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Original Article

The short-term effect of air pollution on the incidence of pulmonary tuberculosis in Chongqing, China, 2014-2020

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Abstract
Introduction: Tuberculosis (TB) is one of the top ten causes of death in the world. The purpose of this study was to explore the relationship between the short-term exposure to air pollutants and the risk of pulmonary TB in Chongqing.
Methodology: A distributed lag nonlinear model was used to explore the effect of short-term exposure to air pollutants on the risk of pulmonary TB. Stratified analysis was used to explore the impact of gender and age on the risk of pulmonary TB.
Results: There were 170,934 confirmed cases of pulmonary TB in Chongqing from January 1st, 2014 to December 30th, 2020. There was a positive correlation between the exposure to particulate matter with aerodynamic diameter less than 2.5 µm ($PM_{2.5}$), particulate matter with aerodynamic diameter less than 10 µm (PM_{10}) ozone (O_3) and the incidence risk of TB. The maximum lag-specific relative risk (RR) of pulmonary TB was 1.012 (95% CI: 1.001-1.023, 14 days delay) for each 10 µg/m^3 increase in $PM_{2.5}$; 1.010 (95% CI: 1.003-1.017, 14 days delay) for each 10µg/m^3 increase in PM_{10}; and 1.002 (95% CI:1.000-1.004, 2 days delay) for each 10 mg/m^3 increase in O_3. Stratified analysis showed that the exposure effects of $PM_{2.5}$, PM_{10} and O_3 were different between different genders and age.
Conclusions: This study suggested that exposure to $PM_{2.5}$, PM_{10}, and O_3 was associated with the risk of pulmonary TB, and the risk was higher for males than females, while the exposure to $PM_{2.5}$ and PM_{10} was riskier for people aged 15-60 years.

Key words: tuberculosis, air pollution, DLNM.

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Introduction

Tuberculosis (TB) is caused when *Mycobacterium tuberculosis* infects human lungs. It is one of the legal class B infectious diseases in China and the leading cause of death from a single infectious disease in the world [1]. According to the World Health Organization (WHO) estimate, there were about 10.6 million new cases of TB in the world in 2021 [2]. China was one of the 30 countries with high burden of TB. In 2021, the number of new cases was about 780,000, ranking third in the world after India and Indonesia [2]. China has invested hundreds of millions of dollars in the prevention and treatment of TB every year. However, in the case of drug-resistant TB and multi drug-resistant TB, treatment other than first-line anti TB drugs was required, and regular reexamination, such as computed tomography (CT) and liver and kidney function, also caused considerable mental pressure and economic burden to the patients [3,4]. Therefore, the prevention and treatment of TB still needs more attention.

Air pollutants are one of the main causes of the global disease burden, and have gradually become the focus of attention in recent years [5]. Research had shown that air pollutants might reduce the ability of macrophages to induce innate and adaptive immune responses, leading to a decrease in the phagocytic capacity of alveolar macrophages, a decrease in anti-tuberculosis immune function, a decrease in the ability of the lung tissue to resist infection, and a decrease in local defense function, thereby increasing the risk of infection with pulmonary TB [6]. Therefore, the correlation between air pollution and TB has attracted increasing attention.

With the development and deepening of epidemiological research, more studies showed that air pollutants had an impact on pulmonary TB. One study summarized the relationship and potential mechanism between respiratory bacterial infection and air pollution, and described the relationship between various air pollutants and the incidence of TB [7]. One observational study showed that the positive rate of sputum test of pulmonary tuberculosis patients was significantly correlated with the concentration of fine particles near the residence [8]. Another study showed that the most significant pollutant affecting pulmonary TB was particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), and other pollutants also showed significant correlations [1]. Subsequently, scholars quantitatively analyzed the correlation between atmospheric pollutants and pulmonary TB. For example, a study in Northern California found that, compared with the concentration of the lowest five quantile, the concentration of carbon monoxide (CO) and nitrogen dioxide (NO_2) in the highest five quantile at the individual level in two years was associated with an increase of risk of pulmonary TB by 50% and 42% respectively [9]. A study in Taiwan found that when the average concentration of NO_x increased by 18.8 μg/m^3 every two years, the risk of pulmonary TB increased by 21% [10]. A study based in Hong Kong and Beijing found that the monthly $PM_{2.5}$ concentration in winter in both cities was significantly positively correlated with the reported number of TB in the following 3-6 months [11]. A study in South Korea found that the risk of TB increased when the annual average concentration of sulfur dioxide (SO_2) increased [12].

