Short-term Effect of Ambient Air Pollutants Change on the Risk of Tuberculosis Outpatient Visits: A Time-series Study in Fuyang, China

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Title page

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Running title: Association between ambient air pollutants and TB

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Abstract:

There is growing evidence that air pollution plays a role in TB, but few studies have comprehensively included the six common air pollutants. Our objectives were to investigate the association between short-term exposure to six common air pollutants and the risk of tuberculosis outpatient visits in Fuyang, China, during the period 2015-2020. We combined the two models to explore the effects of exposure to six air pollutants on the risk of tuberculosis outpatient visits, including Poisson generalized linear regression model and distributed lag non-linear model (DLNM). We performed stratified analyses for season, gender and age. We used the lag-specific relative risks and cumulative relative risk obtained by increasing pollutant concentration by per 10 units to evaluate the connection between six air pollutants and TB, $PM_{2.5}$ (RR=1.0018, 95%CI: 1.0004-1.0032, delay of 12 days) and (RR=1.0169, 95%CI: 1.0007-1.0333, lag

0-16 days), SO₂ were 0.9549 (95%CI: 0.9389-0.9712, lag 0 days) and 0.8212 (95%CI: 0.7351-0.9173, 0-20 days lag). Stratified analyses showed that seasonal differences had a greater impact on TB, and male more likely to develop TB than female, older people more likely to develop TB than younger people. Exposure to O₃, CO, PM₁₀, PM_{2.5}, and NO₂ increases the risk of TB outpatient visits, except SO₂ reduces the risk. Male and elderly people should be protected. We need to pay more attention to the impact of seasonal effects on TB.

Keywords: Tuberculosis; Risk of outpatient visit; Ambient air pollutants; DLNM; Time-series study; China.

1. Introduction

Tuberculosis (TB) is a chronic contagion caused by tuberculosis bacilli infection. Mycobacterium TB may invade all sorts of organs of human body, but basically encroach on lung, call pulmonary tuberculosis (PTB). Tuberculosis is a global public health problem that seriously endangers public health. Tuberculosis is one of the most dangerous infectious diseases, causing the world's top 10 deaths (Wang and Guo et al., 2021). There are about 10 million new cases and 1.5 million deaths caused by TB every year. China is a country with a high burden of tuberculosis, ranking second in the world. It is reported that in 2019, an estimated 8.9 million to 11 million people worldwide were infected with TB, with China ranking third, accounting for 8.4 percent of the global total (WHO, 2020). We know from previous studies that poor nutrition, weather,

diabetes, smoking, weakened immune systems, HIV/AIDS, air pollution, alcohol consumption and many other factors all play a large or small role in the progression of TB (Kim, 2014; Rivas-Santiago and Sarkar et al., 2015; Elf and Eke et al., 2017; Li and Mao et al., 2019).

With the development and deepening of epidemiological studies, more and more evidences show the influence of air pollutants on tuberculosis. A recent review summarized the links and potential mechanisms between respiratory bacterial infections and air pollution, described the association between various air pollutants and the occurrence and development of tuberculosis by analyzing existing epidemiological studies (Pompilio and Di Bonaventura, 2020). Another literature review also showed that the pollutant with the greatest impact on TB was fine particulate matter $PM_{2.5}$ ($<2.5\mu m$), nitrogen dioxide (NO_2), fine particulate matter PM_{10} ($<10\mu m$) and sulfur dioxide (SO_2) also showed significant correlation (Popovic and Soares Magalhaes et al., 2019). A meta-analysis published in March of this year pooled 17 related studies and suggested that long-term exposure to PM_{10} , SO_2 or NO_2 was associated with higher TB incidence (Xiang and Xu et al., 2021). An ecological study conducted in the United States, China, and Canada has observed a correlation between coal consumption and tuberculosis. The decline in TB rates has coincided with a decline in household coal consumption, indicating the link between air pollution and TB (Tremblay, 2007). However, the available results on the relationship between air pollution and TB risk are inconsistent. Two studies in Mexico have shown that exposure to airborne particle inhibits the body's immune response to the TB bacterium. $PM_{2.5}$ and

