the gray areas are the 95% confidence intervals.

m^3), SO_2 (5 μg/m^3), and CO (0.4 mg/m^3) over a period of 0–72 h was associated with a higher risk of asthma ED visits by 7.0% (95% CI: 5.4%, 8.6%), 6.7% (95% CI: 5.1%, 8.2%), 18.1% (95% CI: 15.4%, 21.0%), 6.5% (95% CI: 4.8%, 8.2%), and 7.4% (95% CI: 5.7%, 9.1%), respectively (Table 2). However, for O_3 (63 μg/m^3), each IQR increase over 0–72 h was linked to a reduced risk of ED visits for asthma by −6.6% (95% CI: −9.2%, −3.9%) (Table 2).

The association between hourly exposure to air pollutants and the risk of ED visits for asthma was most pronounced during the concurrent hour of exposure (lag 0 h), gradually attenuated over a period of 3–12 h and then diminished thereafter (Fig. 1). Compared with the other studied lag periods, the strongest associations for $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 were observed at lag 0–3 h, while for CO, the most pronounced associations were at approximately lag 11–17 h.

The exposure-response relationships for the association between $PM_{2.5}$, PM_{10}, SO_2 and O_3 and the risk of ED visits for asthma were approximately linear, indicating that the risks of asthma increased with increasing concentration of $PM_{2.5}$, PM_{10}, SO_2 and O_3 (Fig. 2).

