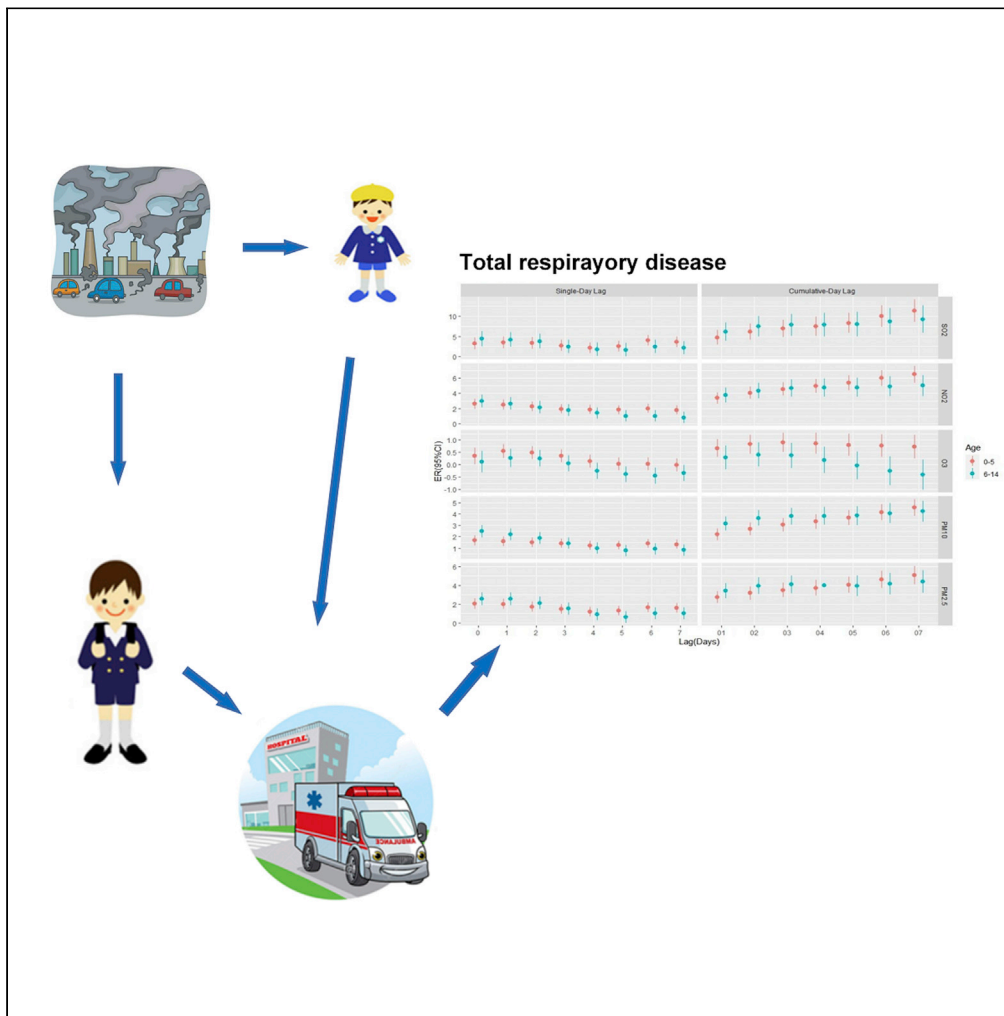


Article

Association of short-term exposure to air pollution with emergency visits for respiratory diseases in children



Miao He, Yaping Zhong, Yuehan Chen, Nanshan Zhong, Kefang Lai

klai@163.com

Highlights

Air pollution associates with children emergency visits for respiratory diseases

NO₂ and PM₁₀ are risk indicators for respiratory diseases in children

Young children are more sensitive to gaseous pollutants

School-age children are more sensitive to PM₁₀

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Article

Association of short-term exposure to air pollution with emergency visits for respiratory diseases in children

Miao He,^{1,3} Yaping Zhong,^{1,3} Yuehan Chen,² Nanshan Zhong,² and Kefang Lai^{2,4,*}

SUMMARY

Ambient air pollutants are health hazards to children. This study comprised 773,504 emergency department visits (EDVs) at 0–14 years of age with respiratory diseases in southern China. All air pollutants were positively associated with EDVs of total respiratory diseases, especially pneumonia. NO₂, PM₁₀, and PM_{2.5} had intraday effects and cumulative effects on asthma EDVs. The effect of SO₂, PM₁₀, and PM_{2.5} on pneumonia EDVs was stronger in girls than in boys. The effect of NO₂ on acute upper respiratory tract infection EDVs was greater in children aged 0–5 years old; however, the effect of PM₁₀ on acute upper respiratory tract infection EDVs was greater in the 6–14 years group. In a two-pollutant model, NO₂ was associated with bronchitis and pneumonia, and PM₁₀ was associated with acute upper respiratory tract infection. In this time-series study, NO₂ and PM₁₀ were risk indicators for respiratory diseases in children.

INTRODUCTION

Air pollution has become an important public health issue for most cities around the world. Recently, a systematic analysis for the Global Burden of Disease in 204 countries and regions from 1990 to 2019 reported that, among children 0–9 years old, the largest increase in risk exposure was ambient particulate matter air pollution (GBD 2019 Risk Factors Collaborators 2020). There has been a pronounced increase in the literature on the adverse effects of ambient air pollution on children's health (Lee 2021; Bates 1995).

Children are susceptible to the adverse health effects of air pollution due to their immature immune systems, their underdeveloped lung and metabolic systems, and the co-occurrence of infection with respiratory pathogens (Lee 2021). In addition, children are proportionally more exposed than adults to ambient air pollution because they have high ventilation rates and mouth breathing and spend more time outdoors for playing (Gouveia et al., 2018). The consequences of exposure to air pollution during early life include impaired lung function and an increased risk of respiratory illness (Xiao et al., 2016).

