Short-term effect of sulfur dioxide (SO₂) change on the risk of tuberculosis outpatient visits in 16 cities of Anhui Province, China: the first multi-city study to explore differences in occupational patients

Xin-Qiang Wang¹ · Jia-Wen Zhao¹ · Kang-Di Zhang¹ · Wen-Jie Yu¹ · Jie Wang¹ · Ying-Qing Li¹ · Xin Cheng¹ · Zhen-Hua Li¹ · Yi-Cheng Mao¹ · Cheng-Yang Hu³ · Kai Huang⁴ · Kun Ding¹ · Xiao-Jing Yang¹ · Shuang-Shuang Chen² · Xiu-Jun Zhang¹ · Xiao-Hong Kan^{1,2}

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Abstract

A growing number of biological studies suggest that exogenous sulfur dioxide (SO₂) at a certain concentration may promote human resistance to *Mycobacterium tuberculosis*. However, the results of most relevant studies are inconsistent, and few studies have explored the relationship between SO₂ exposure and tuberculosis risk at provincial level. In addition, occupational exposure has long been considered to have a certain impact on the human body, so for the first time, we discussed the differences between different occupations in the study on the relationship between air pollutant exposure and tuberculosis risk, and evaluated the impact of occupational exposure. This study aimed to explore the association between short-term SO₂ exposure and the risk of outpatient visits to tuberculosis in Anhui province and 16 prefecture-level cities from 2015 to 2020. We used several models for multi-stage analysis, including distributed lag nonlinear model (DLNM), Poisson generalized linear regression model, and random-effects model. The association was assessed using the 28-day cumulative lag effect RR and 95%CI for each 10-unit increase in SO₂ concentration. We divided all patients into the following six occupations: Worker, Farmer, Retired people, Children and Students, Cadre and Office clerk, and Service staff (catering, business, etc.). Sex, age, and season were analyzed by subgroup. Finally, the robustness of the multi-pollutant model was tested. At provincial level, the overall effect value of SO₂ was RR=0.8191 (95%CI: 0.7702–0.8712); after grouping all patients by occupation, the association found only among Farmers (RR = 0.7150, 95%CI: 0.6699–0.7632, lag 0–28 days) and Workers (RR = 0.8566, 95%CI: 0.7930–0.9930, lag 0–4 days) was still statistically significant. Estimates for individual cities and using random-effects models to estimate average associations showed that SO₂ exposure was associated with a reduced risk of outpatient TB visits in 14 municipalities, which remained significant when aggregated (RR = 0.9030, 95%CI: 0.8730–0.9340). Analysis of patients grouped by occupation in each municipality showed that statistical significance was again observed only in the Farmer (RR = 0.8880, 95%CI: 0.8610–0.9160) and Worker (RR = 0.8250, 95%CI: 0.7290–0.9340) groups. Stratified analysis of age, sex, and season showed that the effect of SO₂ exposure was greater for middle-aged people (18–64 years old) and males, and less for seasonal changes. In summary, we found that exposure to SO₂ reduces the risk of outpatient visits to tuberculosis, with farmers and workers more susceptible to SO₂. Gender and age had a greater impact on the risk of TB outpatient visits than seasonal variations.

Keywords Tuberculosis · Sulfur dioxide · DLNM · Occupation · China · Multi-city

Introduction

Tuberculosis (TB) is an infectious disease that seriously harms human health and is a public health and social problem concerned by the world. Since the 1940s, with the advent of anti-TB drugs and the implementation of directly

Xin-Qiang Wang and Jia-Wen Zhao contributed equally to this work.

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Extended author information available on the last page of the article

observed treatment, short-course (DOTS), the global TB epidemic has been effectively controlled. However, the TB control situation is still grim today (WHO 2020). There are about 10 million new cases and 1.5 million deaths caused by TB every year. China accounts for 8.5% of the global total, ranking second in the world. According to the estimates of the World Health Organization, an uncured active TB patient can infect 10 to 15 people through close contact in a year. Since the start of the COVID-19 pandemic, TB management and control have been deeply affected, most notably by the dramatic decline in the number of newly reported and diagnosed TB cases globally (WHO 2021). Previous studies have shown that air pollution, poor nutrition, weakened immune systems, diabetes, smoking, HIV/AIDS, alcohol consumption, and many other factors play a role in the development of TB (Kim 2014; Rivas-Santiago et al. 2015; Elf et al. 2017; Li et al. 2019).