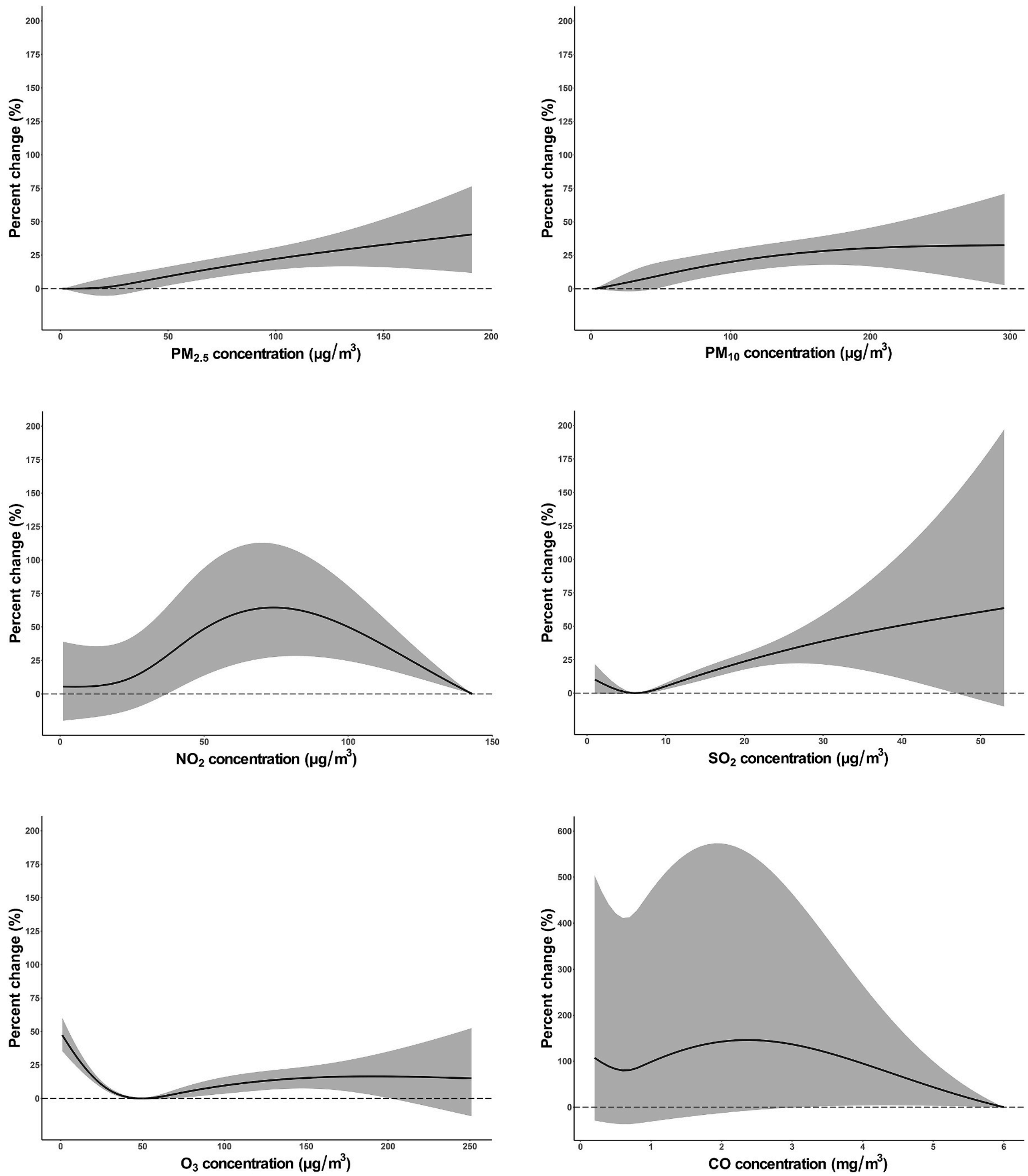


Fig. 2. The cumulative exposure–response curves for the associations between air pollutants and risk of emergency department visits for asthma over lags 0–72 h. Note: The black solid lines are the average odds ratio in the risk of asthma emergency department visits and the gray areas are the 95% confidence intervals. A, Fine particulate matter ($PM_{2.5}$); B, particulate matter with an aerodynamic diameter $\leq$10 μm (PM_{10}); C, nitrogen dioxide (NO_2); D, sulfur dioxide (SO_2); E, ozone (O_3); F, carbon monoxide (CO).

3.3. Subgroup analyses

To identify susceptible subpopulation, we conducted stratified analyses by subgroups defined by age, sex, seasons, city, and day of time. We found that the risk was higher among male patients, school children, residents of Hangzhou city, during the spring season, or at night-time (**Table 3**).

3.4. Sensitivity analysis

We performed several sensitivity analyses to confirm the robustness of our findings. We constructed two-pollutant models and found that our results were not materially different except when adjusting for NO_2. In this case, the effects of $PM_{2.5}$, PM_{10}, SO_2, O_3, and CO were found to be statistically insignificant (Table S9 & Fig. 3). Furthermore, we conducted additional assessments by varying the number of knots placed at equal intervals on the log scales of lag, as well as extending the maximum lag hours. These variations did not substantially alter our findings (Tables S10–S11).

Table 3
Risk of emergency department visits for asthma associated with an interquartile range increase in air pollutants over lags 0–72 h by subgroups defined by age, sex, season, city, and time of day.

Characteristics	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO
Age, years						
0-5	8.1 (5.7, 10.7)	5.3 (3.0, 7.6)	22.1 (17.5, 27.0)	7.4 (4.6, 10.2)	−16.8 (−21.0, −12.4)	13.2 (10.1, 16.4)
6-18	13.5 (9.5, 17.6)*	12.6 (8.8, 16.5)*	36.6 (29.2, 44.6)*	12.1 (8.1, 16.3)	−1.5 (−7.8, 5.2)	12.8 (8.5, 17.2)
19-64	3.6 (0.7, 6.7)*	5.0 (2.0, 8.0)	9.3 (4.6, 14.2)*	3.56 (0.5, 6.7)	−2.9 (−7.8, 2.2)	1.8 (−1.3, 5.0)
≥ 65	3.6 (−0.9, 8.2)	2.9 (−1.5, 7.5)	6.1 (−0.8, 13.5)*	4.0 (−0.5, 8.7)	−1.9 (−9.8, 6.7)*	2.3 (−2.4, 7.2)*
Sex						
Male	7.8 (5.7, 10.0)	7.4 (5.4, 9.4)	20.3 (16.6, 24.1)	7.2 (4.9, 9.5)	−6.7 (−10.2, −3.1)	7.8 (5.5, 10.1)
Female	6.0 (3.7, 8.4)	5.8 (3.5, 8.1)	15.7 (11.6, 19.9)	5.6 (3.1, 8.1)	−6.4 (−10.5, −2.2)	7.0 (4.4, 9.7)
Season						
Spring (Mar–Jun)	10.7 (8.5, 12.9)	11.7 (9.4, 14.0)	24.6 (19.9, 29.4)	10.5 (8.0, 13.1)	−29.6 (−35.2, −23.5)	14.8 (11.8, 17.9)
Summer (Jun–Sep)	−2.1 (−6.0, 2.0)	−0.3 (−3.8, 3.3)	2.1 (−3.2, 7.7)*	2.3 (−1.2, 5.9)*	−3.0 (−9.2, 3.6)	2.6 (−0.9, 6.1)
Autumn (Sep–Dec)	6.1 (0.8, 11.6)	3.0 (−2.8, 9.1)*	11.0 (3.8, 18.6)*	−6.9 (−11.5, −2.1)*	6.6 (0.6, 13.0)	7.4 (3.2, 11.8)*
Winter (Dec–Mar)	−1.3 (−4.0, 2.4)	1.1 (−2.0, 4.3)	17.1 (11.5, 22.9)*	1.6 (−2.5, 5.8)*	−3.4 (−8.1, 1.4)	−4.2 (−7.9, −0.3)
City						
Hangzhou	8.1 (6.4, 10.0)	7.1 (5.5, 8.9)	19.2 (16.1, 22.4)	7.2 (5.4, 9.1)	−11.9 (−15.1, −8.6)	9.8 (7.7, 12.0)
Jinhua	4.3 (−3.7, 12.9)	−0.2 (−10.6, 11.3)	12.7 (−0.5, 27.7)	6.0 (−1.6, 14.2)	9.3 (−3.6, 24.0)*	−2.8 (−10.9, 6.1)*
Zhoushan	1.4 (−2.3, 5.3)*	3.3 (−0.7, 7.5)	15.7 (9.3, 22.5)	−2.4 (−7.3, 2.8)*	1.0 (−4.1, 6.4)	2.9 (−0.3, 6.3)*
Time of day						
Daytime	6.6 (5.0, 8.2)*	6.2 (4.6, 7.8)*	16.7 (13.8, 19.6)*	5.2 (3.4, 7.1)*	−6.9 (−9.6, −4.0)	7.1 (5.2, 8.9)
Nighttime	12.9 (7.1, 19.0)	12.6 (7.1, 18.4)	35.2 (25.5, 45.6)	14.5 (9.8, 19.4)	−8.3 (−17.3, 1.8)	12.9 (6.7, 19.3)

