Acute effects of air pollution on respiratory disease mortalities and outpatients in Southeastern China

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The objective of this study was to investigate the potential association between air pollutants and respiratory diseases (RDs). Generalized additive models were used to analyze the effect of air pollutants on mortalities or outpatient visits. The average concentrations of air pollutants in Hangzhou (HZ) were 1.6–2.8 times higher than those in Zhoushan (ZS), except for O₃. In a single pollutant model, the increased concentrations of PM₂.₅, NO₂, and SO₂ were strongly associated with deaths caused by RD in HZ, while PM₂.₅ and O₃ were associated with deaths caused by RD in ZS. All air pollutants (PM₂.₅, NO₂, SO₂, and O₃) were strongly associated with outpatient visits for RD in both HZ and ZS. In multiple pollutant models, a significant association was only observed between PM₂.₅ and the mortality rate of RD patients in both HZ and in ZS. Moreover, strong associations between SO₂, NO₂, and outpatient visits for RD were observed in HZ and ZS. This study has provided evidence that both the mortality rates and outpatient visits for RD were significantly associated with air pollutants. Furthermore, the results showed that different air pollutant levels lead to regional differences between mortality rates and outpatient visits.

China is currently experiencing severe air pollution caused by increasing coal consumption, motor vehicle usage, and industrial dust, which are linked to rapid economic development¹. The adverse impacts of air pollution on public health are enormous and have increased social concerns. An increasing number of studies have been conducted to investigate the associations between air pollution and certain diseases. Respiratory diseases have been found to have a close relationship with air pollution because the respiratory system is directly exposed to the external environment. Associations between air pollution and respiratory diseases have been observed in studies from many countries, including China²–⁹. Despite the increasing number of air quality studies conducted in China, air pollution epidemiology studies on the effects of PM₂.₅ and O₃ in Chinese populations are still limited¹⁰.

Hangzhou (HZ) (between 119.982°–120.388°E and 30.082°–30.398°N) is one of the largest cities in the Yangtze River Delta (YRD) region, which is considered as one of the most rapidly developing regions in China. As a result of urbanization and industrialized processes, HZ has severe air pollution like many Chinese cities¹¹–¹³. Several studies have been conducted on the detrimental effects of air pollution on residents’ health in HZ²,¹⁴,¹⁵ as part of nationwide investigations on China’s air pollution and the resulting health effects. However, most research on air pollution and respiratory diseases has been carried out in heavily polluted areas, so comparisons with other less polluted areas are lacking. Therefore, the city of Zhoushan (ZS) (between 121.932°–122.257°E and 29.658°–30.186°N), an island city with the best air quality in the region¹⁶, was selected as a comparison region to quantify the effect of air pollution on residents in a less polluted area.

The objective of this study was to assess the effects of air pollutants such as PM₂.₅, SO₂, NO₂, and O₃ on the mortality rates of respiratory disease (RD), including one subcategory of RD, chronic obstructive pulmonary disease (COPD), and on hospital outpatients with RD in two cities with high and low levels of air pollution.