As a common air pollutant, sulfur dioxide (SO_2) is closely related to people's life. SO_2 is the most common and simplest sulfur oxide, one of the major atmospheric pollutants. Volcanoes spew the gas when they erupt, and sulfur dioxide is also produced in many industrial processes. Because coal and oil generally contain sulfur, sulfur dioxide is produced when burned (Chen et al. 2007). When sulfur dioxide dissolves in water, it forms sulfite. When the human body inhales SO_2 , a series of chemical reactions will occur with the moisture of the mucous membrane of the upper respiratory tract, resulting in severe respiratory irritation (Ge et al. 2017). A multi-city study in Shanghai, Hong Kong, and Wuhan showed that SO_2 was associated with increased daily mortality and morbidity (Kan et al. 2010). However, heterogeneity of SO_2 concentration and different effects on populations in different geographical environments may lead to different results found in one study in Hong Kong and London (Wong et al. 2006). Changes in SO_2 concentration were associated with the risk of hospitalization for respiratory diseases in Hong Kong, while no significant association was found in London (Wong et al. 2002). Although some domestic and foreign studies have shown a correlation between SO_2 exposure and tuberculosis, the results are inconsistent. A time series study in Hefei, China, found that SO_2 exposure was negatively correlated with the risk of outpatient visits to tuberculosis, reaching statistical significance after a lag of 5 days, and the cumulative lag effect reached its maximum after 14 days (Huang et al., 2020a, b). A study in Shandong, China, found that SO_2 was associated with a reduced risk of MDR-TB and had a protective effect (Song et al. 2021). A retrospective study in Spain found that the SO_2 concentration of 1.5 weeks before admission was significantly associated with the risk of hospitalization in patients with HIV-infected tuberculosis in univariate analysis, while the results remained significantly unchanged in multivariate analysis (Álvaro-Meca et al. 2016). However, some studies

have found adverse effects of SO_2 on TB patients. A Bayesian spatiotemporal analysis in Hubei Province, China, found that for every 10 increase in SO_2 concentration, the risk of pulmonary tuberculosis increased ($\text{RR}=1.046$), and a significant response was also observed in children (Liu et al. 2020). In a multi-regional study on the correlation between air pollution and tuberculosis incidence in Seoul, South Korea, it was found that each 1 ppb increase in SO_2 concentration was significantly associated with an increased risk of tuberculosis ($\text{RR}=1.046$, 95%CI: 1.028–1.065) (Sohn et al. 2019). A long-term effect of SO_2 on tuberculosis was found in Jiangsu Province, China (Li et al. 2019), with a lag of 0–21 weeks, $\text{RR}=1.11$ (95%CI: 1.16–1.62). Although many studies have analyzed the association between SO_2 and TB, no study has examined whether the effect of SO_2 exposure on TB is influenced by occupational factors. In one study in South Africa, an increased risk of TB death was found among agricultural laborers, cleaners, workers exposed to silica dust and agricultural workers (Kootbodien et al. 2018). So we hypothesized that occupation might be a contributing factor to TB, similar to gender and age (Huang et al., 2020a, b).

Although some relevant studies at home and abroad have shown that SO_2 exposure has an impact on the incidence or death of TB, the result is not consistent, and these studies are limited to a certain city or region, very few studies have taken the province as their study area, and no studies have examined whether the effect of SO_2 exposure on TB is influenced by occupation. Therefore, this study aims to explore the relationship between the risk of tuberculosis outpatient visits and SO_2 concentration in 16 cities of Anhui Province, and to group TB patients according to occupation for subgroup analysis. A subgroup analysis was performed for seasonal variation, age, and sex to assess corrective effect.

Material and methods

Ethical statement

This study was approved by the Anhui Medical University Ethics Committee. All patient information included in the study was unidentified and anonymous.

Study area

Anhui, referred to as “Wan,” is a provincial-level administrative region of China, located between 114°54′–119°37′ E and 29°41′–34°38′ N (Fig. 1). Anhui province has 16 prefecture-level cities and 6 county-level cities, with Hefei as the provincial capital. Anhui province covers an area of about 140,100 km², ranking the third in East China and the 22nd in China, including 67,000 km² of Huaihe River basin, 66,000 km² of Yangtze River Basin, and 6,500 km² of Xin'an River

Fig. 1 The geographical location of Anhui Province and 16 cities and tuberculosis outpatient number in cities of Anhui Province from 2015 to 2020

Basin. The Yangtze River flows through central and southern Anhui with a total length of 416 km, while the Huai River flows through northern Anhui with a total length of 430 km. Anhui province is bordered by Zhejiang, Jiangsu, Shandong, Henan, Hubei, and Jiangxi provinces. The landform is dominated by plains, hills, and low mountains. According to the seventh national census, Anhui province has a permanent population of 61.027 million. Two of the 16 cities have more than eight million permanent residents. In 2021, The GDP of Anhui province once again ranked among the top 10 in China, but with the rapid economic development, there are corresponding air pollution problems.