PM₁₀ can inhibit the human body to produce cytokines and antimicrobial peptides, impair the immunity of the human lung, promotes the occurrence and development of TB (Sarkar and Rivas-Santiago et al., 2019; Torres and Carranza et al., 2019). However, other studies indicated that short-term or long-term exposure to PM_{2.5} or PM₁₀ was not associated with TB risk (Liu and Cui et al., 2018; Xu and Liao et al., 2019; Xiang and Xu et al., 2021). A study in Seoul, South Korea, has confirmed that the interquartile increase in SO₂ concentration was associated with a 7% increment in TB incidence (Hwang and Kang et al., 2014), but a recent study conducted in Hefei, suggests that exposure to SO₂ is inversely associated with tuberculosis (Huang and Ding et al., 2020). Exposure to pollutants such as NO₂ and ozone (O₃) can affect the number of TB clinics (Lin and Lin et al., 2019; Huang and Ding et al., 2020; Liu and Zhao et al., 2021). In addition, although there is a lot of research in developed countries, but, still less research in China, so more research is urgently needed to assess the relationship between TB and air pollution in China. Fuyang located in the northwest of Anhui Province, is a city with a large population. Because of the rapid development of economy and the constant growth of population, Fuyang is facing a serious air pollution problem.

The association between various air pollutants and TB has also been explored in time series studies conducted in multiple Chinese cities (Chengdu, Hefei and Wuhan) (Zhu and Xia et al., 2018; Huang and Ding et al., 2020; Huang and Xiang et al., 2020). However, few studies have comprehensively explored the effects of exposure to six pollutants. Therefore, we aim to explore the relationship between daily exposure to

PM₁₀ (particulate matter < 10 µm in aerodynamic diameter), sulfur dioxide (SO₂), PM_{2.5} (particulate matter < 2.5 µm in aerodynamic diameter), nitrogen dioxide (NO₂), ozone (O₃), carbon monoxide (CO) and the risk of tuberculosis outpatient visits in Fuyang. Subgroup analyses for seasonal variation, sex, and age were also performed to assess their correction effects.

2. Material and methods

2.1 Ethical statement

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

2.2 Study location

Fuyang (114°52 ' -116 °49' E, 32°25 ' -34 °04' N) is located in the southern part of the Huang-Huai-Hai Plain. It is a northwest city with the largest population in Anhui Province (**Fig. 1**). By the end of 2019, the permanent resident population of Fuyang City was 8.259 million, an increase of 52000 over the previous year, with a year-on-year increase of 0.63%. Fuyang city is located in the southern margin of the warm temperate zone, a warm temperate semi-humid monsoon climate. The four seasons are distinct and the rainfall is moderate. Because Fuyang is near the Huaihe River in the

south, and the north subtropical humid monsoon climate is in the south of the Huaihe River, the climate of Fuyang is characterized by a transition zone from warm temperate zone to north subtropical zone ([Anhui Provincial Bureau of Statistics of China, 2020](#)). In recent years, due to population growth and economic development, Fuyang City has faced a serious air pollution problem.

2.3 Tuberculosis data

Tuberculosis is a Class B infectious disease, which is one of the infectious diseases that must be reported in China. All case reports in this study were collected from the Tuberculosis Prevention and Control Institute of Anhui Chest Hospital and reported by Fuyang Center for Disease Control and Prevention. We collected admission information for all TB patients from January 1, 2015 to December 31, 2020, including age, gender, home address and date of current visit. In addition, because of the long incubation period of TB, typically between four and eight weeks, the patient's time of infection is hard to confirm. Therefore, we included both recurrent and new cases in this study (Huang and Yang et al., 2020).

2.4 Environmental data (including meteorological data and pollution data)

The meteorological data and pollutant data in this study are from China Meteorological Data Network and Fuyang Environmental Monitoring Center

respectively (<http://data.cma.cn/>). Pollutants include PM_{2.5}, PM₁₀, SO₂, NO₂ (µg / m³, 24h), O₃ (µg / m³, 8h) and CO (mg / m³, 24h). Data were collected from eight fixed monitoring stations in Fuyang. The daily meteorological data we collect are relative humidity (RH, %) and mean temperature (MT, ° C).