Evidence is mounting that ambient air pollution exposure is significantly associated with respiratory diseases in children (Goldizen et al., 2016). The prior studies have demonstrated a significant impact of air pollution on infants and children in terms of morbidity and mortality, which is manifested primarily as a range of respiratory problems (Gouveia et al., 2018; Jakubiak-Lasocka et al., 2015). In this regard, the findings from daily ambient air pollution concentrations and hospital admission counts showed that all ambient air pollutants were positively associated with pneumonia hospitalizations, and all pollutants other than carbon monoxide were positively associated with hospitalizations for bronchitis and asthma in children (Nhung et al., 2018). Exposure to fine particles (PM_{2.5}) is also associated with outpatient visits for acute lower respiratory infections, pneumonia, and acute bronchiolitis/asthma of children under 5 years old (Davila Cordova et al., 2020). Childhood respiratory diseases may be partially preventable with better control of environmental contaminants (Hasunuma et al., 2014; Bayer-Oglesby et al., 2005).

Previous studies on air pollution and respiratory diseases were mainly concentrated in polluted western cities and northern industrial cities in China, such as Beijing, Jinan, Shijiazhuang, and Lanzhou (Zhang et al., 2019; Liu et al., 2019; Song et al., 2018; Ma et al., 2020). However, little has been documented about

¹Department of Environmental Health, School of Public Health, China Medical University, Key Laboratory of Environmental Health Damage Research and Assessment, Shenyang, Liaoning Province 110122, China

²State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong Province 510120, China

³These authors contributed equally

⁴Lead contact

*Correspondence:

klai@163.com

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Table 1. Descriptive statistics of daily emergency department visits of children with respiratory diseases in Guangzhou, 2012–2015

Daily hospital admissions	Mean	SD	Min	P ₂₅	Median	P ₇₅	Max	Summary(%)
Total respiratory diseases								
Total	529.4	215.4	107.0	373.0	496.0	667.0	1391.0	773504
Boy	309.4	124.6	56.0	221.0	290.0	390.0	808.0	452106(58.5%)
Girl	220.0	92.2	41.0	152.0	204.0	278.0	606.0	321398(41.5%)
0–5 years old	360.1	147.2	67.0	253.0	335.0	459.0	918.0	526133(68.0%)
6–14 years old	169.3	77.4	40.0	111.0	156.0	207.0	534.0	247371(32.0%)
Acute upper respiratory infection								
Total	228.8	109.6	44.0	146.0	206.0	291.0	736.0	334215
Boy	130.9	62.6	18.0	84.0	117.0	167.0	415.0	191228(57.2%)
Girl	97.9	48.2	19.0	61.00	88.0	126.0	348.0	142987(42.8%)
0–5 years old	146.0	68.9	26.0	94.0	130.0	189.0	478.0	213377(63.8%)
6–14 years old	82.7	46.8	16.0	49.0	73.0	102.0	357.0	120838(36.2%)
Bronchitis								
Total	87.5	40.1	8.0	60.0	82.0	110.0	244.0	127874
Boy	53.9	24.7	5.0	37.0	51.0	68.0	155.0	78674(61.5%)
Girl	33.7	16.6	2.0	22.0	31.0	43.0	115.0	49200(38.5%)
0–5 years old	67.8	32.6	7.0	45.0	63.0	85.0	208.0	98989(77.4%)
6–14 years old	19.8	10.0	0.0	12.0	18.0	25.0	63.0	28885(22.6%)
Pneumonia								
Total	11.23	6.74	0.00	6.00	10.00	15.00	46.00	16403
Boy	6.60	4.30	0.00	3.00	6.00	9.00	28.00	9643(58.8%)
Girl	4.63	3.26	0.00	2.00	4.00	6.00	21.00	6760(41.2%)
0–5 years old	8.87	5.82	0.00	5.00	8.00	12.00	43.00	12960(79.0%)
6–14 years old	2.36	1.96	0.00	1.00	2.00	3.00	21.00	3443(21.0%)
Asthma								
Total	5.26	3.36	0.00	3.00	5.00	7.00	24.00	7683
Boy	3.62	2.59	0.00	2.00	3.00	5.00	17.00	5290(68.9%)
Girl	1.64	1.50	0.00	1.00	1.00	2.00	10.00	2393(31.1%)
0–5 years old	1.43	1.42	0.00	0.00	1.00	2.00	8.00	2094(27.3%)
6–14 years old	3.83	2.69	0.00	2.00	3.00	5.00	18.00	5589(72.7%)

such effects in children in other cities where the pollution levels have received limited attention, especially less industrialized cities in the south of China. Furthermore, studies on outdoor air pollution and emergency department visits (EDVs), especially in children in Chinese cities, remain limited, although the associations between ambient air pollution and daily hospitalizations and outpatient visits have been well described (Liu et al., 2017; Zhang et al., 2019).

In the present study, we conducted a time-series study to investigate the association between five ambient air pollutants (sulfur dioxide [SO₂], nitrogen dioxide [NO₂], ozone [O₃], inhalable particles [PM₁₀], and PM_{2.5}) and EDVs with respiratory diseases stratified by acute upper respiratory tract infection, bronchitis, pneumonia, and asthma in children in Guangzhou, southern China.

RESULTS

Demographic characteristics

Table 1 shows the descriptive statistics for daily EDVs due to respiratory diseases in Guangzhou in the study period of 2012–2015. During the four-year study period, 773,504 respiratory disease emergency department encounters met our inclusion criteria. Among all encounters, patients were 58.5% (n = 452,106)

Table 2. Descriptive statistics of air pollutants and meteorological factors in Guangzhou, 2012–2015

Data	Mean	SD	Min	P ₂₅	Median	P ₇₅	Max
Air pollutants concentrations							
SO ₂ (μg/m ³)	18.0	9.3	1.5	11.5	16.3	23.0	55.5
NO ₂ (μg/m ³)	55.6	22.5	10.3	39.0	51.0	67.8	169.0
O ₃ (μg/m ³)	79.9	53.2	2.5	37.3	70.8	110.3	296.5
PM ₁₀ (μg/m ³)	65.9	32.5	5.0	41.0	59.5	83.5	244.8
PM _{2.5} (μg/m ³)	47.5	25.6	6.8	28.0	42.5	60.5	193
Meteorologic measures							
Temperature (°C)	23.2	6.4	5.5	18.2	24.9	28.3	33.5
Relative humidity (%)	78.0	11.1	31.0	72.0	79.0	86.0	100.0

boys and 41.5% (n = 321,398) girls, and they were 68.0% (n = 526,133) 0–5 years old and 32.0% (n = 247,371) 6–14 years old. There were 334,215 EDVs (boys: 57.2%; 0–5 years old: 63.8%) for acute upper respiratory tract infection, 127,874 EDVs (boys: 61.5%; 0–5 years old: 77.4%) for bronchitis, 16,403 EDVs (boys: 58.8%; 0–5 years old: 79.0%) for pneumonia, and 7,683 EDVs (boys: 68.9%; 0–5 years old: 27.3%) for asthma.