Data sources

Tuberculosis data

TB is a notifiable infectious disease in China. Outpatient TB patients included in this study were those who visited the outpatient clinic daily and were diagnosed with TB. All cases in this study were reported and collected by Anhui Institute of Tuberculosis Prevention and Control through its subordinate departments (Municipal Center for Disease Control and Prevention). The reported information includes the patient's gender, patient's age, patient's occupation, date of treatment, patient's home address, hospital information, and treatment plan. Patients with incomplete data were excluded from the study. We cleaned all data from January 1, 2015, to December 31, 2020, and deleted the missing data. All data used does not involve patient privacy (Huang et al., 2020a, b).

Methods of obtaining pollutant data

The air pollutants involved in this study include SO_2 ($\mu\text{g}/\text{m}^3$, 24h), $\text{PM}_{2.5}$ (particulate matter < 2.5 μm in aerodynamic diameter, $\mu\text{g}/\text{m}^3$, 24h), and ozone (O_3 , $\mu\text{g}/\text{m}^3$, 8h). Data are collected from environmental monitoring centers in various cities. Each city has fixed environmental monitoring stations; for example, Chuzhou has four monitoring stations, Bozhou has seven monitoring stations, and Hefei, the provincial capital, has up to 11 monitoring stations. The geographic information of all monitoring stations can be queried on the $\text{PM}_{2.5}$ historical data network (<https://www.aqistudy.cn/historydata/>).

Methods of obtaining meteorological data

We obtained data for this study from China Meteorological Data Network (<http://data.cma.cn/>), including wind speed (WS, m/s), mean temperature (MT, $^{\circ}\text{C}$), and relative humidity (RH, %). And we check the data, including removing extreme values and filling in missing data. We use the average values of the previous day and the next day to fill in missing data.

Data processing

The data included in the model in this study included the date of tuberculosis outpatient visit, gender, age, occupation, daily concentration of air pollutants, and meteorological data. We checked whether there were missing values, extreme values, or wrong values in the values of each day,

and corrected the missing values, extreme values, and wrong values by using the mean values of the data before and after the two days.

Statistical analysis

Descriptive statistical

Descriptive statistical methods were used to analyze the distribution of three pollutants, meteorological data, tuberculosis data (provincial distribution and distribution of various cities), and different occupational populations (including mean, standard deviation, and quartile). Spearman rank correlation coefficient and scatter plot were used to describe the correlation between meteorological factors, SO₂, PM_{2.5}, O₃, and tuberculosis outpatients.

Multi-model construction

A two-stage model was used to assess the impact of SO₂ exposure on TB risk and the role of occupational factors in the relationship. The two models are random-effects model and distributed lag nonlinear model (DLNM) (Li et al. 2021).

Previous studies have found that ambient air pollution has a certain delayed effect on human health, and the relationship between them shows a nonlinear exposure-response relationship (Chen et al. 2017; Guo et al. 2017). In the first-stage model analysis, DLNM added a lag effect to the exposure response relationship to test the relationship between SO₂ and the risk of TB outpatient visits (Gasparrini et al. 2010; Gasparrini 2014), and used a generalized linear model (GLM) based on the quasi-Poisson distribution to fit the dimensions of exposure, lag, and response (Kan et al. 2010). In addition, the study focused on the effects of short-term exposure, so we used natural cubic spline functions (ns) to control for long-term trends, seasonal variations, and meteorological factors. Long-term trend and seasonal variation were controlled by 7-dof ns function, and three meteorological factors were controlled by 3-dof ns function (Zhu et al. 2018). We also considered the Holiday effect and day of the week effect (DOW), and classified the dummy variable Holidays, assigning the corresponding value to Holidays and non-holidays, with 1 and 0 representing Holidays and Non-Holidays respectively. Finally, the cross-basis function is established to discuss the two-dimensional relationship among the three (exposure, response, and lag). Depending on the purpose of our study and the length of the incubation period of TB, we set the maximum lag at 28 days (Chen et al. 2010; Chen et al. 2017). In addition, it can be known from previous studies that there is a collinearity relationship between air pollutants and meteorological factors. In order to control the robustness of the model, only variables whose correlation value is less than 0.7 are included (Liu et al. 2017; Huang et al., 2020a, b). The final model of the first phase is as follows:

$$Ht \sim \text{quasiPoisson}(ht) \quad \text{Log}(ht) = \alpha + W_X^T \eta + ns(\text{time}, 7^* \text{year}) + ns(RH, df_1) \\ + ns(MT, df_2) + ns(WS, df_3) + (\beta^* \text{DOW}) + (\gamma^* \text{Holiday})$$

Ht and ht are the actual and expected outpatient visits of t days, respectively; $W_X^T \eta$ is a cross-basis function; df_1 is the degree of freedom of relative humidity; df_2 is the degree of freedom of mean temperature; and df_3 is the degree of freedom of wind speed. γ and β are the regression coefficients of Holiday and Dow respectively.