2.5 Statistical analysis

2.5.1 Descriptive statistical

The demographic characteristics of tuberculosis were analyzed using simple descriptive statistical methods, including sex, age, etc. A simple descriptive analysis of the distribution of air pollutant data and meteorological data was also carried out. The correlation among meteorological factors, air pollutants and tuberculosis outpatient visits was described by Spearman correlation coefficient and scatter plot.

2.5.2 Construction of statistical model

Based on previous biological findings that ambient air pollutants have a delayed effect on health outcomes, most epidemiological studies have found nonlinear exposure–response relationships (Chen and Deng et al., 2017; Guo and Ma et al., 2017). So, we used a distributed lag nonlinear model (DLNM) to examine the relationship between air pollutants and the risk of tuberculosis outpatient visits (Gasparrini, 2014).

In addition, because the numbers of daily reports of TB outpatients were generally considered to be rare events, we used a generalized linear model (GLM) based on the quasi-Poisson distribution to construct a function fitting the exposure-response and effects of lag (Huang and Ding et al., 2020). First, in order to understand the influence of exposure to six air pollutants in the risk of tuberculosis outpatient visits, we used the function of natural cubic spline (7 degrees of freedom per year) to control for long-term trends and seasonal variations (Bhaskaran and Gasparrini et al., 2013; Zhu and Xia et al., 2018). Meanwhile, the ns function with 3 degrees of freedom is used to control the mean temperature (MT) and relative humidity (RH) of meteorological factors (Chen and Chu et al., 2010; Chen and Deng et al., 2017). We also controlled for the day of the week (Dow) and Holiday effect.

Then, we inquired two-dimensional connection between air pollutants and the exposure, lag and response of tuberculosis outpatient visits by the cross-basis functions, with the initial maximum lag day set at 28 days (TB incubation period 28-56 days), using linear cubic spline function fitting exposed - response relationship, natural cubic spline function fitting lag-response relationship, because the purpose of this study was to investigate the effects of short-term exposure. Therefore, we calculated different cumulative lag effects of different pollutants through a single pollutant model, selected the lag days when the first peak or lowest value was reached, and obtained the QAIC (quasi-Poisson Akaike information criteria) values of different lag days (Supplementary **Table S1**). Finally, the best lag date was selected by QAIC (Gasparrini and Armstrong et al., 2010; Huang and Ding et al., 2020). In order to solve the collinearity relationship

between air pollutants and meteorological factors, we only added variables with correlation values less than 0.7 into the model (Liu and Tian et al., 2017). The basic model was as follows:

$At \sim \text{quasiPoisson}(et)$

$$\begin{aligned} \text{Log}(et) = & \alpha + W_X^T \eta + ns(\text{time}, 7 * \text{year}) + ns(MT, df_1) + ns(RH, df_2) \\ & + (\beta * DOW) + (\gamma * Hoilday) \end{aligned}$$

At is the actual tuberculosis outpatient visits in t days, et is the expected tuberculosis outpatient visits t days, $W_X^T \eta$ is a cross-basis function, ns represents the natural cubic spline function, df_1 and df_2 represent the degrees of freedom of average temperature and relative humidity respectively, β and γ are the regression coefficients of Dow and Holiday respectively.

We regarded the Level 1 concentration limits as a reference in the National Environmental Quality Standard (GB3059-2012), used RR (relative risk) estimates and 95% CI (confidence intervals) to represent the lag-specificity and cumulative risk of TB outpatient visits with each 10-unit increasing in six air pollutants concentrations. After a single-pollutant regression model, we modeled the effects of air pollution by gender (male female), age (<15 years old 15-65 years old >65 years old) and season (cold warm). Calculate the RR and 95% CI using the following formula:

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

Where $\widehat{E}_1$ and $\widehat{E}_2$ are the point estimates for the two subgroups, and $\widehat{SE}_1$ and $\widehat{SE}_2$ are the corresponding standard errors, respectively (Huang and Ding et al., 2020).