Air pollutants and meteorology

Table 2 summarizes levels of air pollutants, temperature, and relative humidity for the period 2012–2015 in Guangzhou. Over the entire study period, SO₂, NO₂, O₃, PM₁₀, and PM_{2.5} concentration averaged 18.0 μg/m³, 55.6 μg/m³, 79.9 μg/m³, 65.9 μg/m³, and 47.5 μg/m³, respectively. And daily mean temperature and relative humidity was 23.2°C and 78.0%.

Table 3 presents the correlations among the air pollutants, temperature, and relative humidity, combined across all of the sites. Daily means of NO₂, PM₁₀, and PM_{2.5} were strongly correlated with each other (Pearson correlation coefficients ranged from 0.74 to 0.90). SO₂ was relatively highly correlated with NO₂/PM₁₀/PM_{2.5} (r = 0.57, 0.58, and 0.55, respectively). Maximal 8-h mean O₃ was weakly correlated with PM₁₀ and PM_{2.5} (r = 0.25 and 0.19). The temporal correlations between air pollutants and meteorological factors were low and negatively (0.09 ≤ |r| ≤ 0.32), except O₃ (r = 0.59 and –0.46).

Single pollutant

Figure 1 indicates the estimated effect of each pollutant on EDVs of total respiratory diseases, acute upper respiratory tract infection, bronchitis, pneumonia, and asthma in single-pollutant model and the specific values of ER and its 95% CI are shown in the additional material (Tables S1–S5). For both the single-day and cumulative-day lag effect, SO₂, NO₂, PM₁₀, and PM_{2.5} had a positive and statistically significant association with total respiratory diseases, acute upper respiratory tract infection, and bronchitis EDVs (Figures 1A–1C). All air pollutants had significant associations with EDVs of pneumonia for both the single-day and cumulative-day lag effect, except O₃ at lag 7 days (Figure 1D). NO₂, PM₁₀, and PM_{2.5} had a positive and statistically significant association with asthma EDVs at lag 0 days and for the cumulative-day lag effect (Figure 1E).

Gender difference

Figure 2 and Tables S6–S10 indicate the percentage changes for respiratory EDVs associated with per 10 μg/m³ increase of air pollutants varied by sex group. The effect estimates of NO₂, PM₁₀, and PM_{2.5} on total respiratory diseases in girls were slightly higher than in boys for the cumulative-day lag effect (Figure 2A). The effect estimates of SO₂ and O₃ on acute upper respiratory tract infection in boys were slightly higher than in girls for the cumulative-day lag effect (Figure 2B). The effect estimates of air pollutants on bronchitis for the cumulative-day lag effect, SO₂, and O₃ were slightly higher in boys than in girls; however, NO₂, PM₁₀, and PM_{2.5} were slightly higher in girls than in boys (Figure 2C). The effect estimates of SO₂, PM₁₀, and PM_{2.5} on pneumonia were significantly higher in girls than in boys for the cumulative-day lag effect (p < 0.05; Figure 2D). The effect estimates of NO₂ on asthma were higher in boys than in girls for the cumulative-day lag effect (Figure 2E).

Table 3. Spearman's correlations between air pollutants and meteorological factors in Guangzhou, 2012–2015

	SO ₂	NO ₂	O ₃	PM ₁₀	PM _{2.5}	Temperature	Relative humidity
SO ₂	1.00	0.57 ^a	0.25 ^a	0.58 ^a	0.55 ^a	0.09 ^a	−0.10 ^a
NO ₂		1.00	0.01	0.74 ^a	0.76 ^a	−0.32 ^a	−0.02
O ₃			1.00	0.25 ^a	0.19 ^a	0.59 ^a	−0.46 ^a
PM ₁₀				1.00	0.90 ^a	−0.17 ^a	−0.29 ^a
PM _{2.5}					1.00	−0.29 ^a	−0.27 ^a
Temperature						1.00	0.07 ^a
Relative humidity							1.00

^aSignificant difference ($p < 0.01$).

Age difference

Figure 3 and Tables S11–S15 indicate the percentage changes for respiratory EDVs associated with per 10 $\mu\text{g}/\text{m}^3$ increase of air pollutants varied by age group. The effect estimates of NO₂ and O₃ on total respiratory diseases and acute upper respiratory tract infection were significantly higher in the 0–5 years age group than in the 6–14 years age group, but PM₁₀ was significantly higher in the 6–14 years age group than in the 0–5 years age group ($p < 0.05$; Figures 3A and 3B). The effect estimates of O₃, PM₁₀, and PM_{2.5} on bronchitis were significantly higher in the 0–5 years age group than in the 6–14 years age group at lag 7 days ($p < 0.05$; Figure 3C). The effect estimates of NO₂ on pneumonia were significantly higher in the 6–14 years age group than in the 0–5 years age group at lag 4, lag 5, and lag 05 days ($p < 0.05$; Figure 3D). The effect estimates of NO₂ on asthma were significantly higher in the 0–5 years age group than in the 6–14 years age group at lag 7 days ($p < 0.05$; Figure 3E).