To sum up, more studies had focused on the relationship between long-term exposure to air pollutants and the risk of TB, mainly using time series data at weekly, monthly or annual levels. There were few studies on the impact of short-term exposure to air pollutants on the risk of pulmonary TB, and the results were inconsistent [13,14]. In this study, we collected the data of TB incidence and the corresponding air pollutants and meteorological data from 2014 to 2020. The distribution lag nonlinear model (DLNM) was adopted to explore the relationship between the short-term exposure to air pollutants and the risk of pulmonary TB, and stratified analysis was conducted to find out the differences between different genders and different age groups.

Methodology

Data collection

The daily pulmonary TB data from January 1st, 2014 to December 31st, 2020 of 38 districts and counties in Chongqing were obtained from Chongqing Center for Disease Control and Prevention. According to the national guidelines on tuberculosis control, pulmonary TB cases or suspected cases detected in any health facilities must be reported through the infectious disease reporting system within 24 hours. The diagnosis of pulmonary TB was based on the Diagnosis for Pulmonary Tuberculosis (WS 288-2017) issued by the National Health Commission of People's Republic of China [15]. This study included all clinical and confirmed cases. The data of air pollutants used in this study were from Chongqing Environmental Monitoring Center. The daily concentrations of air pollutants in Chongqing were obtained from Chongqing Environmental Monitoring Center, including data on particulate matter with $PM_{2.5}$ PM_{10}, SO_2, NO_2, CO and O_3 concentrations. O_3 was the average value of the largest continuous 8-hour ozone concentration in a day as the pollution level of that day, and the other five pollutants were the 24-hour average concentrations. The daily meteorological variables of the same period, including mean temperature, precipitation, average relative humidity and sunshine hours for the same period were collected from China Meteorological Data Sharing Service System.

Statistical analysis

First, DLNM was established separately for each pollutant to explore the relationship between short-term exposure of each air pollutant and the risk of pulmonary TB. Next, we divided the population and used subgroup analysis to identify differences between different genders and age groups.

Previous studies had suggested that the number of reported cases of TB followed a quasi-Poisson distribution [14,16]. Therefore, in this study, a time-series DLNM with quasi-Poisson regression was applied to assess the effect of daily air pollution on daily reported TB [14,18]. DLNM can describe the changes of dependent variables in independent variable dimension and lag dimension at the same time by constructing cross basis function, which is widely used to explore the relationship between environmental factors and health outcomes [18,19].

In order to explore the influence of exposure to six air pollutants on the risk of TB incidence, we used the function of natural cubic spline (6 degrees of freedom per year) to control long-term trends and seasonal variations. We also controlled for the impact of the day of the week and holiday effects. Meanwhile, the ns function with 3 degrees of freedom was used to control nonlinear impact of meteorological factors on the risk of TB. Finally, we inquired two-dimensional connection between air pollutants and the exposure, lag and response of TB cases by the cross-basis functions. According to the purpose of our study and the length of TB incubation period, the maximum lag day was set at

14 days. The final single-pollutant model was as follows:

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

$$\log[E(Y_t)] = \alpha + \sum_{l=l_0}^{L} \gamma_l W_{t-1} + \text{dow} + \text{holiday} + \text{ns}(\text{date}) + \text{ns}(\text{tem}_t) + \text{ns}(\text{ruh}_t) + \text{ns}(\text{pre}_t) + \text{ns}(\text{ssd}_t)$$

Where: Y_t represents the incidence of TB; α is the intercept; $W_{(t-l)}$ is a cross-basis function, which specifies the exposure-lag-response relationship simultaneously in the exposure-response and lag-response dimensions. Dow and Holiday are the categorical variables indicating the day of the week and the public holiday, respectively. Daily mean temperature, precipitation, average relative humidity and sunshine hours, as potential confounding variables, were modeled as a natural cubic spline with 3 degrees of freedom. tem_t is the mean temperature (°C); ruh_t is the average relative humidity (%); pre_t is the precipitation (mm); ssd_t is the sunshine hours (h).