The random-effects model was then used to estimate the combined effect value of the 16-city results, a province-wide average estimate of the short-term association between SO₂ and the risk of TB outpatient visits. I^2 values were used to quantify heterogeneity among different cities (Dominici et al. 2006). The final model of the second phase is as follows:

$$HE = \frac{\sum_{i=1}^k d_i FE_i}{\sum_{i=1}^k d_i}$$

where FE_i is the estimated effect of particulate pollutants for city i and d_i is the variance of the estimates effect in city i . The variance of the random-effects summary pollution effect is $\frac{1}{\sum_{i=1}^k d_i}$ (Yin et al. 2017).

In this study, relative risk (RR) and its 95% confidence interval were used to represent cumulative risk and lag specificity with each 10-unit increasing in SO₂ concentration, taking the first-level concentration limit (50 µg/m³) of SO₂ in national environmental quality standards as reference. Moreover, in addition to analyzing the key occupational factors in this study, we also conducted stratified analysis for age, sex, and season. Calculate RR and 95%CI:

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

where $\hat{G}_1$ and $\hat{G}_2$ are the point estimates for the two subgroups, and $\hat{S}\hat{G}_1$ and $\hat{S}\hat{G}_2$ are the corresponding standard errors, respectively (Huang et al., 2020a, b).

Finally, we use multi-pollutant model to test the robustness of the results. Two kinds of analysis software were used in this study, namely R software (version 4.0.0) and StataSE 15 (version 64-bit). In R we used the “dlnm,” “mgcv,” and “splines” packages.

Results

Descriptive results

Table 1 summarizes the variables in this study, including air pollutants, tuberculosis cases in provinces and cities, occupational distribution, and meteorological information. The average daily concentration of SO₂ is 75.91 µg/m³

(4–318 $\mu\text{g}/\text{m}^3$), and the average daily concentration of $\text{PM}_{2.5}$ and O_3 added to the multi-pollutant model is 1 and 2, respectively. From January 1, 2015, to December 31, 2020, a total of 186,623 TB cases were collected in the whole province. Hefei ranked the first (24,394,13.1%), Fuyang the second (21,591,11.5%), and Huangshan the least (4,140,2.2%) among the 16 cities in the province. Based on the information collected, we classified all TB patients into six occupations: Worker, Farmer, Retired people, Children and Students, Cadre and Office clerk, and Service staff (catering, business, etc.). The number of farmer cases

was 137,477, accounting for 73.7% of all cases, and the number of worker cases was 5,036, accounting for 2.7% of all cases. The daily average temperature is 16.59°C ($-6.8\sim 33.3^\circ\text{C}$), the average relative humidity is 76.7% (40~98%), the average wind speed is 2.16 m/s, the highest wind speed is 5.6 m/s, and the lowest wind speed is 0.8 m/s. Scatter diagram and Spearman rank correlation coefficient of pollutant concentration and meteorological factors are shown in **Fig. 2**. The concentration of various pollutants and the distribution of tuberculosis outpatient visits in the province are shown in **Fig. 3**.

Table 1 Summary statistics of active TB case in 16 cities of Anhui Province and air pollutants, meteorology factor of Anhui, 2015–2020