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| City | Variable | PM$_{2.5}$ (µg/m$^3$) | SO$_2$ (µg/m$^3$) | NO$_2$ (µg/m$^3$) | O$_3$ (µg/m$^3$) | Temperature (°C) | Relative humidity (%) | Pressure (hpa) |
|------|----------|----------------------|------------------|------------------|------------------|------------------|---------------------|----------------|
| HZ   | Mean     | 60.124               | 17.251           | 49.538           | 92.174           | 17.566           | 74.033              | 1011.510         |
|      | Standard Deviation | 32.193               | 8.830             | 16.739           | 52.019           | 8.228             | 14.021              | 8.912            |
|      | Min      | 8.286                | 4.250             | 12.625           | 6.429            | −0.100            | 27.000              | 9.893            |
|      | 25$^{th}$ Percentiles | 37.250               | 10.625            | 37.250           | 50.625           | 10.000            | 65.000              | 1003.700         |
|      | Median   | 54.625               | 15.500            | 47.500           | 80.536           | 19.200            | 75.000              | 1011.550         |
|      | 75$^{th}$ Percentiles | 75.714               | 21.375            | 59.000           | 133.429          | 24.200            | 85.000              | 1018.700         |
|      | Max      | 229.375              | 77.125            | 106.625          | 247.375          | 33.200            | 98.000              | 1031.100         |
| ZS   | Mean     | 31.286               | 6.138             | 22.930           | 92.322           | 17.104            | 80.452              | 1012.120         |
|      | Standard Deviation | 21.766               | 4.170             | 13.085           | 32.092           | 7.488             | 11.528              | 8.556            |
|      | Min      | 3.000                | 2.000             | 2.000            | 2.000            | 0.725             | 39.000              | 98.500           |
|      | 25$^{th}$ Percentiles | 17.000               | 3.000             | 14.000           | 72.000           | 10.600            | 74.000              | 1005.000         |
|      | Median   | 26.000               | 5.000             | 21.000           | 90.500           | 18.050            | 82.500              | 1011.950         |
|      | 75$^{th}$ Percentiles | 39.000               | 8.000             | 29.000           | 111.000          | 23.475            | 89.000              | 1018.800         |
|      | Max      | 163.000              | 42.000            | 100.000          | 231.000          | 30.400            | 98.000              | 1030.300         |
|      | t        | 20.010               | 32.000            | 33.780           | −0.070           | 1.120             | −9.560              | −1.330           |
|      | P        | <0.01                | <0.01             | <0.01            | 0.948            | 0.262             | <0.01               | 0.185            |

Table 1. Summary statistics of air pollutants and meteorological factors in both city from 2014–2015.

Results

During the study period, the average concentrations of the air pollutants PM$_{2.5}$, SO$_2$, NO$_2$, and O$_3$ in HZ and ZS were 60.12, 17.25, 49.54, and 92.17 µg/m$^3$ and 31.28, 6.14, 22.93, and 93.32 µg/m$^3$, respectively. The average concentrations of the air pollutants in HZ were 1.6–2.8 times higher than those in ZS ($P < 0.01$), except for O$_3$ ($P > 0.05$) (Table 1). Table 2 shows that the correlations between the air pollutants and meteorological factors had a similar pattern for HZ and ZS. The average daily mortality counts for RD and COPD in HZ and ZS were 7.50 and 2.99 and 4.57 and 1.53, respectively. The daily outpatient counts in HZ and ZS of adult and child patients averaged 416.66 and 229.19 and 78.89 and 53.44, respectively (Table 3). Air pollutants, meteorological factors, and outcomes also showed a seasonal trend (Supplementary Figs S1, S2, and S3).

The associations between mortalities or outpatient visits and air pollutants were adjusted for potential confounding factors in single-pollutant models as presented in Table 4 and Supplementary Tables S1 and S2. An increase of 10 µg/m$^3$ of air pollutants was significantly associated with the following: The ER of mortality of RD increased by 0.99 (95% CI: 0.03–1.95) for PM$_{2.5}$ in HZ and by 2.09 (95% CI: 0.03–4.18) for PM$_{2.5}$ in ZS. The ER of mortality of COPD increased by 1.60 (95% CI: 0.46–2.76), 6.33 (95% CI: 1.72–11.15), and 3.97 (95% CI: 1.58–6.41) for PM$_{2.5}$, SO$_2$, and NO$_2$, respectively, in HZ, whereas no associations were identified in ZS. Outpatient visits of adults with RD increased by 0.67 (95% CI: 0.50–0.84), 3.50 (95% CI: 2.92–4.09), 2.10 (95% CI: 1.76–2.44), and 0.65 (95% CI: −0.83–0.47) for PM$_{2.5}$, SO$_2$, NO$_2$, and O$_3$, respectively, in HZ and also increased by 0.83 (95% CI: 0.23–1.43), 5.81 (95% CI: 3.12–8.58), 3.47 (95% CI: 2.41–4.54), and 0.61 (95% CI: 0.15–1.07) for PM$_{2.5}$, SO$_2$, NO$_2$, and O$_3$, respectively, in ZS. Outpatient visits of children with RD increased by 1.47 (95% CI: 1.22–1.71), 5.70 (95% CI: 4.92–6.49), 4.04 (95% CI: 3.57–4.51), and 0.21 (95% CI: 0.03–0.40) for PM$_{2.5}$, SO$_2$, NO$_2$, and O$_3$, respectively, in HZ and also increased by 1.78 (95% CI: 1.05–2.51), 10.89 (95% CI: 7.38–14.52), 8.02 (95% CI: 6.67–9.38), and
0.84 (95% CI: 0.29–1.40) for PM$_{2.5}$, SO$_2$, NO$_2$, and O$_3$, respectively, in ZS. The best lag day model that was incorporated into the single-pollutant models is shown in Table 4.