When calculating the relative risk (RR), the average value of air pollutants was defined as the reference value. We also calculated the RR and 95% confidence interval for TB when the pollutant concentration increased by 10 units. In addition, we also explored the differences in effects between different subgroups to determine the impact of pollutant exposure on different genders (male, female) and age groups (0-15 years old, 15-60 years old, ≥ 60 years old).

All data analyses were performed in R 4.2.0, with the “dlnm” package to fit the DLNM. Two-sided *p* values less than 0.05 were considered as statistically significant.

Results

Descriptive analysis

Table 1 lists the characteristics of pulmonary TB cases, air pollutants, gender distribution and age distribution in this study. The daily average concentration of $PM_{2.5}$ was 46.16 μg/m^3 (8~212μg/m^3), PM_{10} was 71.35 μg/m^3 (12~293μg/m^3), SO_2 was 12.58 μg/m^3 (4~80μg/m^3), CO was 0.96 mg/m^3 (0.4~3.4 mg/m^3), NO_2 was 41.5 μg/m^3 (9~96 μg/m^3), O_3 was 70.35 μg/m^3 (0~277 μg/m^3). There were 170,934 cases of TB in the city from 2014 to 2020, including 50,504 women and 120,430 men. Among them, 1% were under 15 years old, 30.94% were over 60 years old, and 66.06% were between 15 and 60 years old. The distribution of TB cases and air pollutants from 2014 to 2020 was shown in Figure 1.

Association between $PM_{2.5}$ and the incidence of pulmonary TB

By establishing a model of the relationship between daily PM_2.5 concentration and the cases of pulmonary TB, the exposure effect of $PM_{2.5}$ within 14 lag days could be obtained. As shown in Figure 2, when there was a 10μg/m^3 increase in $PM_{2.5}$ concentration, the risk of TB increased, the association persisted over a 13- to 14-day delay, and the correlation was statistically significant (RR = 1.012, 95% confidence interval (CI): 1.001-1.023, 14 days delay). Stratified analysis showed that the effect of PM_2.5 exposure on the risk of pulmonary TB was different between genders, and the increasing $PM_{2.5}$ exposure concentration was related to the increasing incidence risk for male (RR = 1.013, 95% CI: 1.002-1.024, 14 days delay), while no similar effect was found in female. When stratified by age, only the 15-60-year-old group showed an increasing risk when exposed to an increasing concentration of $PM_{2.5}$.

Table 1. Basic characteristics of reported cases of pulmonary TB and air pollutants in Chongqing from 2014 to 2020.

Variables	n (%)	Mean	Centiles				
			Min	25%	50%	75%	Max
Atmospheric pollutants (μg/m^3)							
$PM_{2.5}$	-	46.16	8	26	38	57	212
PM_{10}	-	71.35	12	43	62	88	293
SO_2	-	12.58	4	7	10	15	80
CO (μg/m^3)	-	0.96	0.4	0.8	0.9	1.1	3.4
NO_2	-	41.5	9	32	40	49	96
O_3	-	70.35	0	29	57	103	277
TB case	-						
Total	170934 (100)	66.88	12	41	52	69	497
Male	120430 (70.45)	47.12	6	29	37	49	356
Female	50504 (29.55)	19.76	2	12	16	22	141
Age < 15 years	1722 (1.00)	0.66	0	0	0	1	6
Age15-60 years	116332 (68.06)	44.4	5	27	35	47	309
Age ≥ 60 years	52880 (30.94)	20.18	1	11.75	16	22	174

Association between PM_{10} and the incidence of pulmonary TB

By establishing a model of the relationship between daily PM_{10} concentration and the cases of pulmonary TB, the exposure effect of PM_{10} within 14 lag days could be obtained. As shown in Figure 3, when there is a 10 μg/m^3 increase in PM_{10} concentration, the risk of pulmonary TB increased, the association persisted over a 13- to 14-day delay, and the correlation was statistically significant (RR = 1.010,95% CI: 1.003-1.017, 14 days delay). Stratified analysis showed that both males and females showed an increasing risk when facing increasing PM_{10} exposure.