Variables	Number (%)	Mean $\pm$ SD	Centiles					
			Min	25%	50%	75%	Max	IQR
Atmospheric pollutants ($\mu\text{g}/\text{m}^3$)								
SO ₂	/	15.03 $\pm$ 6.78	6	9	14	19	52	10
PM _{2.5}	/	49.09 $\pm$ 28.10	3	29	42	61	213	32
O ₃	/	92.77 $\pm$ 42.95	0	64	87	115	220	51
TB case								
Total	186623 (100)	85.14 $\pm$ 41.09	5	39	94	117	204	78
City								
Hefei	24394 (13.1)	11.13 $\pm$ 6.01	0	6	11	15	37	9
Fuyang	21591 (11.5)	9.85 $\pm$ 5.78	0	5	9	13	41	8
Bozhou	15885 (8.6)	7.25 $\pm$ 5.44	0	2	7	11	29	9
Suzhou	14702 (7.9)	6.71 $\pm$ 5.77	0	2	6	10	49	8
Anqing	14280 (7.7)	6.51 $\pm$ 4.15	0	3	6	9	29	6
Luan	14131 (7.6)	6.45 $\pm$ 5.07	0	2	6	10	44	8
Chuzhou	11949 (6.4)	5.45 $\pm$ 3.80	0	2	5	8	27	6
Wuhu	11378 (6.1)	5.19 $\pm$ 3.94	0	2	5	8	27	6
Huainan	10933 (5.8)	4.99 $\pm$ 4.16	0	1	4	8	31	7
Bengbu	10172 (5.4)	4.64 $\pm$ 3.49	0	2	4	7	25	5
Xuancheng	8152 (4.4)	3.72 $\pm$ 2.87	0	2	3	5	39	3
Maanshan	7387 (3.9)	3.37 $\pm$ 2.85	0	1	3	5	20	4
Huaibei	6864 (3.7)	3.13 $\pm$ 2.64	0	1	3	5	17	4
Tonglings	5345 (2.9)	2.44 $\pm$ 2.14	0	1	2	4	15	3
Chizhou	5320 (2.8)	2.43 $\pm$ 2.37	0	1	2	4	26	3
Huangshan	4140 (2.2)	1.89 $\pm$ 1.79	0	1	1	3	12	2
Occupation								
Worker	5036 (2.7)	2.30 $\pm$ 1.94	0	1	2	3	11	2
Farmer	137477 (73.7)	62.72 $\pm$ 32.48	3	29	68	87	156	58
Retired people	8819 (4.7)	4.02 $\pm$ 2.74	0	2	4	6	17	4
Children and Students	7822 (4.2)	3.57 $\pm$ 2.87	0	1	3	5	22	4
Cadre and Office clerk	6933 (3.7)	3.16 $\pm$ 2.55	0	1	3	5	22	4
Service staff (catering, business, etc.)	20536 (11)	9.37 $\pm$ 5.40	0	5	9	13	27	8
Meteorology measure								
Mean temperature ($^{\circ}\text{C}$)	/	16.59 $\pm$ 9.12	−6.8	8.3	17.3	24.5	33.3	16.2
Relative humidity (%)	/	76.70 $\pm$ 11.37	40	68.9	77.8	85.6	98	16.7
Wind speed (m/s)	/	2.16 $\pm$ 0.70	0.8	1.7	2.0	2.5	5.6	0.8

SO_2 , sulfur dioxide; $\text{PM}_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; O_3 , ozone; *Min*, minimum; *Max*, maximum; *IQR*, interquartile range; *TB*, tuberculosis

Correlation analysis

Association between SO₂ exposure and tuberculosis outpatient visits at the provincial level (including stratified analysis of the impact of occupational factors)

The overall exposure response curve for SO₂ and the risk of outpatient visits to tuberculosis is shown in the **Supplementary Fig. 1**, showing a negative correlation between

the two. As shown in the **Fig. 4**, the risk of TB outpatient visits decreased when SO₂ concentration increases by per 10 µg/m³. The cumulative lag effect reached statistical significance at 0–6 days (RR = 0.9722, 95%CI: 0.9455–0.9998), and the cumulative risk continued to decrease, reaching the minimum value at 0–28 days (RR = 0.8191, 95%CI: 0.7702–0.8712). When all patients collected across the province were stratified by occupation, SO₂ exposure remained significant for TB outpatient visits

Fig. 2 Spearman rank correlation coefficients and scatter plot between daily concentration of air pollutants and meteorological factors in Anhui Province, 2015–2020. * $r_s > 0.7$

Fig. 3 Time series of tuberculosis, SO₂, PM_{2.5} and O₃, in Anhui Province, China, from 2015 to 2020. SO₂, sulfur dioxide; PM_{2.5}, particulate matter < 2.5 µm in aerodynamic diameter; O₃, ozone

in the worker and farmer groups. As shown in **Fig. 4**, the cumulative lag effect of 0–28 days in the worker group showed a single peak, and reached statistical significance in 0–4 days (RR = 0.8566, 95%CI: 0.7930–0.9930). The cumulative lag effect of farmers group decreased continuously, and reached the minimum value when the lag was 0–28 days (RR = 0.7150, 95%CI: 0.6699–0.7632). Specific RR values for the province and each occupation are shown in **Supplementary Table 1**.

