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# Association between ambient sulfur dioxide pollution and asthma mortality: Evidence from a nationwide analysis in China

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ABSTRACT

There is a lack of research on the effects of acute exposure to ambient sulfur dioxide ($SO_2$) on mortality caused by asthma, especially nationwide research in China. To explore the acute effect of exposure to ambient $SO_2$ on asthma mortality using nationwide dataset in China from 2015 to 2020 and further evaluate the associations in subgroups with different geographical and demographic characteristics. We used data from China's Disease Surveillance Points system with 29,553 asthma deaths in China during 2015–2020. The exposure variable was the daily mean concentrations of $SO_2$ from the ChinaHigh$SO_2$ 10 km × 10 km daily grid dataset. Bilinear interpolation was used to estimate each individual's exposure to air pollutants and meteorological variables. We used a time-stratified case crossover design at the individual level to analyze the exposure response relationship between short-term exposure to $SO_2$ and asthma mortality. Stratified analyses were carried out by sex, age group, marital status, warm season and cold season, urbanicity and region. Significant associations between short-term exposure to ambient $SO_2$ and increased asthma mortality were found in this nationwide study. The excess risk (ER) for each 10 μg/m$^3$ increase in $SO_2$ concentrations at lag07 was 7.78 % (95 % CI, 4.16–11.52 %). Season appeared to significantly modify the association. The associations were stronger in cold season (ER 9.78 %, 95 % CI:5.82 −13.89 %). The association remained consistent using different lag periods, adjusting for other pollutants, and in the analysis during pre-Corona Virus Disease 2019 (COVID-19) period. Our study indicates increased risk of asthma mortality with acute exposures to $SO_2$ in Chinese population. The current study lends support for greater awareness of the harmful effect of $SO_2$ in China and other countries with high $SO_2$ pollution.

## 1. Introduction

Asthma is a common respiratory disease with varying severity, ranging from very mild occasional wheezing to acute life-threatening airway closure (Hashmi et al., 2022; Papi et al., 2018). The Global Burden of Disease 2019 (GBD2019) Study estimated that asthma caused 1.4 million disability adjusted life years (DALYs) in China in 2019, accounting for 7 % of that in the globe and 92 % of that in east Asia (Anon, 2020). Although asthma is prevalent in China, a nationwide cross-sectional study showed that it remained largely undiagnosed and undertreated (Huang et al., 2019).

The concentration of Sulfur dioxide ($SO_2$) in China is at higher end of the range across the world(Wang et al., 2018; Wu et al., 2021). Previous studies have shown some linkage between SO2, as one of the criteria air

*Abbreviations:* ICD-10, The Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems; ER, Excess risk; CI, Confidence interval; IQR, interquartile range; $SO_2$, Sulfur dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; $PM_{10}$, particulate matter with aerodynamic diameter ≤ 10 μm; $O_3$, Ozone; $NO_2$, Nitrogen dioxide; CO, Carbon monoxide.

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pollutants, and asthma. Some recent studies consistently indicated the association between $SO_2$ and asthma morbidity and exacerbation of asthma symptoms(Bai et al., 2022; Mercan et al., 2020; Tomić-Spirić et al., 2021). A limited number of studies suggested that long-term exposure to $SO_2$ may increase asthma mortality (Kravchenko et al., 2014; Lang and Polansky, 1994; Salinas and Vega, 1995). However, there is a lack of research on the effects of acute exposure to ambient $SO_2$ on mortality caused by asthma. Only several small-scale studies reported that acute exposure to $SO_2$ may increase asthma mortality, but the findings were inconsistent (Saez et al., 1999; Yorifuji et al., 2019). Considering the generally high pollution level, evidence on the potential impact of short-term exposure to $SO_2$ was important for the development and promotion of clean-air policies in China. Nevertheless, only one local small-scale study from one province examined the relationship between acute exposure to $SO_2$ and deaths due to asthma and no associations were found based on data between 2013 and 2018 (Liu et al., 2019). The exposure-response relationship derived from one province is clearly not generalizable to China at the national level and other regions due to the great diversity in terms of $SO_2$ concentration, meteorological conditions and socioeconomic characteristics across different provinces in China. Previous studies found that asthma mortality was different among populations with different geographical (region) and demographic characteristics (Huang et al., 2022; Liu et al., 2022a) and the characteristics of exposure to $SO_2$ were also different in different regions and seasons (Kuerban et al., 2020; Li et al., 2019).