The effects of air pollutants on mortalities and outpatients for the multiple-pollutant model are presented in Table 5. In this model, PM$_{2.5}$, SO$_2$, NO$_2$, and O$_3$ were included, and the lag days were selected based on the results of the single-pollutant model (Table 3). After adjusting for other air pollutants, PM$_{2.5}$ in HZ was significantly associated with the mortality rates of RD and COPD, particularly with the mortality rates of COPD in both males and females. The effect was slightly enhanced compared to the results of the corresponding single-pollutant model.

In HZ, NO$_2$ was significantly associated with the mortality rates of COPD; meanwhile, in ZS, O$_3$ was significantly associated with the mortality rates of RD, especially RD mortalities in females. In both cases, the effects were slightly lower compared to the corresponding single-pollutant models. For outpatient visits of individuals with RD, SO$_2$ and NO$_2$ were significantly associated with outpatient visits of adults and children in both HZ and ZS; only PM$_{2.5}$ was significantly associated with outpatient visits of children in HZ. The effects were slightly lower in comparison to the single-pollutant models. In HZ, O$_3$ was significantly associated with adult outpatient visits; this association was negative in the single-pollutant model but positive in the multiple-pollutant model.

With respect to gender (Table 5 and Supplementary Table S3), the ER values for the mortality rates of COPD as a result of PM$_{2.5}$ concentrations in the atmosphere were higher for females than males in HZ. These patterns were also observed in the mortality rates of RD stemming from O$_3$ in ZS; however, an opposite trend was identified for the mortality rates of COPD stemming from PM$_{2.5}$ in ZS. Seasonal differences in air pollutants were also observed between HZ and ZS and likely affect the rates of RD and COPD (Supplementary Table S4).

### Discussion

During this study, the different impacts of air pollutants on respiratory mortality rates and outpatient visits were evaluated and compared between HZ and ZS, which have distinct air pollution levels. In particular, SO$_2$ and NO$_2$ were strongly associated with respiratory mortality rates and outpatient visits in HZ, and the concentrations of SO$_2$ and NO$_2$ were about 2.81 and 2.16 times higher, respectively, in HZ than in ZS. Moreover, O$_3$ appeared to play a more important role in respiratory mortality rates and outpatient visits in areas with a lower level of air pollution than in areas with a higher level of air pollution.

Because of rapid economic development, HZ has become one of the most heavily air-polluted cities in China. The results of the multiple-pollutant model in this study showed that RD increased 1.29% per 10 μg/m$^3$ increase in...
Significant association between COPD mortality rates and SO2 was only observed in HZ in the single-pollutant model, whereas no positive correlations were found in ZS. However, outpatient visits for RD were strongly associated with SO2 exposure in HZ and ZS for both adults and children; this association was stronger in ZS than in HZ, even though the concentration of SO2 was 2.81 times higher in HZ than in ZS. These results indicate that PM2.5, which is slightly higher than other cities in eastern China (0.95–0.99%) with similar average concentrations in PM2.5, shows lower risk than the results of another study conducted in several cities in the US, Western Europe, and South Korea with lower average concentrations of PM2.5 (1.68–3.90%)20–24.