Association between SO₂ exposure and tuberculosis outpatient visits at the municipal level and average correlation is explored through a random-effects model (including stratified analysis of the impact of occupational factors)

As shown in **Fig. 5**, in 14 of the 16 cities in Anhui Province, the cumulative lag effect of 0–28 days was statistically significant with per 10 µg/m³ increase in SO₂ concentration,

Fig. 4 Cumulative relative risk and 95% confidence interval for active TB cases of each 10-unit increase in daily SO_2 concentration within a lag of 28 days, provincially and across different occupations. SO_2 , sulfur dioxide

and the risk of tuberculosis decreased. Only Huangshan and Tongling showed no statistical significance. After patients in each city were grouped according to occupation, results showed that SO_2 exposure had an impact on the risk of outpatient visits for Children and Students in two cities, that SO_2 exposure had an impact on the risk of outpatient visits for Cadre and Office clerk in two cities, and that SO_2 exposure had an impact on the risk of outpatient visits for Service staff in three cities. Results from eight cities showed that SO_2 exposure had an effect on the risk of outpatient visits in Worker, eleven cities showed that SO_2 exposure had an effect on the risk of outpatient visits in Farmer, and all cities showed no effect on the risk of outpatient visits in Retired

people. After estimating the average correlation of 16 cities by using the random-effects model, it is found that the results of the whole province are still statistically significant ($\text{RR} = 0.9030$, $95\% \text{CI}: 0.8730\text{--}0.9340$), and the results were still statistically significant only in the Farmer ($\text{RR} = 0.8880$, $95\% \text{CI}: 0.8610\text{--}0.9160$) and Worker patient groups ($\text{RR} = 0.8250$, $95\% \text{CI}: 0.7290\text{--}0.9340$) (**Supplementary Table 2**).

Stratified analysis of season, age, and sex

We performed three subgroup analyses on all patients. (1) Divided into male and female groups by gender, it can be seen from **Supplementary Table 3** that the results of 10

Fig. 5 Cumulative relative risk and 95% confidence interval between increased SO_2 concentration of $10 \mu\text{g}/\text{m}^3$ and TB risk within a lag of 28 days in 16 cities of Anhui Province from 2015 to 2020 stratified by occupation. TB, tuberculosis; SO_2 , sulfur dioxide

cities in the male group are statistically significant, while the results of only two cities in the female group are statistically significant. (2) All patients were divided into 0–18 years old group, 18–64 years old group, and ≥ 65 years old group according to age, and the results are shown in **Supplementary Table 4**; results of 4, 10, and 2 cities in the three groups were statistically significant respectively. (3) It is divided into cold season and warm season according to season. According to the geographical and climatic conditions of Anhui Province, April to September is the warm season, and October to March is the cold season. As shown in **Supplementary Table 5**, statistical significance is observed in six cities in the warm season group, and in eight cities in the cold season group. However, one city in the warm season group showed the opposite result. During the warm season in Huainan, SO_2 exposure increases the risk of tuberculosis visits. Using a random-effects model to estimate the mean association of results across the subgroups, SO_2 exposure was found to reduce the risk of outpatient TB visits in all subgroups except the 0–18 years old group.

Sensitivity analysis

Sensitivity analysis was performed using a multi-pollutant model to test the robustness of the model. (1) As shown in **Fig. 6**, $\text{PM}_{2.5}$, O_3 , and $\text{PM}_{2.5}+\text{O}_3$ were added into the single pollutant model of each city respectively, and the results showed no significant change. (2) When $\text{PM}_{2.5}$, O_3 , and $\text{PM}_{2.5}+\text{O}_3$ are added into the single pollutant model of the province and each occupation, the results of the province, workers, and farmers are still statistically significant, with little change (**Table 2**).

Discussion

This study is the first two-stage analysis using distributed lag nonlinear model and random-effects model to explore the influence of SO_2 exposure on the risk of TB visit at the provincial level, and the first in-depth study on the influence of different occupations. Finally, we found that short-term exposure to the air pollutant SO_2 reduced the risk of tuberculosis outpatient visits, and that SO_2 exposure had a greater impact on Farmers and Workers. We also conducted multiple subgroup analyses, and found that SO_2 exposure had a greater impact on male patients and middle-aged patients (19–64 years old). In the seasonal subgroup, there was statistical significance in both cold season and warm season, and no significant difference was found. We use a multi-pollutant model to test the robustness of the model, and the results do not change much after the addition of other pollutants.

We found a negative association between SO_2 and TB outpatient visits, similar to many previous studies (Álvarez-Meca et al. 2016; Ge et al. 2017; Huang et al., 2020a, b; Song et al. 2021). In a study of SO_2 and the risk of tuberculosis in the primary outpatient clinic in Wuhan (Xu et al. 2019), the associated risk was -22.23% (95%CI: $-39.23\sim-0.49$, lag 0 to 16 weeks) when the concentration of SO_2 increased by $10 \mu\text{g}/\text{m}^3$. In terms of biological mechanism, the protective effect of SO_2 on tuberculosis has some credibility. As a facultative intracellular pathogen, *Mycobacterium tuberculosis* (*M. tuberculosis*) can infect alveolar macrophages (AMs) and further replicate and spread in the host (Pieters 2008). The cell surface of *M. tuberculosis* is rich in complex lipid components of wax-D, mycolic acids, and cord factor, which are decisive