Multiple-pollutant model

A multiple-pollutant model was fitted by selecting the optimal lag time of the pollutants for respiratory disease by different genders and age groups. Figure 4 and Tables S16–S20 present the percentage changes for respiratory EDVs associated with per 10 $\mu\text{g}/\text{m}^3$ increase of air pollutants from two-pollutant models with adjustment for SO₂, NO₂, O₃, PM₁₀, and PM_{2.5}. When introducing NO₂, PM₁₀, or PM_{2.5} into the single-pollutant model, the joint air pollution effects robust decreased, due to control for confounding. The joint effects of PM₁₀ on total respiratory diseases were greater in the 6–14 years age group than in the 0–5 years age group ($p < 0.05$; Figure 4A). After adjusting for PM_{2.5}, the effect estimates of O₃ on acute upper respiratory tract infection remained statistically higher in the 0–5 years age group than in the 6–14 years age group ($p < 0.05$; Figure 4B). After adjusting for SO₂ and NO₂, the effect estimates of PM₁₀ on acute upper respiratory tract infection remained statistically higher in the 6–14 years age group than in the 0–5 years age group ($p < 0.05$; Figure 4B). After adjusting for O₃, the effect estimates of PM_{2.5} on acute upper respiratory tract infection were statistically higher in the 6–14 years age group than in the 0–5 years age group ($p < 0.05$; Figure 4B). After adjusting for O₃, the effect estimates of PM₁₀ on pneumonia remained statistically higher in girls than in boys ($p < 0.05$; Figure 4D). After adjusting for SO₂, the effect estimates of PM_{2.5} on pneumonia remained statistically higher in girls than in boys ($p < 0.05$; Figure 4D). The joint effects of NO₂ on asthma remained statistically higher in boys than in girls ($p < 0.05$; Figure 4E). After adjusting for SO₂, the effect estimates of NO₂, PM₁₀, and PM_{2.5} on asthma were statistically higher in the 0–5 years age group than in the 6–14 years age group ($p < 0.05$; Figure 4E).

Sensitivity analysis

Figure S1 and Table S21 illustrate the ER and 95% CI for every 10 $\mu\text{g}/\text{m}^3$ increase in pollutant concentration from the models with varying degrees of freedom per year. Sensitivity analysis showed that the effect of O₃ on the 6–14 years age group was still not statistically significant, which was consistent with the results of the O₃ single-pollutant model. With an increase in the intensity of the smooth trend of the control time, the overall effect of pollutants showed a gradually decreasing trend, but the fluctuation was not large and remained statistically significant.

DISCUSSION

This is the largest population-based study on the acute effects of ambient air pollutants on respiratory health in children in China to date as shown in Figure 5. All ambient air pollutants were positively associated

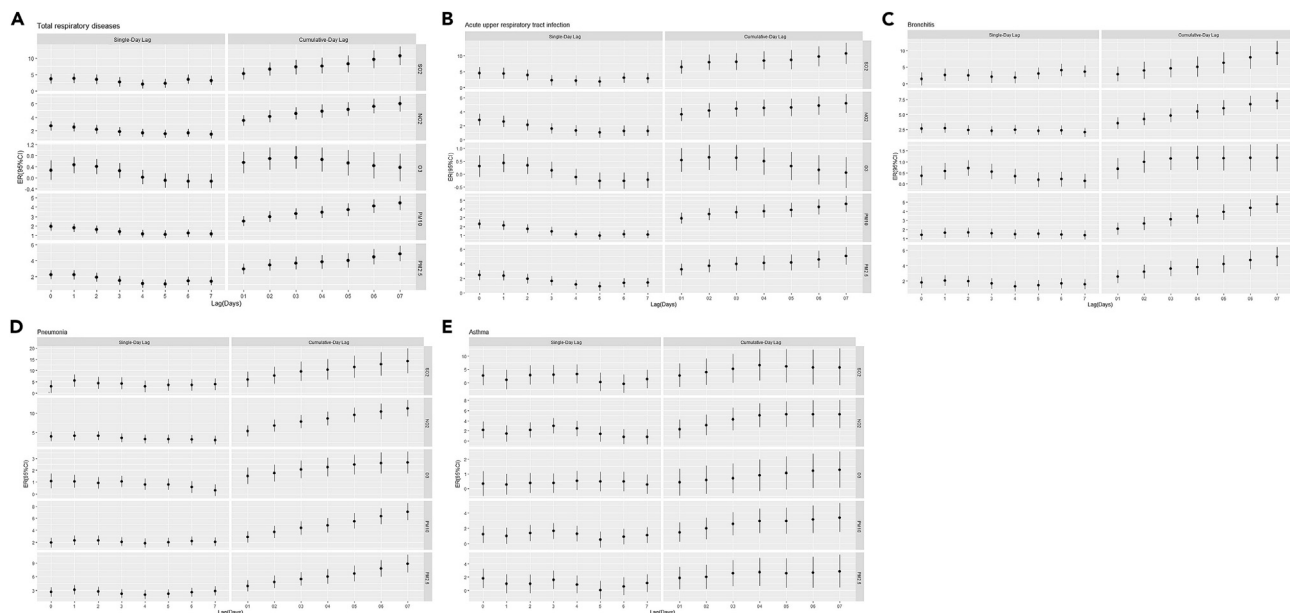


Figure 1. The estimated effect of air pollutants on respiratory EDVs of total children in single-pollutant model (A) total respiratory disease; (B) acute upper respiratory infection; (C) bronchitis; (D) pneumonia; (E) asthma; see also [Tables S1–S5](#).

with EDVs of total respiratory diseases, especially pneumonia. NO_2 , PM_{10} , and $\text{PM}_{2.5}$ had intraday effects and cumulative effects on asthma EDVs. Our findings suggest exposures to NO_2 , PM_{10} , and $\text{PM}_{2.5}$ may transiently increase risk of asthma EDVs in children within 24 h. The effect of SO_2 , PM_{10} , and $\text{PM}_{2.5}$ on pneumonia EDVs was stronger in girls than in boys. The effects of NO_2 on acute upper respiratory tract infection EDVs were greater in the 0–5 years age group; however, the effect of PM_{10} on acute upper respiratory tract infection EDVs was greater in the 6–14 years age group. The significant effects of NO_2 and PM_{10} remained in the two-pollutant models. In a two-pollutant model, NO_2 was associated with bronchitis and pneumonia, and PM_{10} was associated with acute upper respiratory tract infection. Air pollution the day before an emergency call contributed most to the number of respiratory disease cases. Air pollution could successfully predict daily pediatric EDVs.