Note: Values are presented as percentage change and 95% confidence intervals. The concentrations per interquartile range increase in fine particulate matter ($PM_{2.5}$), particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) were 29 μg/m^3, 43 μg/m^3, 30 μg/m^3, 5 μg/m^3, 63 μg/m^3, and 0.4 mg/m^3, respectively.
Abbreviations: $PM_{2.5}$, fine particulate matter; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; and CO, carbon monoxide.
*$p < 0.05$. †Daytime was from 8:00 a.m. to 8:00 p.m. during 1 day; nighttime was the rest of the day.

4. Discussion

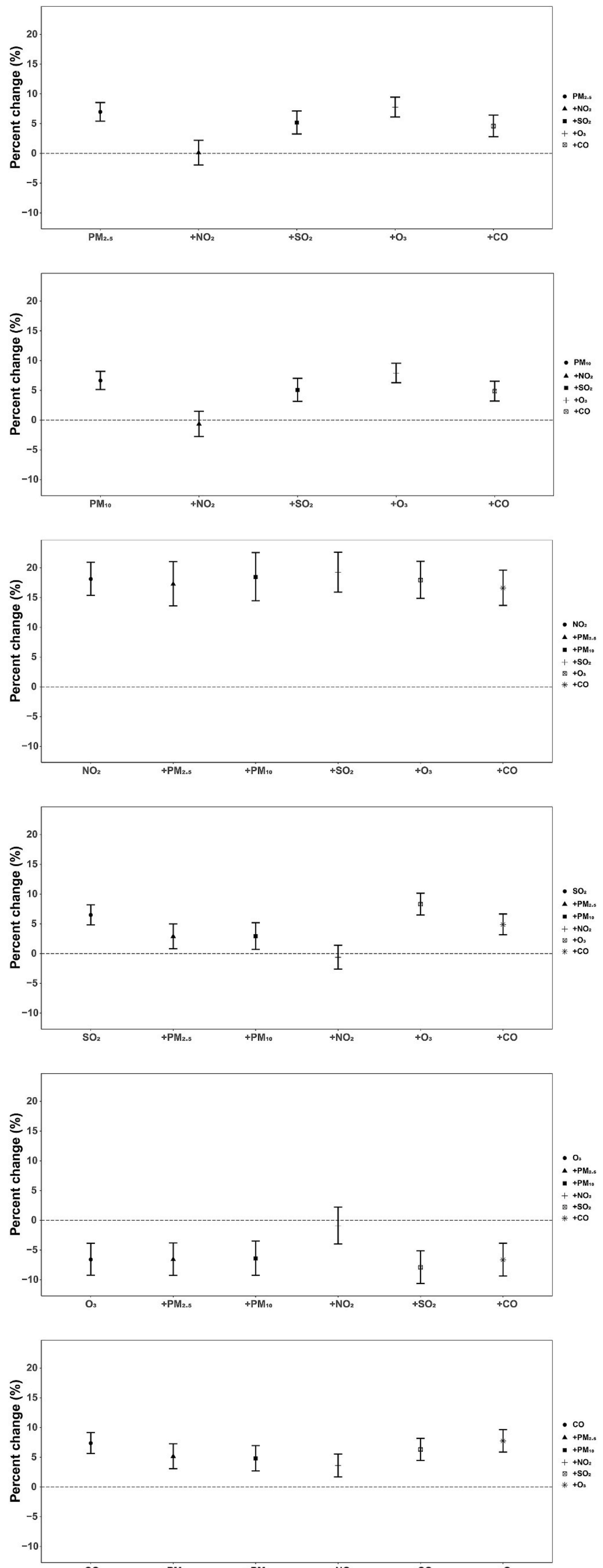
In this multicenter case-crossover study among a total of 121,112 asthma ED visits in three Chinese cities from 2016 to 2021, we found that hourly exposure to air pollution were associated with increased risk of ED visits for asthma. For each IQR increase of $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO over a period of 0–72 h, the risk of asthma increased by 7.0%, 6.7%, 18.1%, 6.5%, and 7.4%, respectively. This association was most pronounced in the concurrent hour of exposure (lag 0 h), gradually attenuated over a period of 3–12 h, and then diminished thereafter. We found that the risk was higher among male patients, school children (6–18 years), residents of Hangzhou city, during the spring season, or at night-time.