To test the robustness of the results, we also performed sensitivity analysis: (a) the

multi-pollutant models were used to adjust for confounding factors among air pollutants;
(b) different degrees of freedom were taken in the ns function of time variables (4-6 df);
(c) changing the degrees of freedom in the ns function of meteorological variables (4-7 df). All analyses were performed through the “splines”, “dlnm” and “mgcv” packages in the R software (version 4.0.0).

3. Results

3.1 Descriptive results

Table1 provides summary statistics of the variables in this study, include TB case, atmospheric pollutants and meteorology measure. The daily mean concentration of PM_{2.5} was 55.18 µg/m³ (0- 276 µg/m³), PM₁₀ was 85.89 µg/m³ (0- 379 µg/m³), SO₂ was 13.33 µg/m³ (2 - 237 µg/m³), CO was 0.77 mg/m³ (2 - 2.9 mg/m³), NO₂ was 32.09 µg/m³ (9 - 93 µg/m³), O₃ was 92.77 µg/m³ (0 - 226 µg/m³). From 2015 to 2020, there were 21,591 cases of tuberculosis, 6384 females and 15,207 males. Among them, 0.94% were younger than 15 years old, 30.26% were older than 65 years old, and 68.8% were between 15 and 65 years old. The minimum and maximum daily mean temperature were 7.8°C and 33.5°C respectively. The minimum value of relative humidity is 33% and the maximum is 99%. **Fig. 2** shows Spearman correlation coefficient and scatter plot. The distribution of air pollutant concentrations and tuberculosis hospitalizations from 2015 to 2020 are presented in **Fig. 3**.

3.2 Relations analysis

3.2.1 Overall association between daily TB outpatient visits and air pollutants

As shown in Supplementary **Fig. S1**, from the overall exposure response effect, it can be concluded that the exposure concentrations of PM₁₀, PM_{2.5}, NO₂, O₃ and CO have a positive relationship with the risk of tuberculosis, while SO₂ has a negative relationship with the risk of tuberculosis.

3.2.2 Association between daily TB outpatient visits and PM_{2.5}

We can see from the **Fig. 4**, when a 10 µg/m³ increase in PM_{2.5} concentration, the risk of TB increased, and the association persisted over a 12 to 20 day delay (RR=1.0018, 95%CI: 1.0004-1.0032, delay of 12 days; RR=1.0019, 95%CI: 1.0004-1.0035, delay of 20 days). At the same time, the cumulative lag effect reached statistical significance in 0-16 days (RR=1.0169, 95%CI: 1.0007-1.0333, lag 0-16 days). Subgroup analysis showed that the effects of PM_{2.5} exposure in male, 15 to 65 years old, and ≥ 65 years old subgroup were statistically significant. However, an opposite result was found in the cold and warm subgroup, cold (RR=1.0025, 95%CI: 1.0002-1.0047, lag 13 days) and warm (RR=0.9947, 95%CI: 0.9899-0.9994, lag 2 days) (**Fig. 5, Fig. 6** and Supplementary **Table S2**).

3.2.3 Association between daily TB outpatient visits and PM₁₀

In the single pollutant model, the daily lag effect of increasing PM₁₀ concentration by 10 µg/m³ reached statistical significance on the 14th day, and lasted until the 20th day (RR = 1.001, 95%CI: 1.0002-1.0019, with a 14-day lag. RR = 1.0013, 95%CI: 1.0002-1.0024, lag 20 days). The cumulative lag effect reached statistical significance when the lag was 0-21 days (RR = 1.0137, 95%CI: 1.0006-1.027, lag 0-21 days). The stratified analysis showed that the effects of PM₁₀ exposure were statistically significant in male, 15-60 years old, and cold subgroups. But similar to PM_{2.5}, there was an opposite effect in the warm season subgroup (RR = 0.996, 95%CI: 0.9926-0.9994, with a lag of 2 days) (**Fig. 4, Fig. 5, Fig. 6** and Supplementary **Table S3**).