Fig. 6 Relative risk and 95% confidence interval for cumulative association between a $10 \mu\text{g}/\text{m}^3$ increase in concentration of SO_2 and TB risk in 16 cities (multi-pollutant model)

Table 2 RR and 95%CI for cumulative association between a 10 $\mu\text{g}/\text{m}^3$ increase in concentration of SO_2 and TB risk in the multi-pollutant model across the Anhui Province

	Single pollutant model			Multi-pollutant model								
	RR	LCI	UCI	SO ₂ +PM _{2.5}			SO ₂ +O ₃			SO ₂ +PM _{2.5} +O ₃		
				RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
Total	0.8191*	0.7702*	0.8712*	0.7622*	0.7190*	0.8080*	0.7646*	0.7220*	0.8097*	0.7654*	0.7219*	0.8116*
Worker	0.6960*	0.5267*	0.9198*	0.6880*	0.5239*	0.9034*	0.6954*	0.5335*	0.9066*	0.6851*	0.5212*	0.9005*
Farmer	0.7150*	0.6699*	0.7632*	0.7147*	0.6686*	0.7639*	0.7205*	0.6749*	0.7692*	0.7166*	0.6703*	0.7661*
Retired people	1.0195	0.7630	1.3623	0.9772	0.7422	1.2868	0.9566	0.7299	1.2537	0.9787	0.7426	1.2900
Children and Students	1.0960	0.8127	1.4782	1.2869	0.9641	1.7178	1.2688	0.9542	1.6870	1.3126	0.9827	1.7532
Cadre and Office clerk	0.6452	0.3732	1.1154	0.6959	0.4153	1.1661	0.6734	0.4054	1.1186	0.7101	0.4233	1.1911
Service staff	0.9054	0.7476	1.0965	0.9008	0.7518	1.0793	0.8908	0.7458	1.0639	0.9068	0.7565	1.0870

SO_2 , sulfur dioxide; $\text{PM}_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; O_3 , ozone; RR, relative risk; UCI, upper confidence interval; LCI, lower confidence interval; TB, tuberculosis

* $P < 0.05$

factors of bacterial virulence (Patrick et al. 2005). More and more attention has been paid to the biological effects of SO_2 , which can induce oxidative damage of proteins, lipids, and other biological macromolecules, thereby inhibiting or even killing *Mycobacterium tuberculosis* entering the body (Rencuzogullari et al. 2001; Malwal et al., 2012a; Wang et al. 2014). One animal study found that interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) can regulate the activity of other cytokines and chemokines to help inhibit *M. tuberculosis*, and when inhaled 14 $\mu\text{g}/\text{m}^3$ SO_2 can increase the levels of IL-6 and TNF- α to fight *M. tuberculosis* (Meng et al. 2005; Sasindran and Torrelles 2011). Other studies have shown that exposure to 12.5 PPM SO_2 for 30 min can lead to 62% alveolar macrophage death and 63% reduction of reactive oxygen species release; the high number of AMs deaths also helps to reduce the proliferation of *M. tuberculosis* and hinder the development of TB (Kienast et al. 1993; Clay et al. 2008). In the field of tuberculosis drug research, it was also found that a small amount of SO_2 can inhibit the growth of *Mycobacterium tuberculosis* (Gomez and McKinney 2004; Sacchetti et al. 2008; Ma et al. 2010). SO_2 can be oxidized by some metal ions to produce sulfur trioxide free radicals that may mediate the damage of biological macromolecules (Armentia-Alvarez et al. 1993; Shi and Mao 1994; Pena-Egido et al. 2005), and SO_2 can participate in redox reaction reactions to disturb the redox reaction equilibrium of cells (Trotter and Grant 2002; Zhang et al. 2012). Therefore, SO_2 may induce a variety of cytotoxic induction mechanisms. A study of the prodrug combination of SO_2 found that the more potent the drug was at producing SO_2 , the more potent it was at inhibiting *Mycobacterium tuberculosis* (Malwal et al., 2012b). Therefore, in summary, SO_2 can slow the progression of TB and reduce the risk of hospital visit.

In addition, after adjusting the multi-pollutant model, the results are still robust.