Using hourly measurement data, we found that exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO might contribute to enhanced risk of ED visits for asthma, which were consistent with most previous studies conducted at the daily timescale (Dąbrowiecki et al., 2022; Liu et al., 2019; Lu et al., 2020). For example, a time-stratified case-crossover study conducted in the Kaohsiung City, Taiwan, reported that exposure to an IQR increase in $PM_{2.5}$ (24.1 μg/m^3) and PM_{10} (37.2 μg/m^3) was associated with 17.4% (95% CI: 1.3%, 36.2%) and 15.1% (95% CI: 0.2%, 32.3%) increased in asthma ED visits (Ho et al., 2021). Similarly, a case-crossover study in asthmatic patients observed a positive association between exposure to SO_2, NO_2 and CO and the risk of emergency ambulance dispatches on a daily timescale (Chen et al., 2019). In addition, in line with our findings, previous studies in the United States also supported that exposure to $PM_{2.5}$, O_3 and NO_2 was associated with an increased risk of hospitalization for asthma in the Medicaid population (Wei et al., 2022a). Using daily measurement data, Lu et al. (2020) found a positive association between exposure to PM_{10} or NO_2 and risk of asthma at lag 0 day among 143,057 asthma patients in 17 cities in China.

Although the biological mechanisms connecting exposure to air pollution and the risk of asthma have not been fully elucidated, various plausible biological mechanisms have been proposed and investigated. Exposure to PM can lead to oxidative stress, increased airway hyper-responsiveness, and airway remodeling (Stanek et al., 2011), and it has been linked to impaired lung function and the development of asthma (Cai et al., 2017; Guo et al., 2019; Liu et al., 2022). Exposure to SO_2 has been shown to trigger airway inflammation and the proliferation of eosinophilic granulocytes (Cai et al., 2008), both of which are prominent features of asthma. Additionally, exposure to SO_2 can induce bronchospasm and contribute to the development of airway fibrosis, characterized by the scarring and thickening of the airway walls (Cai et al., 2008). As a typical traffic-related air pollutant, NO_2 exposures can increase airway hyper-responsiveness (Guarnieri and Balmes, 2014), and also have direct irritant and inflammatory effects on airway neuroreceptors and epithelium (Poynter et al., 2006; Seltzer et al., 1986), which will induce or exacerbate asthma. Consequently, these factors can exacerbate airway inflammation and contribute to the onset of asthma.