Previous studies on exposure to SO2 and RD have not reached a coherent conclusion. However, a positive association between SO2 exposure and RD has been reported by several groups. A cross-case study showed that an increased number of asthma episodes was associated with elevated exposure to SO2 emitted from refinery factories25. Another study indicated that children living near a petrochemical site had a higher prevalence of respiratory hospitalizations and symptoms26. In contrast, no associations or only moderate associations between SO2 and respiratory hospitalizations and symptoms26.

Table 4. Excess Risk of respiratory mortalities and outpatients per 10μg/m3 increase of air pollutants in both cities with best lag: single-pollutant model. \( P < 0.05, \* P < 0.01 \) (Excess Risk is adjusted for temperature, relative humidity and atmospheric pressure, day of week, time trend and seasonality for mortality and hospital data, and public holiday only for hospital data); \* Excess Risk (95% confidence interval); \* RD in adults; \* RD in children.

PM2.5, which is slightly lower than other cities in eastern China (0.95–0.99%) with similar average concentrations of PM2.58,17,18. This finding is in line with the results of a study conducted across all WHO regions (1.51%)19 but reflects lower risk than the results of another study conducted in several cities in the US, Western Europe, and South Korea with lower average concentrations of PM2.5 (1.68–3.90%)20–24.
partially explain the inconsistent results of previous studies with respect to the influence of SO\textsubscript{2} on RDs. with O\textsubscript{3} in both males and females in ZS, while no association between the mortality rates of RD and O\textsubscript{3} was observed in HZ. It seems that the effects of O\textsubscript{3} on mortality rates could be attenuated by other air pollutants, and atmospheric pressure, day of week, time trend and other pollutants for mortality and hospital data, and public holiday only for hospital data); aExcess Risk (95% confidence interval); bRD in adults; cRD in children.

The present results showed that NO\textsubscript{2} was associated with deaths from COPD in HZ but not in ZS; however, there was a significant association between outpatient visits for RD and NO\textsubscript{2} pollution in both HZ and ZS. These results are consistent with the findings for SO\textsubscript{2}, indicating that some air pollutants may need to reach a specific threshold to cause adverse effects on human health.

The present study has several strengths. First, the investigations were conducted in two cities with different levels of air pollution in the same province. Second, the number of outpatient visits as well as mortality rates was used to analyze the effects of air pollutant levels on human health. Third, four high-ranking air pollutants were used to analyze the effects of air pollutant levels on human health. The adverse effects of PM\textsubscript{2.5} on human health have attracted increasing public attention. Studies conducted in Xi'an and Guangzhou, two industrialized cities in China, reported that an increase in mortality rates was significantly associated with an increase in PM\textsubscript{2.5} concentrations\textsuperscript{18,30}, which would also suggest a significant impact on the association between SO\textsubscript{2} and outpatient visits for RD may also depend on individual sensitivity, which could