It is worth noting that studies have demonstrated the effects of air pollutants on respiratory diseases at a specific location for public health assessments; therefore, the results might be affected by local air pollutant concentrations, components, climate conditions, and population susceptibility. The present study was conducted in children in Guangzhou, which is representative of the mild air pollution found in cities in southern China. The average concentrations of PM_{10} and $\text{PM}_{2.5}$ were higher than the air quality guideline (AQG) recommendations of the Chinese government (65.9 vs. 50 $\mu\text{g}/\text{m}^3$ and 47.5 vs. 35 $\mu\text{g}/\text{m}^3$, respectively), while the concentrations of SO_2 (18.0 $\mu\text{g}/\text{m}^3$ vs. 50 $\mu\text{g}/\text{m}^3$), NO_2 (55.6 $\mu\text{g}/\text{m}^3$ vs. 80 $\mu\text{g}/\text{m}^3$), and O_3 (79.9 $\mu\text{g}/\text{m}^3$ vs. 100 $\mu\text{g}/\text{m}^3$) reached the AQG standards. Compared to previous studies conducted in heavily polluted cities such as Shijiazhuang, Jinan, and Lanzhou, the average air pollutant concentration in Guangzhou was relatively low. An observed association between air pollution and EDVs was consistent with other studies that demonstrated an increased risk for respiratory disease associated with air pollution (Zhang et al., 2019; Liu et al., 2019; Song et al., 2018; Ma et al., 2020).

Epidemiological studies have consistently demonstrated the acute adverse health effects of air pollution exposure on EDVs for pediatric asthma (Liu et al., 2021; Mazenq et al., 2017; Hwang et al., 2017; Gleason et al., 2014). Some studies have demonstrated the main air pollutants associated with all-cause EDVs (Zhang et al., 2020; Chen et al., 2017a, 2017b) and respiratory disease EDVs (Song et al., 2021; Cheng et al., 2021a). Besides, we also investigated the effect estimates of SO_2 , NO_2 , O_3 , PM_{10} , and $\text{PM}_{2.5}$ on respiratory diseases with the stratification of diseases, such as acute upper respiratory tract infection, bronchitis, pneumonia, and asthma cases. Some differences were observed between air pollutants and diseases (Cheng et al., 2021b).

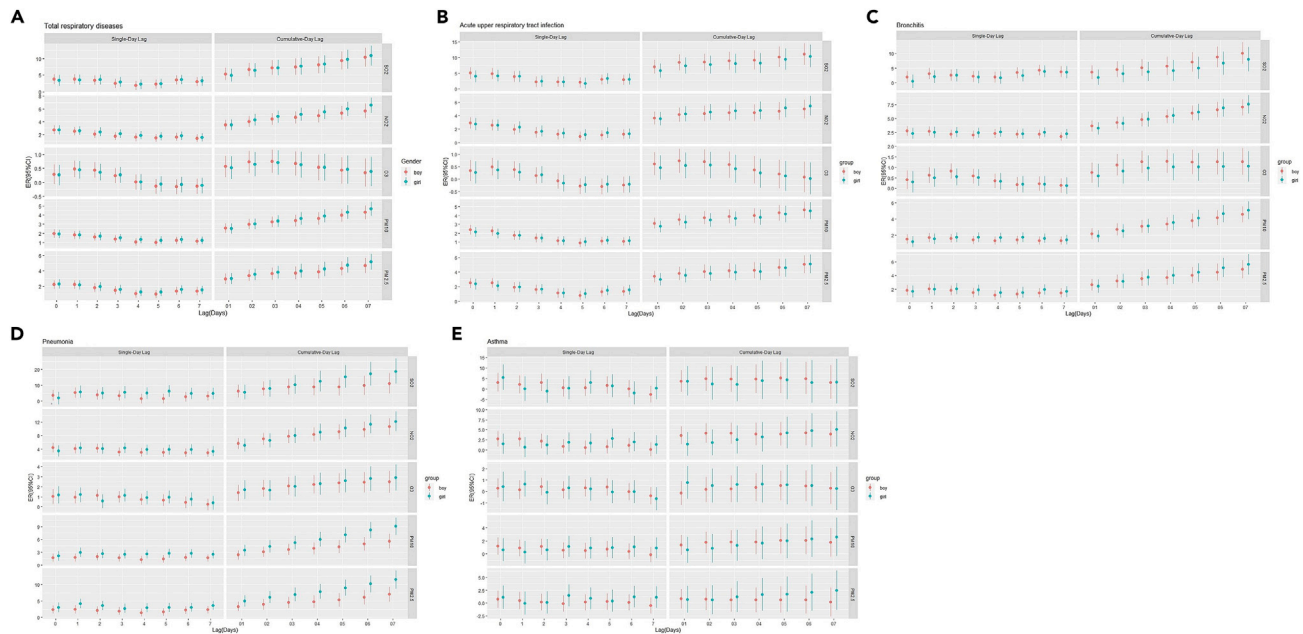


Figure 2. Percentage changes for respiratory emergency room visits associated with per $10 \mu\text{g}/\text{m}^3$ increase in air pollutants by gender subgroup (A) total respiratory disease; (B) acute upper respiratory infection; (C) bronchitis; (D) pneumonia; (E) asthma; see also Tables S6–S10.

We found sensitivity for gender in the association between ambient air pollutants and EDVs in children in this study. Our study identified stronger associations of SO_2 , PM_{10} , and $\text{PM}_{2.5}$ with EDVs for pneumonia in girls than boys, which is consistent with published studies on the acute effects of ambient air pollution on outpatient visits for respiratory disease (Ma et al., 2020; Zhu et al., 2017). In several gender-specific analyses, boys and girls were both susceptible to air pollutants, and sex was not a significant modifier since no significant difference was observed between them (Zhou et al., 2019; Bai et al., 2018). In contrast to our findings, some prior studies have found that the risk of air pollution on respiratory hospital visits is higher in boys than that in girls (Liu et al., 2019; Luong et al., 2020).