We found that exposure to O_3 was associated with a decreased risk of asthma ED visits, which is consistent with studies conducted in Hong Kong (Dai et al., 2018) and Beijing (Zhao et al., 2021), China. However, the existing body of evidence regarding the relationship between O_3 exposure and asthma remains contentious. Several studies have reported that exposure to O_3 adversely affects asthma (Liu et al., 2019; Zhang et al., 2019). O_3 can impact asthma in two opposite ways — it may trigger asthma by inducing oxidative stress, provoking airway inflammation, and increasing reactivity to allergens in asthmatics (Kehrl et al., 1999). On the contrary, O_3 might exhibit a protective effect by shielding the lungs from specific viral infections of the respiratory tract (Johnston et al., 1996). This potential mechanism could explain the protective effects of O_3 observed in this study. Additionally, the observed protective effect of O_3 exposure may be attributable to its inverse correlation with other air pollutants. Therefore, our findings that exposure to O_3 was associated with a decreased risk of ED visits for asthma should be interpreted with caution.

In subgroup analyses by age, asthma ED visits in school children were more affected by $PM_{2.5}$, PM_{10}, and NO_2 compared to preschool-age children, which is consistent with previous studies (Iskandar et al., 2012; Zhang et al., 2019). A plausible explanation for this finding could be that school children are more likely to engage in prolonged outdoor activities, leading to increased exposure to air pollutants. Conversely, preschool children may often be more closely supervised by their parents, potentially resulting in reduced exposure to air pollutants. The differences found between male and female did not reach statistical



(caption on next column)

Fig. 3. The percent change and 95% confidence intervals (95% CIs) for the risk of emergency department visits for asthma associated with an interquartile range increase in air pollutants over lags 0–72 h in the single- and two-pollutant models.
Note: The concentrations per interquartile range increase in fine particulate matter ($PM_{2.5}$), particulate matter with an aerodynamic diameter $\leq$10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) were 29 $\mu g/m^3$, 43 $\mu g/m^3$, 30 $\mu g/m^3$, 5 $\mu g/m^3$, 63 $\mu g/m^3$, and 0.4 mg/m^3, respectively. In each panel, the first column shows the effect estimates and 95% CIs from single-pollutant models and the remaining columns indicate the estimates and 95% CIs for that pollutant after adjusting for the others in -pollutant models.

significance, in accordance with previous studies (Gehring et al., 2015). We observed stronger associations between exposure to air pollution and the risk of ED visits for asthma during the spring season. This can be the increased release of pollen from trees, grass, and weeds during spring contributes to seasonal allergies and exacerbates respiratory symptoms in individuals affected by asthma (Sapkota et al., 2020).

Our study has several limitations. First, we relied on estimated air pollutant concentrations at the hospital address as a proxy for individual air pollution exposure rather than personal exposure measures, which may not accurately reflect the actual personal exposure, potentially leading to exposure misclassification (Baxter et al., 2013; Wei et al., 2022b). Second, while our study design effectively controls for confounders that are time-invariant, the potential for residual confounding due to time-varying lifestyle-related factors cannot be entirely ruled out. Nonetheless, it is unlikely that such confounding would markedly affect our findings, considering that these lifestyle factors generally do not undergo significant changes within a one-month period. In addition, although we controlled for meteorological variables, we did not control for airborne allergens such as pollen and dust due to a lack of monitoring data (Zhu et al., 2022). Thus, the possibility of residual confounding cannot be completely ruled out. Third, considering that our study was conducted in Zhejiang province, it may be limited to generalize our findings to other Chinese cities or countries. Further large-scale studies involving different populations are needed to enhance the understanding of the effects of air pollution on the risk of asthma. Despite these limitations, the strength of our study lies in its use of hourly air pollution data and asthma ED visits records, allowing for the capture of dynamic changes in air pollutant concentrations on a finer sub-daily temporal scale and providing a deeper understanding of the temporal sequence between air pollutant exposure and the risk of asthma attacks.

5. Conclusion

In summary, our time-stratified case-crossover study, including 121,112 asthma ED visits from 11 hospitals in 3 cities, found that exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO, but not O_3, is associated with increased risk of ED visits for asthma shortly after exposure. This association was strongest during the concurrent hour of exposure, rapidly attenuated over a period of 3–12 h, and then diminished afterward.

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CRediT authorship contribution statement

Kun Yuan: Writing – original draft, Methodology, Data curation, Investigation. **Yangchang Zhang:** Methodology, Writing – review & editing. **Xin Lv:** Writing – review & editing. **Wangnan Cao:** Writing – review & editing. **Zhenyu Zhang:** Writing – review & editing. **Lizhi Wu:** Conceptualization, Writing – review & editing, Data curation, Investigation. **Shengzhi Sun:** Conceptualization, Writing – original draft, Formal analysis, Resources, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2023.120307.

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