Figure 1. Distribution of pulmonary TB cases, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 in Chongqing from 2014 to 2020.

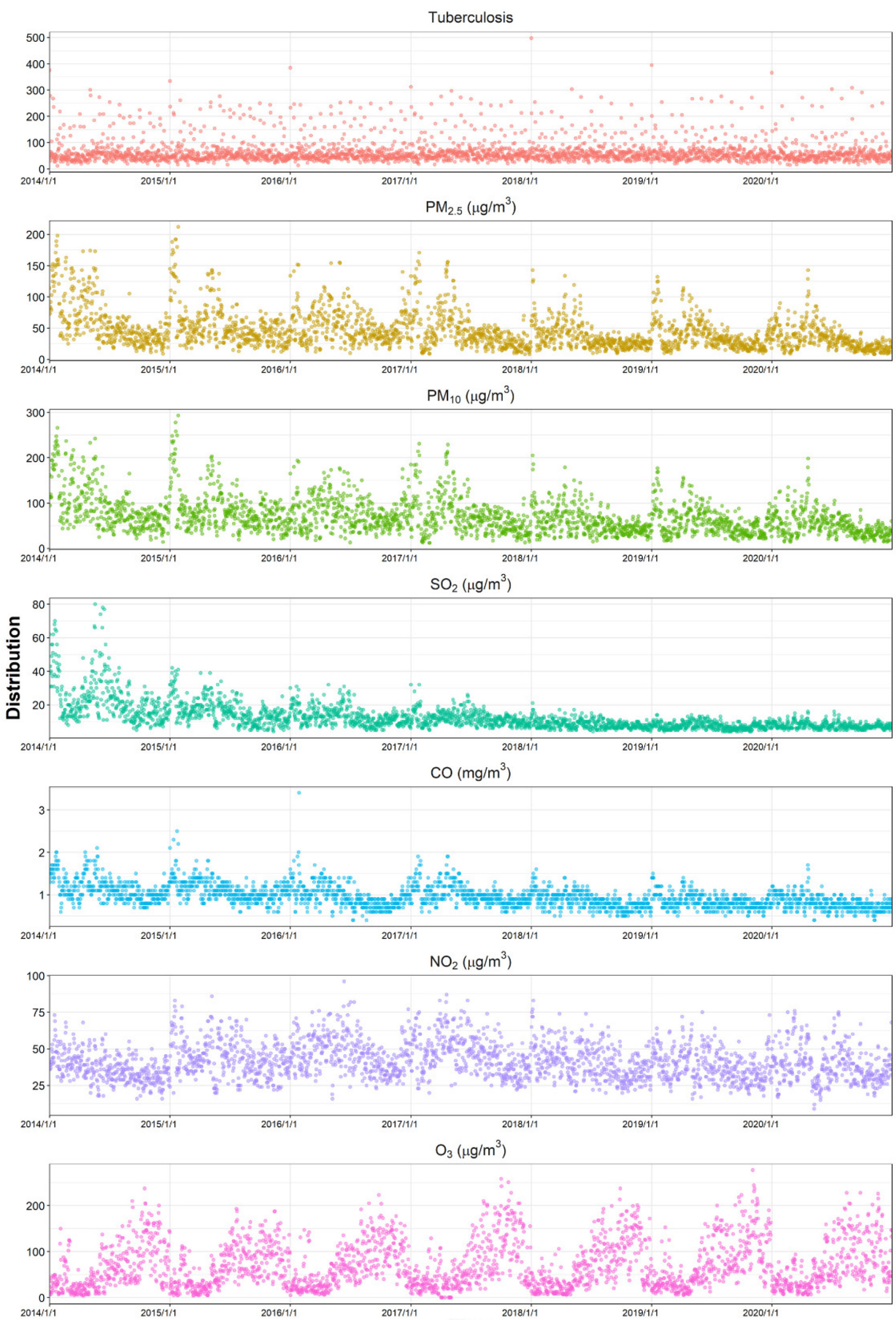


Figure 2. Lag-specific relative risks (95% CI) of per 10-unit increase in the daily concentrations of $PM_{2.5}$ on pulmonary TB. The impact of $PM_{2.5}$ exposure on different genders and age groups.