In the age-stratified analysis, the impacts of NO_2 on acute upper respiratory tract infection and asthma were more significant in children aged <5 years, but the impact of PM_{10} on acute upper respiratory tract infection was more significant in children aged 6–14 years. One possible reason is that children younger than 5 years old are more vulnerable to gas pollutants such as NO_2 than older children. It is generally recognized that this high degree of vulnerability among younger children can be attributed to their immature lungs, higher breathing rate, and predominantly oral breathing characteristics, which increases their exposure and susceptibility to respiratory infections. These factors, combined with the underdeveloped immune function, may add together to make infants and younger children more susceptible to gas air pollutants (Ma et al., 2020). Children in the 6–14 years age group start to participate in more outdoor activities, and their awareness of self-protection against air pollution is still weak. They have higher ventilation rates and mouth breathing, which may pull PM_{10} deeper into children’s lungs and, in combination with an immature respiratory system, clearance of PM_{10} is slower and more difficult (Ma et al., 2020). It is also proposed that children aged 6–17 years are more vulnerable to $\text{PM}_{2.5}$ exposure (Liu et al., 2019), and the effect of PM_{10} and $\text{PM}_{2.5}$ on total respiratory hospital outpatients is higher in older children (Song et al., 2018).

Similar to previous studies, a certain lag effect and a cumulative effect of air pollutants on short-term effects with EDVs were revealed in the present study. The maximum effect occurred on the day or the day before EDVs. A 0–1 day lag effect of SO_2 , NO_2 , PM_{10} , and $\text{PM}_{2.5}$ on EDVs for total respiratory diseases was found. It has been reported that the maximum effects of NO_2 , SO_2 , and PM_{10} on the risk of hospital admissions for respiratory diseases occur on the day of admission (Phung et al., 2016). A non-linear artificial neural network model showed a statistically significant difference between $\text{PM}_{2.5}$ exposure and hospital admission by 1 lag day (Polezer et al., 2018). In this study, we observed that a $10 \mu\text{g}/\text{m}^3$ increase in O_3 daily concentrations increased the respiratory disease EDV daily numbers with 2, 3, 4, or 5 days cumulative effects (lag0–1, lag0–2, lag0–3, and

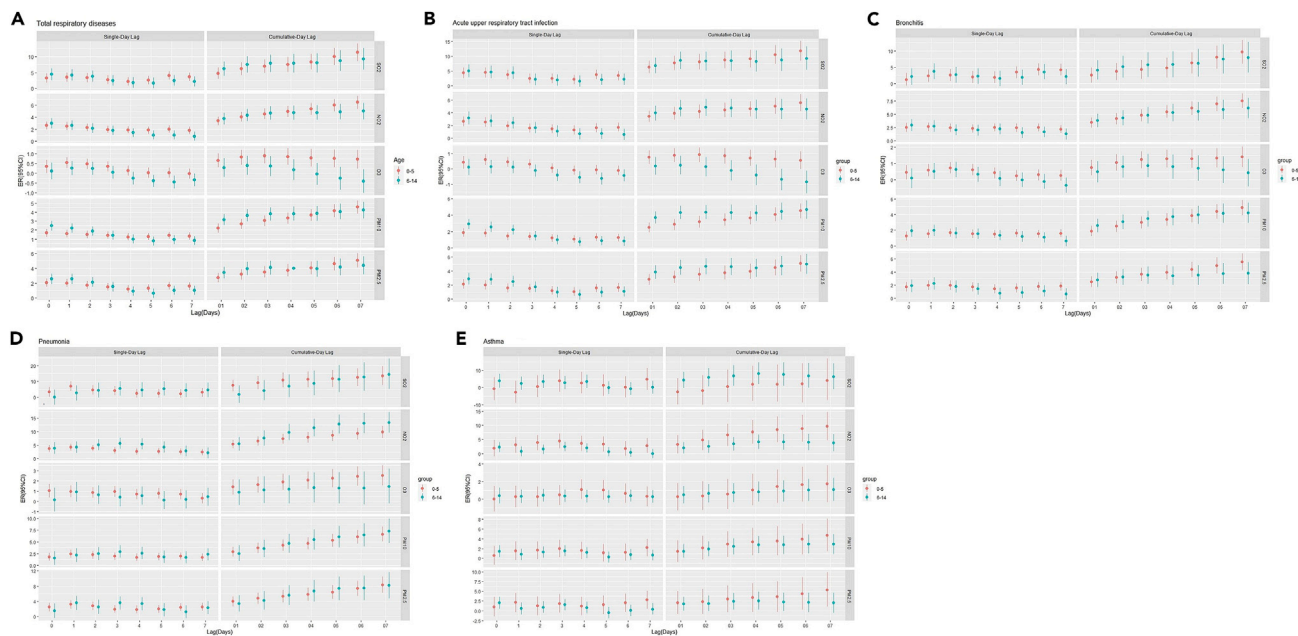


Figure 3. Percentage changes for respiratory emergency room visits associated with per 10 $\mu\text{g}/\text{m}^3$ increase in air pollutants by age subgroup (A) total respiratory disease; (B) acute upper respiratory infection; (C) bronchitis; (D) pneumonia; (E) asthma; see also [Tables S11–S15](#).

lag0–4, respectively). Recently, a retrospective study also showed a positive association between the cumulative effects of 6 days (lag0–5) for O_3 and lower respiratory diseases in children (Zhu et al., 2017).

It was not difficult to find that the cumulative risk estimate of each pollutant from the single-pollutant model was higher than that from the two-pollutant models. One general observation was the tendency of air pollutant estimates to shrink in two-pollutant models, due to the control for confounding. The finding of the very stable coefficients seen for NO_2 and PM_{10} across all two-pollutant models is remarkable in the case of total respiratory diseases, whereas PM_{10} was significant for acute upper respiratory tract infection and NO_2 for bronchitis and pneumonia. These rather stable NO_2 and PM_{10} findings for respiratory diseases are a clear argument for the use of NO_2 and PM_{10} as markers of ambient air pollution in health impact assessments for respiratory diseases in children.

Our study has four strengths. First, this is the largest sample size study to date on the impact of air pollution on children's EDVs for respiratory diseases. Second, in this study, the diseases were classified in detail, i.e. acute upper respiratory tract infection, bronchitis, pneumonia, and asthma, whereas previous studies on EDVs mainly focused on asthma-related diseases or on all respiratory diseases. Third, in this study, air pollution data from multiple air monitoring points and emergency data from multiple medical centers were used. Fourth, this study analyzed air pollution and respiratory disease in a city without heavy air pollution in southern China.