3.2.4 Association between daily TB outpatient visits and CO

As shown in the **Fig. 4**, when the lag time was 11 days, the single-day lag risk of CO single pollutant model reached statistical significance (RR=1.0037, 95%CI:1.0005-1.0068, lag 11 days). The cumulative lag effect of CO exposure showed a bimodal distribution. The first time was statistically significant with a lag of 0-1 days (RR=1.013, 95%CI:1.0001-1.0261, lag 0-1 days), and the second time was statistically significant with a lag of 0-13 days (RR=1.0337, 95%CI:1.0036-1.0647, lag 0-13 days). When stratified by sex, age, and season, the effect of CO exposure was still statistically

significant in male, 15-65 years old, > 65 years old, and cold quarter subgroups (**Fig. 5**, **Fig. 6** and Supplementary **Table S4**).

3.2.5 Association between daily TB outpatient visits and O₃

Fig. 4 shows that O₃ exposure immediately increased the risk of TB outpatient visits (RR = 1.049, 95%CI: 1.0012-1.0086, 0 days lag). The cumulative risk curve was bimodal and statistically significant after 0-4 and 0-9 days of lag. In the subgroup analysis, the effect of O₃ had a short-term significant effect in male, female, > 65 years old, 15-65 years old, and cold quarter subgroup (**Fig. 5**, **Fig. 6** and Supplementary **Table S5**).

3.2.6 Association between daily TB outpatient visits and SO₂

Different from other pollutants, when an increase of 10 µg/m³ in SO₂ concentration, the risk of TB outpatient visits was reduced. In the single pollutant model, the single-day lag risk of SO₂ reached statistical significance at 0 days (RR = 0.9549, 95%CI: 0.9389-0.9712, lag 0 days). The cumulative lag risk reached its lowest at 20 days (RR = 0.8212, 95%CI: 0.7351-0.9173, 0-20 days lag). In the subgroup analysis, all subgroups except the < 15 years old had statistical significance (**Fig. 5**, **Fig. 6** and Supplementary **Table S6**).

3.2.7 Association between daily TB outpatient visits and NO₂

As shown in the **Fig. 4**, the cumulative risk reached statistical significance with a lag of 0-2 days (RR = 1.0242, 95%CI: 1.0059-1.0428, lag 0-2 days). Stratification results showed that NO₂ exposure was still significant in the cold season group (RR=1.0329, 95%CI: 1.0114-1.0548, lag 0 days) (**Fig. 5, Fig. 6** and Supplementary **Table S7**).

3.3 Sensitivity analysis

Sensitivity analysis: the multi-pollutant model, change the degree of freedom of the time variable ns (4-6df) and the meteorological variable ns (4-7df), the main results showed no significant change (**Table 2** and Supplementary **Table S8-25**). The results show that the model has good performance and the calculation results are reliable.

4. Discussion

In this study, we used time series analysis to evaluate the short-term impact of air pollution exposure on the risk of tuberculosis outpatient visits in Fuyang from 2015 to 2020. We found exposure to O₃, CO, PM₁₀, PM_{2.5}, and NO₂ increases the risk of TB outpatient visits, and SO₂ reduces the risk. In addition, subgroup analysis showed that the pollutants had a greater impact on men and the elderly. The multi-pollutant model

results showed that the effects of PM_{2.5}, CO, SO₂ and NO₂ on the TB visit risk remained stable after adjustment, while the effects on PM₁₀ and O₃ were reduced to some degree.

The findings of this study, which are supported by several previous studies, suggest that tuberculosis is affected by PM_{2.5} concentrations (Jassal and Bakman et al., 2013; Smith and Schoenbach et al., 2014; Liu and Tian et al., 2017). Two recent time series studies in the Chinese cities of Jinan and Hefei also confirmed the risk of PM_{2.5} on tuberculosis (Liu and Cui et al., 2018; Huang and Ding et al., 2020). Several potential mechanisms can be used to explain the harm of PM_{2.5} on TB: (1) When PM_{2.5} exposure is increased, the immune function of human respiratory system will be altered or impaired. Exposure may harm lung immunity by inducing nitrosation stressors and oxidation (Nel, 2005). (2) PM_{2.5} can weaken mucociliary clearance function and alveolar macrophage activity (D'Amato and Cecchi et al., 2010; Smith and Paszkiewicz et al., 2010). (3) PM_{2.5} affects the immune function of anti-mycobacterium T cells by disrupting the synthesis and secretion of inflammatory factors (Ibironke and Carranza et al., 2019). (4) PM_{2.5} can carry minerals, metal ions and other external impurities into the bronchioles and alveoli, causing various forms of inflammation and damaging the body's immune function (Bai and Su et al., 2018; Cheng and Zhu et al., 2019; Popovic and Soares et al., 2019). Therefore, in combination with the results of this study and previous studies, it can be seen that PM_{2.5} can damage the immune response of the lungs and accelerate the progress of tuberculosis. We can see that from some epidemiological studies, PM₁₀, it has a similar effect and reaction mechanism to PM_{2.5} (Rivas-Santiago and Sarkar et al., 2015; Kim and Yu et al., 2020; Pompilio and Di Bonaventura, 2020;