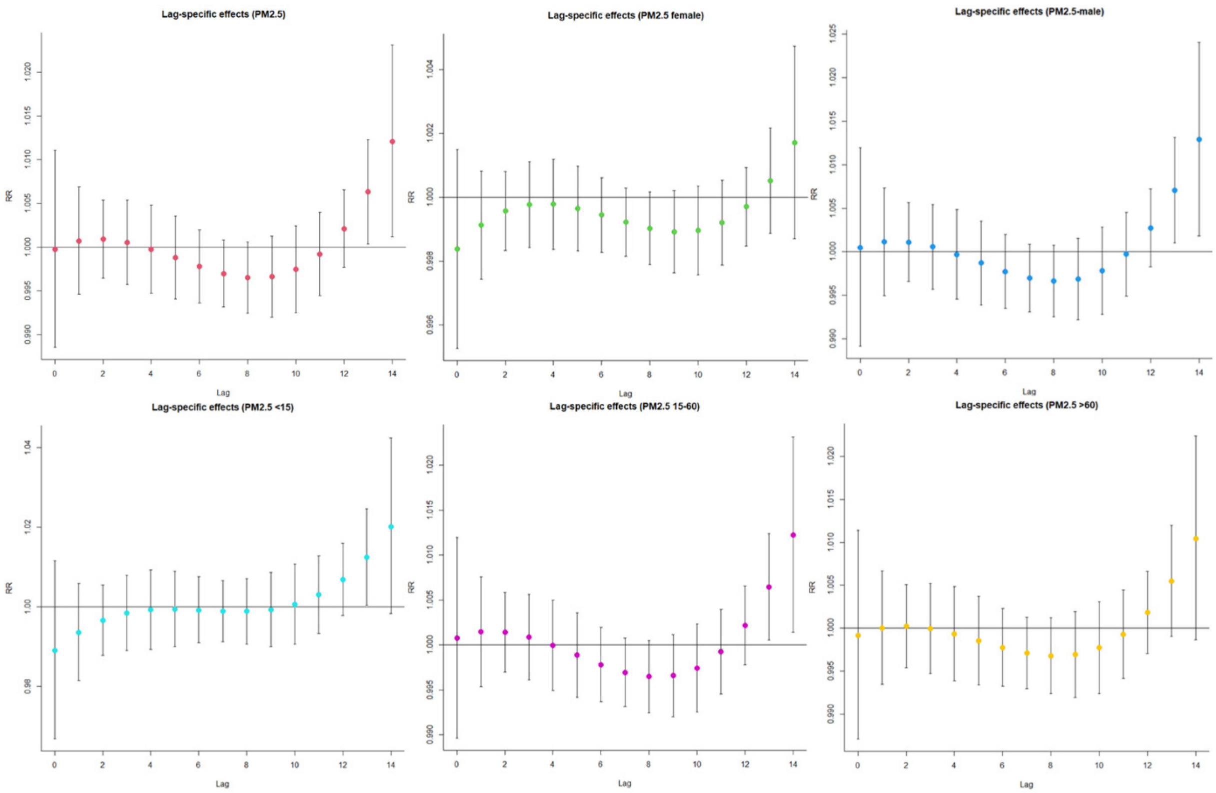