In summary, this study shows that short-term exposure to ambient air pollutants significantly increases the risk of EDVs from total respiratory diseases in children, especially for pneumonia in girls. Children less than 5 years of age are more sensitive to gaseous pollutants like NO_2 , whereas older children are more vulnerable to respiratory damage by particulate matter such as PM_{10} . Our results also demonstrate that NO_2 and PM_{10} are indicators of air pollution risk, since the estimated effects of NO_2 and PM_{10} were stable in the multiple-pollutant models. Precautions and protective measures and efforts to reduce exposure to air pollution should be strengthened, especially for children.

Limitations of the study

First, we cannot measure air pollution through personal air samples, and we did not take into account the impact of indoor air pollution. Second, the definition of outcomes in this study eventually relies on the diagnosis and ICD10 coding at the time of discharge, where misclassification of the type of respiratory

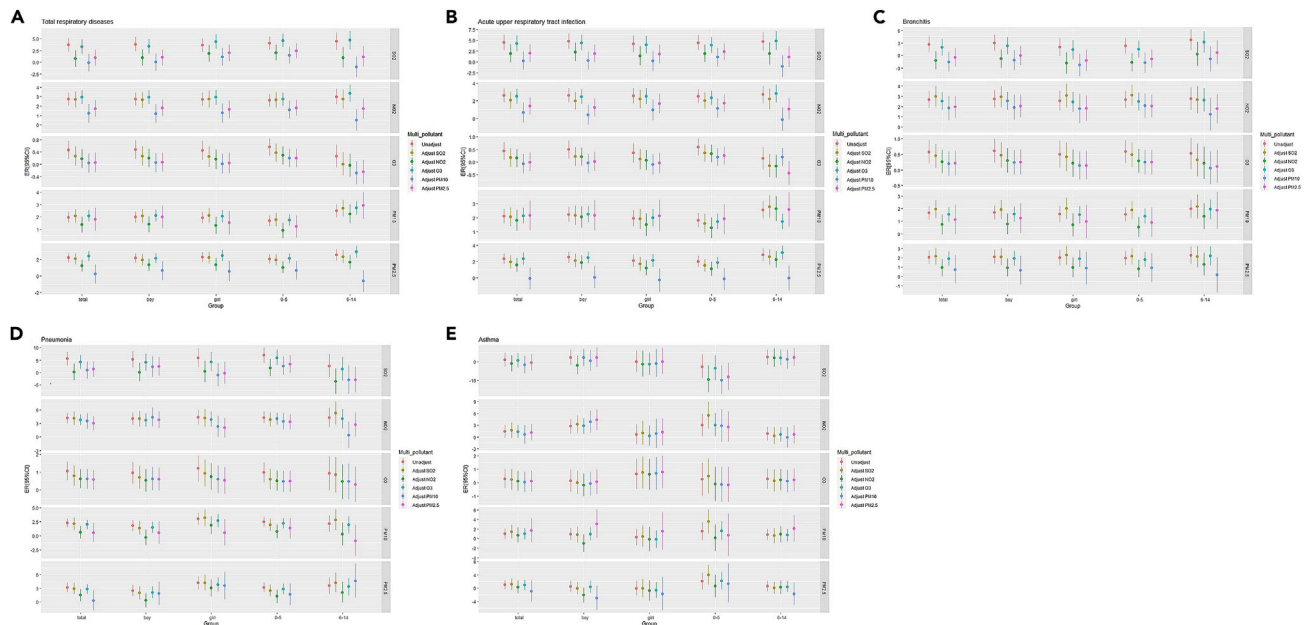


Figure 4. For each $10 \mu\text{g}/\text{m}^3$ increase in pollutant concentration in the multiple-pollutant model, the ER (and 95% CI) of emergency visits for respiratory diseases of the total population aged 0–14, boy, girl, children aged 0–5 and 6–14 subgroup (A) total respiratory disease; (B) acute upper respiratory infection; (C) bronchitis; (D) pneumonia; (E) asthma; see also Tables S16–S20.

disease might happen, particularly in the youngest age group. The varying magnitude of misclassifications of clinical diagnosis and ICD10 codes may have introduced bias.

STAR★METHODS

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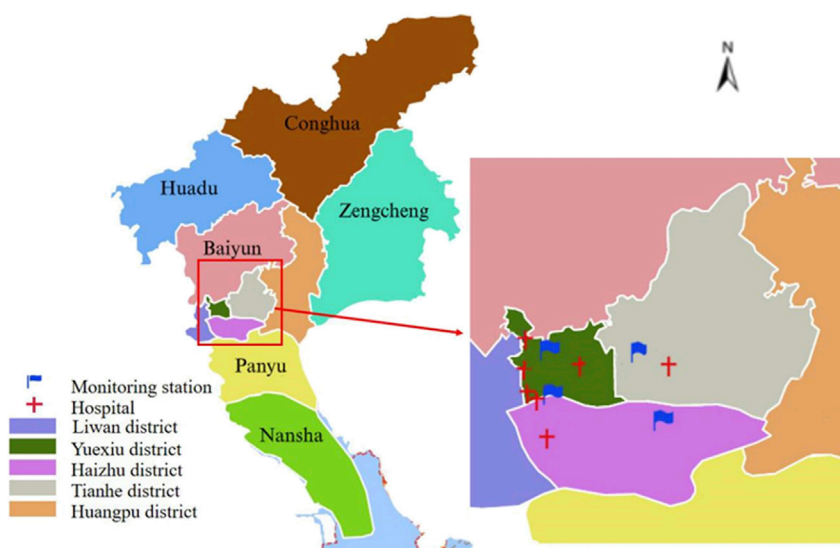


Figure 5. Locations of 7 hospitals and 4 air pollution monitoring stations in Guangzhou, China in the study

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.isci.2022.104879>.

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AUTHOR CONTRIBUTIONS

M.H. Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft. Y.Z. Methodology, Validation, Writing - original draft. Y.C. Validation, Data curation, Writing - review & editing. N.Z. Writing - review & editing. K.L. Conceptualization, Funding acquisition, Project administration, Writing - review & editing.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest or financial interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
R software	The R Core Team	https://www.r-project.org/
mgcv package	Mu et al. (2021)	https://rdocumentation.org/packages/mgcv/versions/1.8-31/topics/mgcv.package
ggplot2 package	Postma and Goedhart (2019)	https://rdocumentation.org/packages/ggplot2/versions/3.3.2

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Prof. Kefang Lai (klai@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Data: The authors declare that all data supporting the findings of this study are available within the article or available from the corresponding author upon reasonable request.