The purpose of this study is to explore the acute effect of exposure to ambient $SO_2$ on asthma mortality using nationwide dataset in China from 2015 to 2020. In this study, we further evaluated the associations in subgroups with different sex, age, marital status, season, urban-rural locale and region.

## 2. Materials and methods

### 2.1. Study population

This study was conducted based on data collected from China's Disease Surveillance Points system (DSPS), which has been proved to be representative at both national and provincial level and has been extensively used to estimate the national and provincial burden of disease in China (Liu et al., 2016; Zhou et al., 2016). The sampling scheme and detailed descriptions of the DSPS were published elsewhere (Liu et al., 2016). We used underlying cause of death to define cases in our study and only those with asthma as underly cause of death in the death certificate was included. The DSPS has a stringent quality control procedure with standard protocol by trained coders in hospitals or local CDC offices and multi-level review and checking for accuracy of the coding. Cases whose underlying cause of death was asthma (J45-J46) were identified using the 10th version of the International Classification of Diseases (ICD-10). Between January 1, 2015 and December 31, 2020, we obtained 29,553 deaths due to asthma from DSPS. We collected the participants' residential addresses and demographic information, including age, sex, marital status, educational level, and date of death. As shown in **Figure SM1**, we geocoded the address information into latitude and longitude by Baidu Maps API (http://lbsyun.baidu.com/) as used in previous study (Liu et al., 2022b).

### 2.2. Assessment of exposure and other covariates

The exposure variable was the daily mean concentrations of $SO_2$ from the ChinaHigh$SO_2$ 10 km × 10 km daily grid dataset from 2015 to 2020. ChinaHigh$SO_2$ is one of the series of datasets for ground-level air pollutants for China (i.e., ChinaHighAirPollutants, CHAP, available at https://weijing-rs.github.io/product.html). To remedy the limitations of ground-based air pollution observation, an ensemble learning model of Space-Time Extra-Tree was developed to estimate daily seamless ambient gaseous pollutants across China, with additional input variables including the ground-based measurements, satellite tropospheric gas column, modelled surface gas simulation, meteorological analysis, and emission inventory (Wei et al., 2022a; Wei et al., 2022b). This ChinaHigh$SO_2$ dataset (available at https://doi.org/10.5281/zenodo.5765553) was evaluated at different spatiotemporal scales against the ground measurements using the widely used out-of-sample ten-fold cross-validation approach. Cross-validates show that the daily surface $SO_2$ estimates agree well with ground-based measurements with an average coefficient of determination (CV-$R^2$) of 0.84 and the root-mean-square error (RMSE) of 10.07 $\mu g/m^3$ in China, and more than 80 % of the stations have high correlations (CV-$R^2 > 0.6$) with small uncertainties (RMSE $< 12$ $\mu g/m^3$) throughout the country (Wei et al., 2022a). This illustrates an overall high quality of the ChinHigh$SO_2$ dataset for future multi-field applications, especially in investigating the short-term impacts of air pollution exposure on public health. Details can be found in previous study (Wei et al., 2022a). Besides, daily ambient high-resolution and high-quality $PM_{2.5}$ (Wei et al., 2021a), $PM_{10}$ (Wei et al., 2021b), $O_3$ (Wei et al., 2022b), $NO_2$ (Wei et al., 2022c), and CO (Wei et al., 2022a) concentrations for the same period are also collected from the CHAP database.

Daily mean temperature and mean relative humidity in China at 10 km x10 km grids were obtained from the fifth generation of European ReAnalysis (ERA5)-Land reanalysis data set (Muoz-Sabater et al., 2021), which was widely used in climate-related research globally. Bilinear interpolation was used to estimate each individual's exposure to $SO_2$, other air pollutants and meteorological variables. The principle of this method is to take a weighted average of the nearest four grids around a specific location (Cao et al., 2021; Dong et al., 2020).