| Pollutant | Variable | ER(95% CI) in HZ\textsuperscript{a} | ER(95% CI) in ZS\textsuperscript{a} |
|-----------|----------|----------------------------------|----------------------------------|
| PM\textsubscript{2.5} | Mortality counts | | |
| | Male | 1.290(0.294–2.295)\textsuperscript{a} | 1.969(–0.183–4.167) |
| | Female | 1.344(–0.068–2.777) | 2.744(–0.330–5.913) |
| | COPD | 1.737(0.521–2.967)\textsuperscript{b} | 2.669(–0.304–5.731) |
| | Male | 1.788(0.242–3.359)\textsuperscript{b} | 4.795(0.510–9.262) |
| | Female | 1.931(0.076–3.821) | 2.111(–2.462–6.899) |
| | Outpatient counts | | |
| | Adults\textsuperscript{a} | 0.132(–0.059–0.323) | –0.165(–0.892–0.568) |
| | Children\textsuperscript{c} | 0.465(0.210–0.720)\textsuperscript{b} | 0.261(–0.534–1.062) |
| SO\textsubscript{2} | Mortality counts | | |
| | Male | 3.621(–1.195–8.671) | 2.839(–12.338–20.645) |
| | Female | –5.286(–11.196–1.018) | –12.616(–26.064–3.277) |
| | COPD | 4.101(–0.651–9.082) | –11.051(–24.587–4.914) |
| | Male | 2.967(–3.150–9.469) | 16.951(–5.303–44.435) |
| | Female | 3.469(–4.983–12.674) | –20.743(–38.655–2.399) |
| | Outpatient counts | | |
| | Adults\textsuperscript{a} | 1.882(1.214–2.554)\textsuperscript{b} | 2.813(0.075–5.625) |
| | Children\textsuperscript{c} | 2.150(1.239–3.069)\textsuperscript{b} | 4.482(0.844–8.252) |
| NO\textsubscript{2} | Mortality counts | | |
| | Male | 1.201(–0.745–3.186) | –1.579(–5.057–2.026) |
| | Female | 0.966(–1.870–3.884) | –3.247(–8.204–1.978) |
| | COPD | 2.620(–0.251–5.574) | –1.086(–5.805–3.870) |
| | Male | 2.381(–0.900–5.772) | –6.164(–12.719–0.884) |
| | Female | 4.153(–0.476–8.998) | 6.678(–0.135–14.188) |
| | Outpatient counts | | |
| | Adults\textsuperscript{a} | 1.469(1.093–1.846)\textsuperscript{b} | 1.324(0.002–2.664) |
| | Children\textsuperscript{c} | 2.098(1.581–2.617)\textsuperscript{b} | 2.032(0.679–3.404) |
| O\textsubscript{3} | Mortality counts | | |
| | Male | –0.700(–1.699–0.309) | 1.879(0.230–3.554) |
| | Female | –0.603(–1.567–0.371) | 2.090(–0.308–4.545) |
| | COPD | –0.806(–1.832–0.231) | 2.175(–0.120–4.523) |
| | Male | –0.975(–2.637–0.716) | 2.325(–0.878–5.632) |
| | Female | –1.201(–2.773–0.396) | 2.351(–1.084–5.906) |
| | Outpatient counts | | |
| | Adults\textsuperscript{a} | 0.222(0.062–0.383)\textsuperscript{b} | 0.348(–0.117–0.814) |
| | Children\textsuperscript{c} | –0.198(–0.396–0.008) | –0.249(–0.814–0.320) |

Table 5. Excess Risk of respiratory mortalities and outpatients per 10 μg/m\textsuperscript{3} increase of air pollutants in both cities: multiple-pollutant model. \textsuperscript{a}P < 0.05, \textsuperscript{b}P < 0.01 (Excess Risk is adjusted for temperature, relative humidity and atmospheric pressure, day of week, trend and other pollutants for mortality and hospital data, and public holiday only for hospital data); \textsuperscript{c}Excess Risk (95% confidence interval); \textsuperscript{d}RD in adults; \textsuperscript{e}RD in children.

the association between SO\textsubscript{2} and outpatient visits for RD may also depend on individual sensitivity, which could partially explain the inconsistent results of previous studies with respect to the influence of SO\textsubscript{2} on RDs.

The adverse effects of PM\textsubscript{2.5} on human health have attracted increasing public attention. Studies conducted in Xi’an and Guangzhou, two industrialized cities in China, reported that an increase in mortality rates was significantly associated with an increase in PM\textsubscript{2.5} concentrations\textsuperscript{18,30}, which would also suggest a significant impact on RD. In the present study, the mortality rates of RD and COPD in males were associated with a 10 μg/m\textsuperscript{3} increase in the concentration of PM\textsubscript{2.5} in both HZ and ZS, which is consistent with the results of previous studies; however, the association was stronger in ZS, which had a lower concentration of PM\textsubscript{2.5}, than in HZ, which had a higher concentration of PM\textsubscript{2.5}. This may be explained by differences in sample sizes, climates, lifestyles, etc.