Xiang and Xu et al., 2021). PM_{2.5} and PM₁₀ are so small in diameter that they can pass through the physical barrier of the respiratory tract. The aerosol nuclei containing *Mycobacterium tuberculosis* were colonized deep in lung tissue with PM_{2.5} and PM₁₀ as carriers. This is also a risk factor for TB infection (Yang and Zhang et al., 2020).

We observed a protective effect of sulfur dioxide. Similar protective effects have been reported in cities such as Madrid in Spain and Ningbo and Hefei in China (Alvaromeca and Diaz et al., 2016; Ge and Fan et al., 2017; Huang and Ding et al., 2020). This protective effect of SO₂ is thought to be due to the antibacterial properties of SO₂. The ability of SO₂ to block enzyme activity in microbial cell membranes may account for the antimicrobial properties (Ge and Fan et al., 2017). An in vitro study of SO₂ also demonstrated its inhibitory effect on the growth of *Mycobacterium tuberculosis* (Malwal and Sriram et al., 2011). One study reported that male mice inhaled small amounts of SO₂ can increased levels of inflammatory cytokines in lung tissue and inhibited the proliferation of *Mycobacterium tuberculosis* (Meng and Liu et al., 2005). However, some related studies have obtained the opposite result of our conclusion, that SO₂ is a risk factor (Liu and Zhang et al., 2020; Liu and Zhao et al., 2021). Therefore, it is necessary to further study the mechanism of action of SO₂ in the human body to provide a more comprehensive and scientific explanation.

With regard to O₃, we observed a positive correlation with the risk of TB, the lag effect was observed to be statistically significant at 0 day, indicating an acute effect of O₃ on the human body. The independent effect of O₃ on increased TB risk also was observed in a multi-city model study in Shandong Province, China (Liu and Zhao et al.,

2021). Laboratory evidence has shown that O₃ increases the incidence of airway inflammation, impairs lung function and affects lung gas exchange (Smith and Van Den Eeden et al., 2016). However, a nested case-control study in Northern California showed that O₃ exposure above the lowest quintile resulted in a reduced risk of tuberculosis. A time series study from Hefei, China, also concluded that O₃ reduces the risk of tuberculosis outpatient visits (Smith and Van Den Eeden et al., 2016; Huang and Ding et al., 2020). Due to the differences in study results and the unclear biological mechanisms of O₃ associated with TB infection, further studies are recommended to explain the effect of O₃ on TB risk.

The results of this study suggested that CO exposure increases the risk of TB outpatient visits. Similar protective effects have been reported in northern California, those exposed to CO in the highest quintile had a 50% increase in TB prevalence compared with those exposed to the lowest quintile (Smith and Van Den Eeden et al., 2016). Two studies in Wuhan and Jinan in China showing positive effects of CO on TB (Liu and Cui et al., 2018; Xu and Liao et al., 2019). One study suggests that heme oxygenase is produced by carbon monoxide, which inhibits the body's immune response and inflammation (Chin and Otterbein, 2009). In addition, CO may activate the interleukin-10 cascade in pulmonary macrophages, leading to *M. tuberculosis* reactivation. Microbiological studies have shown that Mycobacterium can use CO as carbon source and energy source for growth and reproduction under aerobic conditions (Park and Hwang et al., 2003; Tremblay, 2007). An experiment in mice found that exposure to diesel exhaust, including CO, reduced mRNA expression of several pro-

inflammatory cytokines and cell-signaling enzymes that control *Mycobacterium tuberculosis* infection (Hiramatsu and Saito et al., 2005).