### 2.3. Study design

Based on high quality surveillance data, this study used a time-stratified case crossover design at the individual level to analyze the exposure response relationship between short-term exposure to $SO_2$ and asthma mortality. Time-stratified case crossover study is a widely used epidemiological design to study the effects of environmental pollution, meteorological factors and extreme weather events on human health (Jaakkola, 2003; Liu et al., 2019), and to explore the association between disease and exposure by comparing individual exposure in different periods. The case period and the control period are in the same year, month, and day of week. In the same time layer, control periods are randomly distributed and the case period is not fixed in a certain position (Janes et al., 2005). Thus, this study design can simultaneously control the confounding factors including the seasonality, time trends and the day of week and obtain unbiased estimates of parameters (Janes et al., 2005; Szyszkowicz, 2019). We initially obtained 29,553 deaths due to asthma during 2015–2020. Three cases with missing data on residential address and 162 cases without data on pollutants were excluded. Therefore 29,388 (99.4 %) asthma death cases and 99,690 control days (1:3.4) were included in the final analysis. The study obtained ethics approval from the ethics committee at the School of Public Health, Sun Yat-sen University.

### 2.4. Statistical analysis

Spearman correlation coefficient was used to examine the correlation between air pollutants and meteorologic variables. Conditional logistic regressions were applied to explore the effects of short-term exposures to ambient $SO_2$ on mortality due to asthma for different lag periods. To adjust for potential meteorological confounding factors, natural cubic spline functions with 5 degrees of freedom (df) were applied to daily mean temperature and relative humidity. Excess risks (ERs) with corresponding 95 % confidence intervals (CIs) in asthma mortality associated with a 10 $\mu g/m^3$ increase in $SO_2$ concentration were reported. ER= $[\exp(\beta \times 10) - 1] \times 100$ %, where $\beta$ is the exposure-response relationship coefficient.

Two types of parameters including single-day lags and moving average of multi-day lags were used to address the lag effects. We assessed the effects from the current day to seven lag days and the variables were lag0 to lag7 and moving average lag01 to lag07. Stratified analyses were carried out by sex, age group (<75 years and ≥75 years), marital status (married vs. other), warm season (May to October) and cold season (November to April), urbanicity (urban and rural) and region (north and south). The definition of urbanicity is the same as that in previous publications (National Center For Chronic And Non-Communicable Disease Control And Prevention, Chinese Center For Disease Control and Prevention, 2021). The urban and rural areas are divided according to the district/county where the death cases resided. The urban areas include the sub districts of municipalities and prefecture-level cities, while the rural areas include counties and county-level cities. North and south China was defined using the most common classification with Tsinling Mountains and Huai River as the boundary. Figure SM1 shows the provinces of northern and southern China. The potential effect modification was explored by comparing the point estimate and standard error of strata-specific ER as used in previous studies (Liu et al., 2022b; Liu et al., 2019).

Sensitivity analyses were conducted in two manners to test the robustness of the associations between $SO_2$ and asthma mortality. First, we applied two-pollutant models to adjust for other pollutants including $PM_{2.5}$, $PM_{10}$, CO, $NO_2$ and $O_3$ by adding another pollutant with the same lag structure as a continuous variable to the single pollutant ($SO_2$) model. Additionally, the analysis was performed in asthma deaths during pre-Corona Virus Disease 2019 (COVID-19) pandemic (2015–2019) period. Because previous studies have shown that COVID-19 pandemic may affect both air pollution (Chen et al., 2020; Le T et al., 2020) and asthma (Abrams et al., 2020; Skevaki et al., 2020).

All statistical analyses were performed in R version 4.2.1 (R Foundation for Statistical Computing). Two-sided P-values less than 0.05 were statistically significant.

## 3. Results

### 3.1. Descriptive results

Among the 29,388 cases included in the study, the majority of cases were males (56.9 %), married (60.3 %), aged 75 years and over (64.4 %), lived in rural areas (59.1 %) or in the South (65.9 %), and died in the cold season (57.6 %) (Table 1). The median concentrations of $SO_2$ (lag07) during case and control days in the north and south region were 15.1 μg/m$^3$ and 12.1 μg/m$^3$, respectively. The median concentrations of $SO_2$ (lag07) in the cold and warm season were 15.3 μg/m$^3$ and 10.9 μg/m$^3$, respectively.

Table 2 demonstrates the distribution of $SO_2$ (lag07) and meteorologic factors (lag1) on all observation days and stratified by control and case days. The mean concentrations of $SO_2$ on case days and control days were 16.8 μg/m$^3$ and 16.7 μg/m$^3$, respectively. **Table SM1** showed that $SO_2$ was correlated with other pollutants and meteorological factors. As shown in **Table SM2**, the median concentrations of $PM_{2.5}$, $PM_{10}$, $O_3$, $NO_2$, and CO at lag 07 during 2015–2020 were 38.1 μg/m$^3$, 65.0 μg/m$^3$, 81.9 μg/m$^3$, 27.4 μg/m$^3$ and 0.9 mg/m$^3$, respectively.