Studies in the Pearl River Delta region of Southern China and in Shanghai reported that O\textsubscript{3} exposure was also associated with mortality risks\textsuperscript{31,32}. In the present study, the mortality rates of RD were significantly associated with O\textsubscript{3} in both males and females in ZS, while no association between the mortality rates of RD and O\textsubscript{3} was observed in HZ. It seems that the effects of O\textsubscript{3} on mortality rates could be attenuated by other air pollutants, which is partially supported by the correlation coefficients of the analyzed air pollutants in the present study.

In addition, NO\textsubscript{2}, another principal air pollutant in China, was reported to be linked to deaths from RD\textsuperscript{35}. The present results showed that NO\textsubscript{2} was associated with deaths from COPD in HZ but not in ZS; however, there was a significant association between outpatient visits for RD resulting from NO\textsubscript{2} pollution in both HZ and ZS. These results are consistent with the findings for SO\textsubscript{2}, indicating that some air pollutants may need to reach a specific threshold to cause adverse effects on human health.

The present study has several strengths. First, the investigations were conducted in two cities with different levels of air pollution in the same province. Second, the number of outpatient visits as well as mortality rates was used to analyze the effects of air pollutant levels on human health. Third, four high-ranking air pollutants were selected to investigate the relationship between air pollution and RD.
The limitations of the analysis should also be noted. One limitation of our study was that although the hospitals included in this study were the pulmonary hospital in HZ and the largest hospital in ZS, some patients may have visited other hospitals. Therefore, additional hospitals should be included in future studies. Another limitation was that RD outpatients were not divided into more detailed subgroups including acute upper respiratory tract infections, COPD, pneumonia, etc., so the responses of different types of RD to air pollutants could not be investigated in our study. The effects of air pollutants on subgroups of RD should be further investigated in future studies.

Conclusions
In summary, a significant association between air pollutants and RD was found both in terms of mortality rates and outpatient visits. Also, the different air pollutant levels in HZ and ZS lead to regional differences in mortality rates and outpatient visits. In line with previous studies, these results suggest that the government should accelerate the implementation of environmental protection policies to improve the quality of life of its citizens.

Materials and Methods
Air pollution and meteorology data. Concentrations of PM$_{2.5}$, SO$_2$, NO$_2$, and O$_3$ were collected between 1 January, 2014 and 31 December, 2015, from eight environmental monitoring stations in urban areas of HZ and from one environmental monitoring station in an urban area of ZS. Daily mean temperature, relative humidity, and atmospheric pressure measurements were provided by the Zhejiang Meteorological Administration. Twenty-four-h means were used for all air pollutants except O$_3$, which is conventionally measured at a maximum interval of 8 h. The locations of the stations are shown in Fig. 1 and Supplementary Table S5 (HZ: Hemuxiaoxue, Xixi, Yunxi, Zhejiangnongda, Binjiang, Xiasha, Wologqiao, and Zhaohuiwuqu; ZS: Linchengxinqu).

Mortality data. The mortality records for RD in HZ and ZS during the study period were obtained from the local mortality register of the Zhejiang Provincial Center for Disease Prevention and Control. These records were encoded using the 10th revision of the international classification of diseases and related health problems (ICD-10) and included the dates of mortality, ages, genders, and addresses of deceased patients.

Hospital outpatient data. Outpatient data for RD were obtained between 1 January, 2014 and 31 December, 2014, in one tertiary hospital located in HZ and another located in ZS. The data obtained from these hospitals are geographically representative because patients in these hospitals generally reside in the corresponding local areas. These data were also encoded using ICD-10. Patients who visited either the same doctor or multiple respiratory doctors more than once within 15 days were excluded from the data. The locations of the hospitals are provided in Fig. 1 and Supplementary Table S5 (Hangzhou Red Cross Hospital; Zhoushan People’s Hospital).