Our study showed a positive correlation between NO₂ and TB, two time series studies in Chengdu and Hefei also reached similar conclusions (Zhu and Xia et al., 2018; Huang and Ding et al., 2020). A study in Taiwan has shown that NO₂ is associated with tuberculosis which contributed 1.2–9.8% to developing TB (Lin and Lin et al., 2019). Regarding the mechanism of action of NO₂, related studies have shown that inhalation of NO₂ may reduce the ability of mice to kill bacteria in the lungs and increase the risk of respiratory bacterial infection (Goldstein and Eagle et al., 1973). From a biochemical point of view, NO₂ is an irritating gas that can corrode and damage the alveoli and lower respiratory tract, and NO₂ is a component of photochemical smog and has acute toxic effects on the lungs (Wang and Chen et al., 2014; Smith and Van Den Eeden et al., 2016). These may be the reasons for NO₂'s influence on TB outpatient visit risk.

In the subgroup analysis, we found that pollutant exposure had a more significant impact on the male group, and all pollutants except NO₂ were statistically significant. This may be due to men's greater exposure to outdoor environments and lifestyle factors such as smoking and drinking. In addition, there are significant differences in hormonal status and airway physiology between males and females, which may also be one of the reasons (Sopori and Kozak et al., 1998; Przybylski and Nowakowska-Arendt et al., 2014). In the age subgroup, the effects of pollutants on older age groups were greater. The possible reason is that with age, the body's immune defenses decline, and the body is more likely to be exposed to pollutants than younger people (Zhang and Ni et al.,

2019; Huang and Ding et al., 2020). Interestingly, contrary results were observed for PM_{2.5} and PM₁₀ in the cold and warm seasons. In the cold season group, the risk of tuberculosis diagnosis was still increased, while in the warm season group, PM_{2.5} and PM₁₀ reached statistical significance when they lagged by 2 days and 1 day, respectively, reducing the risk of tuberculosis outpatient visits. Some possible reasons can explain this phenomenon :(1) The temporal distribution of particulate matter pollutants showed obvious seasonal differences, with high in cold season and low in warm season. (2) During periods of high ambient air pollutants, particularly particulate matter exposure at high concentrations visible to the naked eye, humans prefer to stay indoors, leading to increased exposure and further increasing the risk of tuberculosis (Huang and Xiang et al., 2020). But the actual mechanism remains unclear, and more research is needed to determine the cause.

Our study has several strengths. First, we explored for the first time the relationship between air pollution exposure and tuberculosis outpatient visits in Fuyang city, which is the most populous city in Anhui province and has a good representation. Second, the impact of six contaminants on TB visit risk was thoroughly explored, and the sensitivity analysis showed that the results were robust and reliable. However, there are still some shortcomings. First of all, this study adopted the average daily concentration of fixed stations as the exposure concentration of air pollution, without excluding the influence of spatial heterogeneity of air pollution. Second, the ecological fallacy is inevitable. Third, this study was limited to one area in Fuyang, which means that our findings should be carefully extended to other areas.

5. Conclusion

The results showed that six air pollutants all had an impact on the risk of tuberculosis outpatient visits. PM₁₀, PM_{2.5}, NO₂, O₃ and CO increased the number of tuberculosis outpatient visits, while SO₂ decreased the number of tuberculosis outpatient visits. Men and the elderly are more likely to be affected by air pollution, and the effects of season are more pronounced than age or sex. Therefore, we should give more comprehensive prevention and treatment to high-risk groups. Meanwhile add more measures to against the effects of seasonal changes.

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Author's contributions Xin-Qiang Wang and Xiao-Hong Kan collaboratively designed the study, both making substantial intellectual contribution. Xin-Qiang Wang and Ying-Qing Li analyzed the data and drafted the manuscript, Xiao-Hong Kan and Xiu-Jun Zhang revised the manuscript. Cheng-Yang Hu, Kai Huang, Kun Ding, Xiao-

Jing Yang, Xin Cheng, Kang-Di Zhang, Wen-Jie Yu, Jie Wang, Yong-Zhong Zhang, Zhen-tao Ding contributed in collecting the data. Xin-Qiang Wang and Ying-Qing Li 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

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Consent for publication Not applicable.