### 3.2. Regression results

Fig. 1 showed that acute exposure to $SO_2$ produced statistically significant increase in asthma mortality both in single-day lag pattern and moving average multi-day lag structures. Significant increase of asthma mortality was observed for each 10 μg/m$^3$ increase of $SO_2$ concentration at lag07 (the 8-day moving average concentrations) with the strongest association. The ER was 7.78 % (95 % CI: 4.16–11.52 %).

**Table 1**
Characteristics of Study Population and Distribution of $SO_2$ at Lag07, 2015–2020.

| Baseline Characteristic | No. ( %) | $SO_2$ (μg/m$^3$) | |
|---|---|---|---|
| | | Median (IQR) | P-Value† |
| **Overall** | 129,078 (100) | 12.9 (10.1) | 0.987 |
| Case days | 29,388 (22.8) | 12.9 (10.2) | |
| Control days | 99,690 (77.2) | 12.9 (10.1) | |
| **Sex** | | | <0.001 |
| Male | 16,722 (56.9) | 12.7(10.0) | |
| Female | 12,666 (43.1) | 13.3(10.3) | |
| **Age group (years)** | | | 0.027 |
| <75 | 10,465 (35.6) | 12.9(9.9) | |
| ≥ 75 | 18,923 (64.4) | 13.0(10.2) | |
| **Education** | | | <0.001 |
| Junior High school and below | 27,260 (92.8) | 13.0(10.1) | |
| High school | 1608 (5.5) | 12.5(10.6) | |
| College degree or above | 515 (1.7) | 11.4(9.9) | |
| **Marital status** | | | 0.182 |
| Married | 17,709 (60.3) | 12.9(9.9) | |
| Other | 11,679 (39.7) | 13.0(10.5) | |
| **Season** | | | <0.001 |
| Cold | 16,935 (57.6) | 15.3(12.8) | |
| Warm | 12,453 (42.4) | 10.9(6.8) | |
| **Urban or Rural** | | | <0.001 |
| Urban | 12,005 (40.9) | 12.5(10.2) | |
| Rural | 17,383 (59.1) | 13.3(10.0) | |
| **Region** | | | <0.001 |
| North | 10,029 (34.1) | 15.1(16.1) | |
| South | 19,359 (65.9) | 12.1(8.5) | |

Abbreviations: IQR = interquartile range; SO2 = sulfur dioxide; Lag07 = 8-day moving average.
† P-Value for Kruskal-Wallis H test

**Table 2**
Distribution of $SO_2$ (Lag07) and Meteorologic Factors (Lag1) during Case and Control Days in China, 2015–2020.

| | Mean | SD | Min | 25$^{th}$ | Median | 75$^{th}$ | Max |
|---|---|---|---|---|---|---|---|
| **Overall** | | | | | | | |
| $SO_2$, μg/m$^3$ | 16.7 | 14.4 | 0.0 | 9.1 | 12.9 | 19.2 | 360.4 |
| Temperature, °C | 14.4 | 9.7 | -34.1 | 7.0 | 15.1 | 22.4 | 36.6 |
| Relative humidity, % | 69.2 | 17.8 | 0.2 | 59.2 | 72.9 | 82.6 | 99.9 |
| **Case days** | | | | | | | |
| $SO_2$, μg/m$^3$ | 16.8 | 14.8 | 0.0 | 9.1 | 12.9 | 19.3 | 360.4 |
| Temperature, °C | 14.3 | 9.8 | -31.7 | 6.9 | 15.0 | 22.4 | 35.0 |
| Relative humidity, % | 69.1 | 17.9 | 0.3 | 59.0 | 72.8 | 82.5 | 99.8 |
| **Control days** | | | | | | | |
| $SO_2$, μg/m$^3$ | 16.7 | 14.2 | 0.0 | 9.1 | 12.9 | 19.2 | 299.4 |
| Temperature, °C | 14.4 | 9.7 | -34.1 | 7.1 | 15.2 | 22.4 | 36.6 |
| Relative humidity, % | 69.2 | 17.8 | 0.2 | 59.3 | 73.0 | 82.6 | 99.9 |

Abbreviations: Lag07 = 8-day moving average; Lag1 = the previous day; SD = standardized deviation; 25th = the 25th percentile; 75th, the 75th percentile; SO2 = sulfur dioxide.