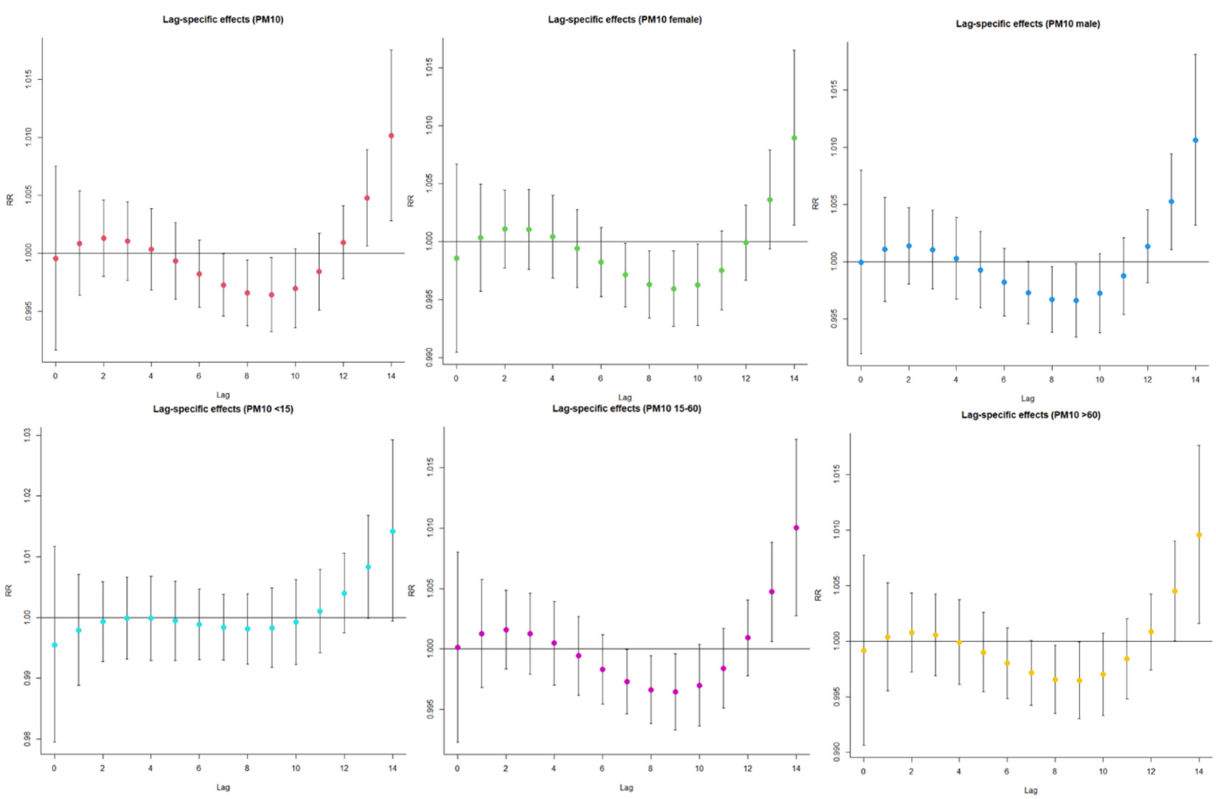