Code: This study did not generate any code.

Other items: Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Study area

Guangzhou, located in the Pearl River Delta (PRD), the capital of Guangdong Province, is the largest city in southern China and an important commercial and financial center with a population in the millions.

METHOD DETAILS

EDVs data

Data on EDVs were collected from seven large general top-level hospitals in Guangzhou between January 1, 2012 and December 31, 2015 (1,461 days). All seven hospitals were located in the densely populated central urban area of Guangzhou and provided 24-h accident and emergency services for residents. Each hospital has its own information system that recorded patient demographic information, home address, symptoms, diagnosis and the date of the emergency. From these hospitals, we obtained data on EDVs for children aged 0–14 years. We limited the study area to four urban districts in Guangzhou, so patients who lived outside these four urban districts were excluded from our study (Figure 5).

We checked the recorded symptoms for each case to further confirm its classification, and collected according to the International Classification of Disease revision 10 (ICD10) for diseases of the respiratory system (ICD10: J00~J99). Cause-specific respiratory hospitalizations were identified based on the ICD-10 codes: acute upper respiratory tract infection (ICD-10: J00-J06), bronchitis (ICD-10: J20), pneumonia (ICD-10: J18) and asthma (ICD-10: J45). Unclear or undiagnostic cases were excluded.

Air pollution and meteorological data

Air pollution data for SO₂, NO₂, O₃, PM₁₀ and PM_{2.5} from January 1, 2012 to December 31, 2015 were obtained from the Guangzhou Environmental Monitoring Central Station, including four general monitoring stations that were scattered in the study area. The daily concentrations of air pollutants were calculated as

the 24 h mean concentration, except for O₃, which was calculated as the 8-h mobile mean concentration. During the study period of 1,461 days, there were 12 days (0.8%) with missing data for SO₂, 15 days (1.0%) with missing data for NO₂, 21 days (1.4%) with missing data for PM₁₀ and PM_{2.5}, and 25 days (1.7%) with missing data for O₃. We accounted for the missing data with the linear interpolation method. We imputed missing data by replacing a missing concentration on a specific day with the average of the previous and next day values, if they are both available. If this was not the case, we replaced missing concentration with the first available value going back or forth. In this study, we used the composite (i.e., mean of the value for the four fixed monitoring stations) air pollutant concentrations for SO₂, NO₂, O₃, PM₁₀ and PM_{2.5}.

Meteorological data, including daily mean temperature (°C) and relative humidity (RH, %) were obtained for the same study period from the National Oceanic and Atmospheric Administration (NOAA).

QUANTIFICATION AND STATISTICAL ANALYSIS

A generalized additive model (GAM), based on a quasi-Poisson distribution, was used to perform a time series analysis on EDVs for respiratory diseases. Natural cubic spline (ns) functions were applied to control for time trends, as well as weather elements (i.e., daily mean temperature and RH). The core model also adjusted for public holidays and the day of the week (DOW). In this study, by changing the degrees of freedom of the natural cubic spline function, observing the change of image and combining with the Akaike's information criterion (AIC) value, we could comprehensively judge the degrees of freedom (df). So, a natural cubic spline with 7 df per year was used to control for seasons and long-term trends, and a df of 6 and 5 was used for temperature and RH, respectively. Public holidays and DOW were used as dummy variables. This model is described as follows:

$$Y_t \sim \text{Poisson}(\mu_t)$$

$$\text{Log}(\mu_t) = \text{int_except} + \beta X_t + \text{ns}(\text{time}, 7 * 4) + \text{ns}(\text{temp}, 6) + \text{ns}(\text{humidity}, 5) + \text{DOW}_t + \text{Holiday}$$

where Y_t is the daily count of EDVs for respiratory on day t; X is the daily concentration of a given air pollutant; β is regression coefficient; ns is the natural cubic spline; time indicates long-term trends and seasonality using calendar time (days); humidity is the daily mean relative humidity; temp is the daily mean temperature.

According to the regression coefficient (β) obtained by the model, the excess risk (ER) was reported as a percentage increase with a 95% confidence interval (95% CI) in daily EDVs for a 10 μg/m³ increase in air pollution concentrations. The equations of ER and 95%CI are shown below:

$$ER = (\exp(\beta * 10) - 1) * 100\%$$

$$ER(95\%CI) = (\exp((\beta \pm 1.96 * se) * 10) - 1) * 100\%$$

where se is the standard error.

Subgroup analysis was conducted according to gender or age (0–5 years old or 6–14 years old). The data of each subgroup was introduced into the model, and the effects of air pollutants on different gender and age subgroups were obtained. In order to verify whether there were statistically significant differences between subgroups, the 95%CI for the differences among subgroups were calculated by the following equation:

$$(\hat{Q}_1 - \hat{Q}_2) \pm 1.96 \sqrt{(\hat{SE}_1)^2 + (\hat{SE}_2)^2}$$

Here, Q^(^)1 and Q^(^)2 refer to the estimates for the two categories (e.g., boys and girls), and SE^(^)1 and SE^(^)2 refer to standard errors.

Finally, we conducted three analyses to explore the sensitivity of main results. First, the lag effects of air pollutants were performed with different lag days, including single-day lags (from lag 0 to lag 7) and cumulative-day lags (from lag 01 to lag 07). Single-day lags were air pollutant concentrations of the same day (lag 0) and the past one to seven days (lag 1–7). Cumulative-day lags were moving-average air pollutant concentrations of the same day and the previous days; for example, lag 02 indicated air pollutant concentrations of a three-day moving-average of that day and the previous two days. Second, two-pollutant models were fitted to evaluate the confounding effects of SO₂, NO₂, O₃, PM₁₀ and PM_{2.5}. In the multiple-pollutant models, the pollutant corresponding to the maximum single-lag day is used as the research variable, and

other pollutants with the same lag time are introduced. Third, we used alternative df for calendar days (5–9 per year).

Before conducting the model analyses, Spearman's rank correlation analysis was used to identify the correlation of different air pollutants and meteorological factors. All the statistical analyses were conducted with R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and the "mgcv" package. The results of the statistical tests were two-sided, with values of $p < 0.05$ considered statistically significant.