### 3.3. Stratified analysis

Results shown in Fig. 2 indicated no significant effect modification by sex, age, marital status, urban or rural and region (all P for effect modification > 0.05). We only observed effect modification for season (P = 0.02), with significant association (ER 9.78 %, 95 % CI:5.82−13.89 %) in cold season and no significant association between $SO_2$ exposure and asthma mortality in warm season.

### 3.4. Sensitivity analysis

The association was found to be robust when adjusting for other pollutants in two-pollutant models (Fig. 3). In view of the impact of the

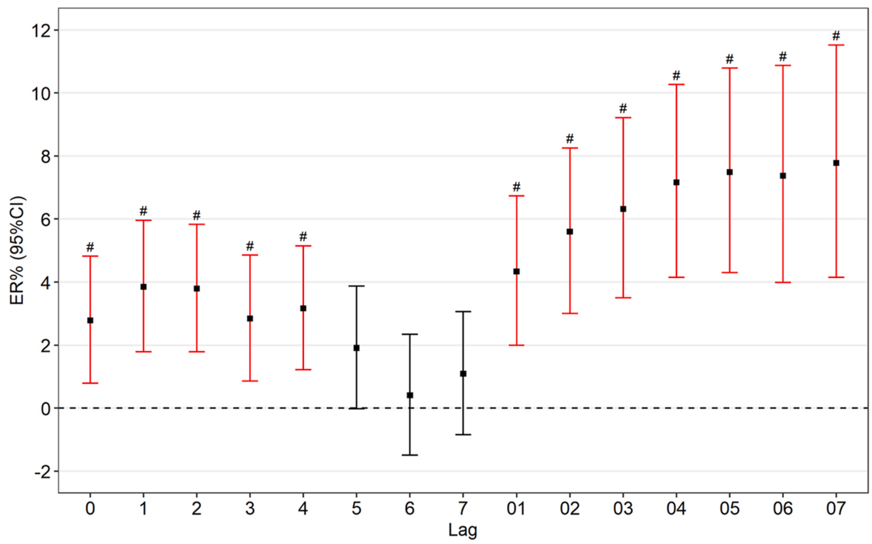


**Fig. 1.** ERs (95 % CIs) for asthma mortality associated with each 10 μg/m³ increase of exposures to $SO_2$ in China from January 1, 2015 to December 31, 2020. Abbreviations: ER = excess risk; CI = confidence interval; $SO_2$ = sulfur dioxide. #P < 0.01. The X-axis is the single lag days from lag0 to lag7, and the moving average lag days from lag 01 to lag 07.

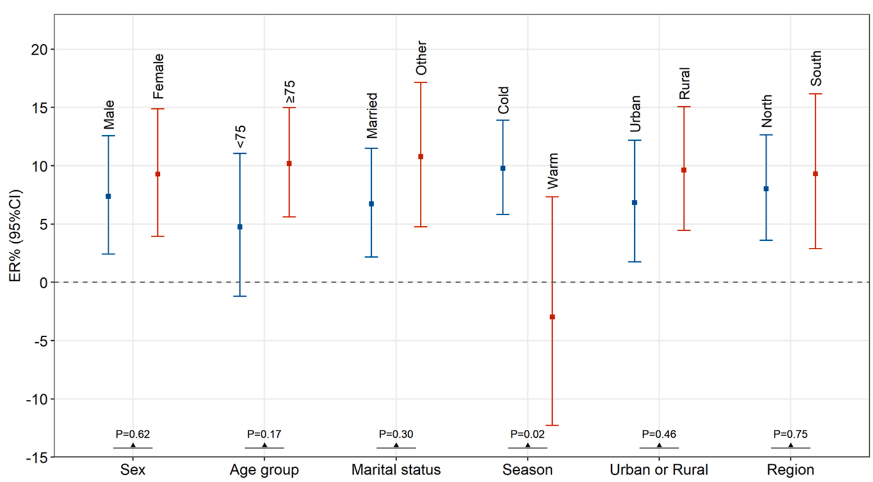


**Fig. 2.** ERs (95 % CIs) for asthma mortality associated with each 10 μg/m³ increase in exposure to $SO_2$ (lag07) stratified by sex, age, marital status, season, urban-rural locale and region. Abbreviations: ER = excess risk; CI = confidence interval; Lag07 = 8-day moving average; $SO_2$ = sulfur dioxide. P < 0.05 indicates significant effect modification.