Data analysis. The diseases were categorized as RD (ICD-10 codes J00-99) or COPD (ICD-10 codes J40-44). The mortality data were divided into two gender groups, male and female, and two age groups, <65 years (non-elderly) and ≥65 years (elderly), as most deaths occurred in the elderly. Because of the relatively low daily mortality rate in the <65 years age group, the effect of air pollutants on mortality rates for this age group was not analyzed. The outpatient data were divided into two groups, RD in adults (age > 18) and RD in children (age ≤ 18). Patients younger than 18 years often visit pediatric clinics in China, so data from both adult and pediatric clinics were used. The whole year was divided into two seasons, a warm season (April to September) and a cold season (January to March and October to December), according to the seasonal characteristics of HZ and ZS. Only the mortality records that included current residential addresses within the range of the above-mentioned stations were analyzed. These data from records were examined along with the mean concentrations of air pollutants from all stations according to city and date. The distance from each hospital to the stations was determined using the SoDA package in R. The data collected from stations within 10 km of each hospital were averaged. The Zhaohuiwuqu and Zhejiangnongda stations were paired with the hospital in HZ; the Linchengxinqu station was paired with the hospital in ZS (Fig. 1).

For all analyses, the level of significance was set at $P < 0.05$. The descriptive statistics and correlations were calculated for mortalities, outpatient visits, air pollutants, and meteorological factors using the SAS 9.2 software (Cary, NC, USA). The $t$ test was used to compare the continuous variables, and the Spearman correlation was used to evaluate the correlations among the air pollutants and the meteorological factors.

The associations between the mortalities of outpatients and air pollutants were adjusted for meteorological factors, days of the week, public holidays, time trends, and seasonality and were estimated using generalized additive models (GAM) in the MGC GV packages in R vision 3.3.1. The weather conditions, including daily mean temperature, relative humidity, and atmospheric pressure, were controlled using natural spline smoothing functions. The adjustments for time trends and seasonality were made using natural spline smoothing functions of time. The degrees of freedom (df) for the functions were determined via generalized cross validation (GCV). In addition, dummy variables were used for days of the week and public holidays to control for potential confounding factors. To control for any lag effect, the concentrations of air pollutants on the current day (lag0) and the previous six days (lag1–6) were incorporated into the model. The best time lag model was selected according to the minimum P values; only single lag models were considered. Using residual plots and partial autocorrelation function (PACF) plots in the TSA packages in R vision 3.3.1, the residual models were examined to determine the presence of autocorrelations. All results were presented as excess risk (ER) of outpatient mortality per 10 mg/m$^3$ increase of each air pollutant in comparison to the baseline at a 95% confidence interval (CI). The resulting model was as follows:

$$\text{Log}[\text{E}(Y_i)] = \alpha + \beta Z_{i-1} + \text{ns (time, df)} + \text{ns (X_i, df)} + \text{DOV + holiday}$$
where \( Y_t \) is the number of daily respiratory mortalities or outpatients at day \( t \); \( E(\hat{Y}_t) \) is the expectation of the Poisson distribution of \( Y_t \); \( \alpha \) is the intercept; \( Z_{t-1} \) is the concentration of air pollutants in lag(i) day, \( i = 0 \) to 6; \( \beta \) is the regression coefficient; \( ns(time, df) \) refers to the natural spline smoothing functions of the day of study \( (df = 2 \times 2) \); \( ns(X_t, df) \) refers to the natural spline smoothing functions of meteorological factors, such as daily mean temperature \( (df = 3) \), relative humidity \( (df = 3) \), and atmospheric pressure \( (df = 3) \); \( DOW \) represents the dummy variables for the day of the week; and holiday is the dummy variable for public holidays, which was only used in the model for outpatient visits. The significant differences between the values of the ER of the group variables (e.g., male and female) were determined by calculating the 95% CI as follows:

\[
(\hat{Q}_1 - \hat{Q}_2) \pm 1.96 \sqrt{SE_1^2 + SE_2^2}
\]

where \( \hat{Q}_1 \) and \( \hat{Q}_2 \) are the values of ER for the two groups, and \( SE_1 \) and \( SE_2 \) are their respective standard errors.38

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Author Contributions
Z.M., Q.F., Z.C., X.W., and X.L. designed research; D.L., L.Z., G.M., and L.W. performed research; P.X., Z.W. and X.P. analyzed data, and Q.F. wrote the main manuscript text. All authors have reviewed the manuscript and have given approval to the final version.

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