When the total patients were grouped by occupation, we found that Farmers and Workers were more affected by SO_2 exposure. The possible reasons are as follows: (1) Workers are most exposed to occupational dust, and pneumoconiosis patients are more susceptible to air pollution. (2) Farmers and workers spend more time outdoors than most occupations and have more exposure to SO_2 (Comstock 1996). The difference in the effect of SO_2 among occupational patient needs to be further explored by more studies. When subgroup analysis was performed by sex, age, and season, we found that the effects of SO_2 exposure were greater for males and middle-aged adults (19–64 years old). Statistical significance was also observed in the older group (≥ 65 years old), but not in the juvenile group (0–18 years old). Statistical significance was observed in both cold and warm seasons, with no significant difference. The negative correlation was stronger in men than in women, possibly due to their larger lung capacity and higher consumption in the process of labor (Wong et al. 2006). There are also studies that suggest that the difference between men and women is due to men's bad habits or biological differences between men and women, bad habits such as drinking, smoking, staying up late, and so on, physiological differences such as hormonal differences and differences in airway structure (Sopori et al. 1998; Przybylski et al. 2014). The effect of SO_2 exposure on middle-aged patients is greater than that of the elderly, possibly because the overall intake of SO_2 is highest in adults aged 18–64 years old. Another explanation is that older people are more susceptible to *M. tuberculosis* than adults aged 18–64 because of their weakened defenses (Ge et al. 2017). Similar to the overall results, SO_2 exposure still reduced the risk of TB visit in 16 cities during warm and cold seasons. However, in a single-city analysis, we found an opposite

result in Huainan, where SO₂ exposure increased the risk of TB. The possible explanation is that the chemical properties of SO₂ are unstable and the temperature in Huainan warm season is high. SO₂ can react with other components in the air to generate new chemical products, which may lead to the reduction of the concentration of SO₂ (Clapp LJ 2001).

Therefore, the control of SO₂ is conducive to the fight against TB, and certain progress has been made in the synthesis of new drugs to inhibit *Mycobacterium tuberculosis*. More research in this direction is needed in the future to explore faster and more effective drugs.

The advantages of this study are as follows: (1) this study takes the whole Anhui province as the research area, with a large sample size and better representativeness of research results; (2) the first provincial study of the association between SO₂ exposure and the risk of tuberculosis visits; (3) for the first time, occupational factors were included in the study of the relationship between tuberculosis risk and exposure to air pollutants. Of course, this study still has some shortcomings. First of all, the data of air pollutants come from each fixed monitoring station. The average daily concentration is used as the concentration of air pollutants in this study, which cannot exclude the influence of spatial heterogeneity of air pollution. Secondly, the classification of occupations in this study is too simple due to the limitation of data sources. The influence of a particular occupation can only be judged in general. Finally, we did not consider the effect of other confounding factors, such as economic status and smoking history.

Conclusion

This study finally found that exposure to the air pollutant SO₂ reduced the risk of outpatient visits for tuberculosis. Farmers and workers were more likely to be affected by SO₂ exposure, with gender and age having more significant effects than season. Men and middle-aged (18–64 years) patients are more affected by SO₂ exposure. Therefore, it is of great significance to establish a sound pollutant monitoring system for the prevention and control of tuberculosis, and specific control of sulfur dioxide may help to reduce the occurrence of tuberculosis outpatient visits.

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Author contribution Xin-Qiang Wang and Xiao-Hong Kan collaboratively designed the study, both making substantial intellectual contribution. Xin-Qiang Wang and Jia-Wen Zhao analyzed the data and

drafted the manuscript; Xiao-Hong Kan and Xiu-Jun Zhang revised the manuscript. Kang-Di Zhang, Wen-Jie Yu, Jie Wang, Ying-Qing Li, Xin Cheng, Zhen-Hua Li, Yi-Cheng Mao, Cheng-Yang Hu, Kai Huang, Kun Ding, Shuang-Shuang Chen, and Xiao-Jing Yang contributed in collecting the data. Xin-Qiang Wang and Jia-Wen Zhao contributed equally. All authors read and approved the final manuscript.

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Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Not applicable.

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Authors and Affiliations

Xin-Qiang Wang¹ · Jia-Wen Zhao¹ · Kang-Di Zhang¹ · Wen-Jie Yu¹ · Jie Wang¹ · Ying-Qing Li¹ · Xin Cheng¹ · Zhen-Hua Li¹ · Yi-Cheng Mao¹ · Cheng-Yang Hu³ · Kai Huang⁴ · Kun Ding¹ · Xiao-Jing Yang¹ · Shuang-Shuang Chen² · Xiu-Jun Zhang¹ · Xiao-Hong Kan^{1,2}

✉ Xiu-Jun Zhang
zhangxiujun@ahmu.edu.cn

✉ Xiao-Hong Kan
kanxiaohong@ahmu.edu.cn

¹ Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei 230032, China

² Anhui Chest Hospital, 397 Jixi Road, Hefei 230022, China

³ Department of Humanistic Medicine, School of Humanistic Medicine, Anhui Medical University, 81 Meishan Road, Hefei 230032, China

⁴ The Second Affiliated Hospital of Anhui Medical University, 678 Furong Road, Hefei 230601, China