COVID-19 pandemic in 2020 on air pollution levels and asthma deaths, we conducted the analyses in asthma deaths during pre-COVID-19 pandemic (2015–2019) period. Fig. 4 indicates that the ERs in the pre-COVID-19 period were larger than the overall estimates during the whole study period.

## 4. Discussion

Significant associations between short-term exposure to ambient $SO_2$ and increased asthma mortality were found in this nationwide study. Season appeared to significantly modify the association. The association remained consistent using different lag periods, adjusting for other pollutants, and in the analysis during pre-COVID-19 period.

To our knowledge, two earlier small-scale studies in Japan and Spain have studied the acute effect of $SO_2$ on asthma death, but their results are not consistent (Saez et al., 1999; Yorifuji et al., 2019). A time case crossover design based on historical data from 1972 to 1991 in Yokkaichi, Japan, found that $SO_2$ exposure increased the risk of asthma mortality (lag0) (Yorifuji et al., 2019). Another study (Saez et al., 1999) examined the association between short-term exposure to $SO_2$ and daily count of deaths from asthma in Barcelona during 1986–1989 using generalized estimating equations and no significant relationship was found. The inconsistent results were possibly due to the differences in study design and setting, methodology for statistical analyses and levels of air pollution. A more recent study (Liu et al., 2019) carried out in one central province in China explored the acute effects of ambient $SO_2$ exposure on asthma mortality during 2013–2018. However, this study did not provide evidence to support a relationship between short-term $SO_2$ exposure and deaths from asthma. In contrast, we found that $SO_2$ significantly increased asthma mortality in both urban and rural areas and south and north region. Although the same time-stratified case crossover study design was adopted, we used different data sources for air pollutants and different methods to assess individual level exposure to air pollutants and meteorological variables. In our study, we used the high quality ChinaHigh$SO_2$ data with high cross-validation coefficient of determination and low root mean square error. In order to reduce misclassifications on exposure level, residential address for each case was used to estimate the individual exposure to $SO_2$ by bilinear

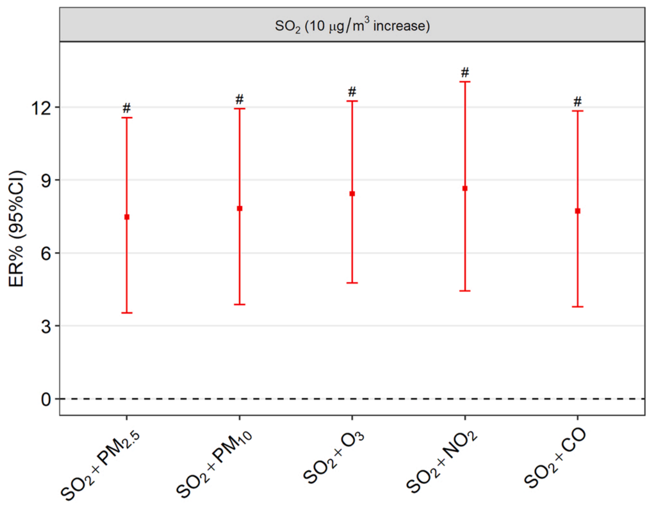


**Fig. 3.** ERs (95 % CIs) for asthma mortality associated with each 10 μg/m$^3$ increase in exposure to $SO_2$ (lag07) estimated by two-pollutant models using conditional logistic regression models, adjusting for temperature and relative humidity. Abbreviations: ER = excess risk; CI = confidence interval; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{10}$ = particulate matter with an aerodynamic diameter ≤ 10 μm; $O_3$ = ozone; $NO_2$ = nitrogen dioxide; Lag07 = 8-day moving average; $SO_2$ = sulfur dioxide; CO = carbon monoxide. #P < 0.01.

interpolation. Furthermore, the larger sample size, wider coverage and substantial variations of $SO_2$ levels, climate and socioeconomic characteristics in different regions across China may all contribute to the different findings.