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Figure Captions:

Fig. 1. The geographical location of Fuyang City and tuberculosis outpatient number in cities of Anhui Province from 2015-2020.

Fig. 2. Spearman rank correlation coefficients and scatter plot between daily air pollutant concentrations and meteorological factors in Fuyang, 2015–2020. *: $r_s > 0.7$

Fig. 3. Time series of Tuberculosis, O₃, PM_{2.5}, PM₁₀, SO₂, NO₂, and CO in Fuyang, China, from 2015 to 2020.

Fig. 4. Lag-specific relative risks (95% CI) and cumulative risks (95% CI) of per 10-unit increase in the daily concentrations of air pollution on TB outpatient visits on different lag days, according to the single-pollutant model; TB, tuberculosis; PM_{2.5}, particulate matter < 2.5 µm in aerodynamic diameter; PM₁₀, particulate matter < 10 µm in aerodynamic diameter; CO, carbon monoxide; O₃, ozone; SO₂, sulfur dioxide;

NO₂, nitrogen dioxide.

Fig .5. Lag-specific relative risks (95% CI) of per 10-unit increase in the daily concentrations of air pollution on TB outpatient visits on different lag days, according to the single-pollutant model stratified by age; TB, tuberculosis; PM_{2.5}, particulate matter < 2.5 µm in aerodynamic diameter; PM₁₀, particulate matter < 10 µm in aerodynamic diameter; CO, carbon monoxide; O₃, ozone; SO₂, sulfur dioxide; NO₂, nitrogen dioxide.

Fig .6. Lag-specific relative risks (95% CI) of per 10-unit increase in the daily concentrations of air pollution on TB outpatient visits on different lag days, according to the single-pollutant model stratified by gender and season; TB, tuberculosis; PM_{2.5}, particulate matter < 2.5 µm in aerodynamic diameter; PM₁₀, particulate matter < 10 µm in aerodynamic diameter; CO, carbon monoxide; O₃, ozone; SO₂, sulfur dioxide; NO₂, nitrogen dioxide.

Figures

Figure 1

The geographical location of Fuyang City and tuberculosis outpatient number in cities of Anhui Province from 2015-2020.

Figure 2

Spearman rank correlation coefficients and scatter plot between daily air pollutant concentrations and meteorological factors in Fuyang, 2015–2020. *: $r_s > 0.7$.

Figure 3

Time series of Tuberculosis, O3, PM2.5, PM10, SO2, NO2, and CO in Fuyang, China, from 2015 to 2020.

Figure 4

Lag-specific relative risks (95% CI) and cumulative risks (95% CI) of per 10-unit increase in the daily concentrations of air pollution on TB outpatient visits on different lag days, according to the single-pollutant model; TB, tuberculosis; PM2.5, particulate matter < 2.5 μm in aerodynamic diameter; PM10, particulate matter < 10 μm in aerodynamic diameter; CO, carbon monoxide; O3, ozone; SO2, sulfur dioxide; NO2, nitrogen dioxide.

Figure 5

Lag-specific relative risks (95% CI) of per 10-unit increase in the daily concentrations of air pollution on TB outpatient visits on different lag days, according to the single-pollutant model stratified by age; TB, tuberculosis; PM2.5, particulate matter < 2.5 μm in aerodynamic diameter; PM10, particulate matter < 10 μm in aerodynamic diameter; CO, carbon monoxide; O3, ozone; SO2, sulfur dioxide; NO2, nitrogen dioxide

Figure 6

Lag-specific relative risks (95% CI) of per 10-unit increase in the daily concentrations of air pollution on TB outpatient visits on different lag days, according to the single-pollutant model stratified by gender and season; TB, tuberculosis; PM2.5, particulate matter < 2.5 μm in aerodynamic diameter; PM10, particulate matter < 10 μm in aerodynamic diameter; CO, carbon monoxide; O3, ozone; SO2, sulfur dioxide; NO2, nitrogen dioxide.

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