Some animal experiments showed that $SO_2$ can affect the airway inflammatory and immune responses of the asthmatic rats and enhance the susceptibility to ovalbumin by aggravating inflammatory responses in lungs, up-regulating pro-inflammatory cytokine expression, and causing the Th1/Th2 imbalance, which might contribute to the increased risk of asthma (Li et al., 2014; Li et al., 2017). Several studies (Goldstein and Weinstein, 1986; Sheppard, 1988) have examined the effects of acute inhalation of $SO_2$ on human subjects, indicating that high concentration of $SO_2$ was demonstrated to cause significant decrements in airway function, especially in subjects with asthma. It has been shown that $SO_2$ and its derivatives could increase epidermal growth factor (EGF), EGF receptor, intercellular adhesion molecule-1, and cyclooxygenase-2 expression in human bronchial epithelial cells and the inflammation and overproduction of mucus in asthma exacerbation may be explained by the transcription and translation processes (Li et al., 2007; Tomić-Spirić et al., 2021). $SO_2$ is a water soluble irritant which exerts its primary effect on mucous membranes of the upper respiratory tract (Greenberg et al., 2017). It may induce bronchoconstriction and cause dyspnea in subjects with asthma due to decreased airway caliber mediated by constriction of airway smooth muscle. Tracheitis, respiratory epithelial abscission and local pneumonia may occur when exposed to low concentration for a long time, which increases the hospitalization rate and mortality rate of children, the elderly, asthmatics and other high-risk groups suffering from emphysema, asthma and other chronic obstructive respiratory diseases (Greenberg et al., 2017; Liu et al., 2014; Yorifuji et al., 2019). In addition, research showed that China's $SO_2$ emissions are not only huge in total, but also very high in intensity. The air pollution in China has been "soot type" for a long time. The particulate matter and $SO_2$ emitted by coal combustion have become the main pollutants in many cities in China (Kan et al., 2009; Kan et al., 2012). $SO_2$ pollution was significantly related to particulate matter pollution. pollution. Previous research has shown that particulate matter pollution may increase asthma mortality in China (Liu et al., 2022b), which may also be one of the reasons why $SO_2$ is related to asthma mortality.

Cold has been known as one of the risk factors for asthma attack (Mohr et al., 2008). We found increased risk of asthma mortality in cold season but not in warm season in this study. SO2 is a ubiquitous air pollutant mainly produced by combustion and processing of sulfur containing fossil fuels (Sheppard, 1988). In line with this fact, the concentrations of $SO_2$ in winter times were substantially higher than that in other seasons as a result of more local emissions from domestic heating and adverse weather conditions (Zhao et al., 2016). Similarly, one study from South Korea (Kim et al., 2012) also found exposure to temperature drops and increased $SO_2$ levels were associated with the occurrence of acute refractory asthma exacerbation in winter. Similar to another study (Wu et al., 2021) on the relationship between SO2 and all-cause mortality, we did not observe significant differences in the acute effects of $SO_2$ between different gender.

In recent years, more and more population-based epidemiological studies have focused on the harmful effect of exposure to ambient particulate matter pollution on human health (Chen and Hoek, 2020; Chen et al., 2017; Liu et al., 2022b; Orellano et al., 2020; Yin et al., 2017). Significant associations between short-term and long-term exposure to

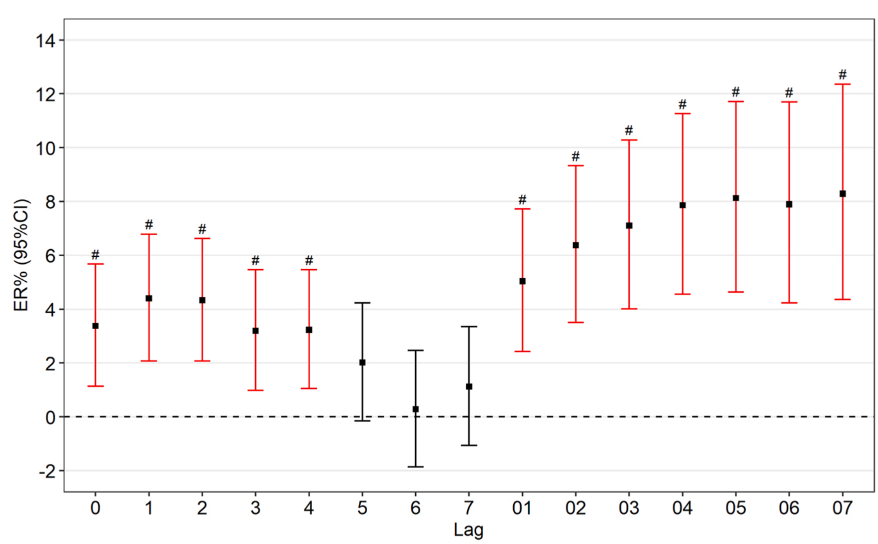


**Fig. 4.** Association between $SO_2$ and asthma deaths during pre-COVID-19 pandemic (2015–2019) period. Abbreviations: ER = excess risk; CI = confidence interval; COVID-19 = Corona Virus Disease 2019; $SO_2$ = sulfur dioxide. #P < 0.01. The X-axis is the single lag days from lag0 to lag7, and the moving average lag days from lag 01 to lag 07.

particulate matter and mortality due to non-accidental cause, cardiovascular diseases and respiratory diseases were confirmed in many large-scale studies (Chen and Hoek, 2020; Chen et al., 2017; Liu et al., 2022b; Orellano et al., 2020; Yin et al., 2017). However, this study found that $SO_2$ was also an important pollutant associated with asthma mortality and warranted more attention, especially in countries with high exposure levels.

To our knowledge, this study provides the largest sample with inclusion of 29 388 death cases from asthma in more than 300 million people during the period 2015–2020, to investigate the association between acute exposure to $SO_2$ and deaths from asthma. Large sample size, coupled with wide range of $SO_2$ concentration across China allow us to carry out subgroup analysis with enough statistical power. Using personal home address instead of data from the county/district level monitoring station to determine exposure level for each case was also a strength in this study. Moreover, the study can benefit from the time-stratified case crossover design in several aspects. Firstly, as the time span between case and controls was restricted in the same month of the year, so the long-term trends and seasonal patterns can be controlled. Secondly, days of the week, which was normally adjusted in time-series studies, would be controlled because the same weekday was applied for case and controls. Thirdly, case in this study served as his or her own controls and individual level confounders were therefore accounted for.

A number of limitations should be noted. First, we were not able to ascertain the true objectively measured personal exposure to $SO_2$ incorporating the real-time monitoring equipment. Using model-based estimates may lead to potential exposure misclassification bias. Second, pollution data from Xinjiang, Tibet and some regions of Heilongjiang Province were excluded to achieve maximum accuracy of exposure measurement. This exclusion is unlikely to affect our findings because the population density in these excluded areas is low and the number of deaths due to asthma is small. Third, the results of this study were based on asthma as the underlying cause of death. It was difficult to distinguish between deaths from asthma or deaths caused by its co-existence due to lack of sufficient information about the incidence of asthma. Fourth, potential residual confounding may still exist due to unmeasured time-varying factors, though the time-stratified case-crossover study design had many strengths. Socio-economic factors or life-time cumulative occupational exposure could also play a role in the asthma mortality, while this study lacked such information. Socio-economic factors, life-time cumulative occupational exposure, allergen exposure, anti-allergic treatment effects could also play a role in the asthma mortality, while this study lacked such information. Future research should consider these factors when exploring the relationship between air pollution and asthma morbidity and mortality. Fifth, the outbreak of COVID-19 in 2020 may have an impact on both the level of pollutants and asthma mortality. The sensitivity analyses including only samples during 2015–2019 were carried out and we found that the results were consistently with our main analyses. Lastly, the study setting in China limited the generalizability of the findings to other countries due to different population and spectrum of air pollution.

## 5. Conclusions

In conclusion, our study indicates increased risk of asthma mortality with acute exposures to $SO_2$ in Chinese population. The current study lends support for greater awareness of the harmful effect of $SO_2$ in China and other countries with high $SO_2$ pollution.

## CRediT authorship contribution statement

**Wei Liu:** Methodology, Formal analysis, Validation, Writing – original draft, Visualization. **Miao Cai:** Methodology, Data curation, Formal analysis, Validation, Visualization. **Zheng Long:** Visualization, Validation. **Lijun Wang:** Data curation, Validation. **Xunliang Tong:** Validation. **Yanming Li:** Validation. **Maigeng Zhou:** Conceptualization, Funding acquisition, Resources Validation. **Jing Wei:** Data curation, Methodology, Resources, Validation. **Hualiang Lin:** Conceptualization, Supervision, Methodology, Resources, Validation. **Peng Yin:** Conceptualization, Supervision, Methodology, Resources, Validation, Writing – review & editing. Peng Yin, Jing Wei and Hualiang Lin are the joint corresponding authors that are solely responsible for this work.

## 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.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2022.114442.

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