Figure 3. Lag-specific relative risks (95% CI) of per 10-unit increase in the daily concentrations of PM_{10} on pulmonary TB. The impact of PM_{10} exposure on different genders and age groups.



Among them, the single day risk of males was higher than that of females, and the lag days were longer (RR = 1.011,95% CI: 1.003-1.018, 14 days delay). When stratified by age, only the 15-60-year-old and > 60-year-old groups showed an increasing risk of PM_{10} exposure. Among them, the single day risk of the 15-60-year-old subgroup was higher than that of the > 60-year-old subgroup, in which the lag days were longer.

Association between O_3 and the incidence of pulmonary TB

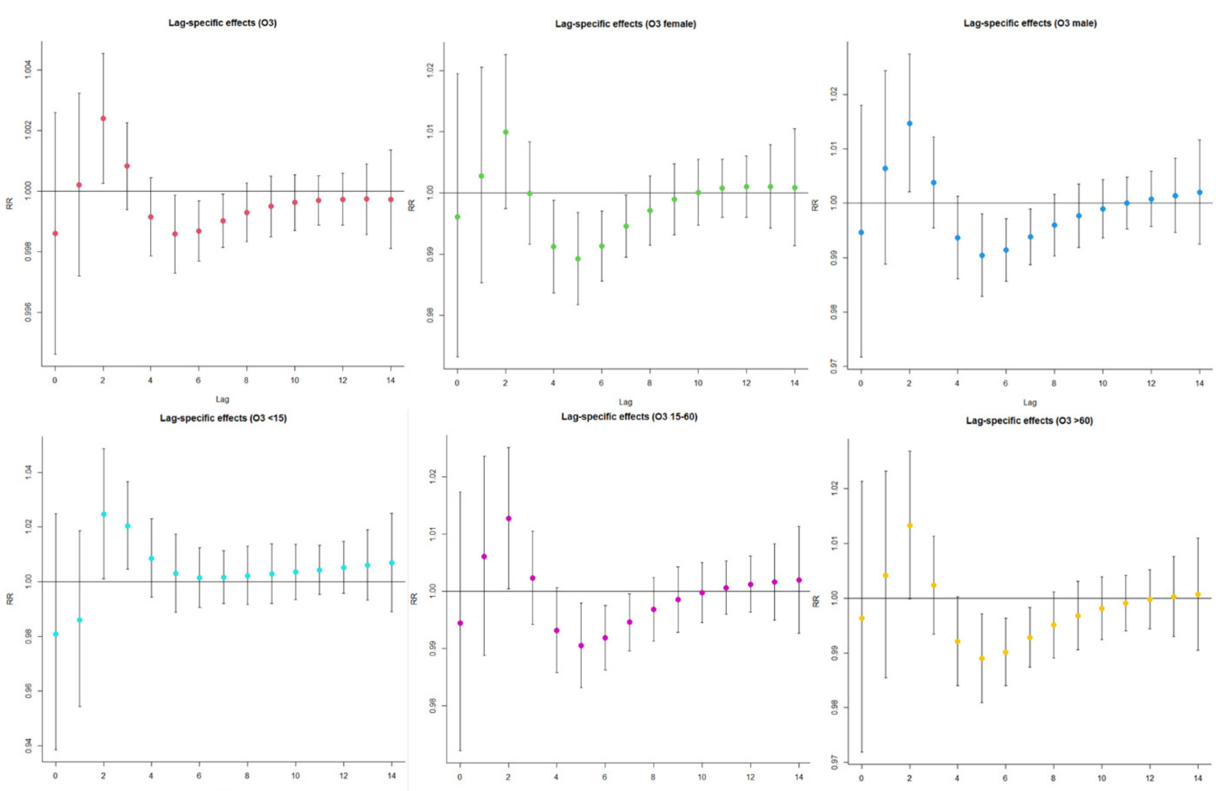
By establishing a model of the relationship between daily O_3 concentration and the cases of pulmonary TB, the exposure effect of O_3 within 14 lag days could be obtained. As is shown in Figure 4, when there was a 10 μg/m^3 increase in O_3 concentration, the risk of pulmonary TB increased; the association persisted over a 2-day delay, and the correlation was statistically significant (RR = 1.002, 95% CI: 1.000-1.004, 2 days delay). Stratified analysis showed that the effect of O_3 exposure on the risk of pulmonary TB was different between genders, and the increasing O_3 exposure concentration was related to the increasing incidence risk in males (RR = 1.014, 95% CI: 1.002-1.024, 2 days delay), while no similar effect was found in females. When stratified by age, only the < 15-year-old and 15-60-year-old groups showed an increasing risk of O_3 exposure. Among them, the single day risk of the < 15-year-old subgroup was higher than that of the 15-60-year-old subgroup, in which the lag days were longer.

Discussion

In this study, DLNM was used to explore the relationship between short-term exposure to air pollutants and the risk of pulmonary TB, and stratified analysis was carried out to explore the differences between different gender and age groups. It was found that the incidence risk of pulmonary TB in Chongqing was related to the exposure to air pollutants, and there was a positive correlation between the concentrations of $PM_{2.5}$, PM_{10}, O_3 and the risk of pulmonary TB. Stratified analysis showed that the exposure effects of $PM_{2.5}$, PM_{10} and O_3 were different between gender, and the risk of male was higher than that of female; the risk of short-term exposure to $PM_{2.5}$ and PM_{10} was greater in people aged 15-60 years.

The results of this study showed that there was a correlation between the increase of $PM_{2.5}$ exposure and the incidence risk of TB, which had a certain lag effect. This was consistent with the results reported by many research institutes in Los Angeles, Shanghai, Beijing and Hong Kong [20–22]. Being a type of atmospheric

Figure 4. Lag-specific relative risks (95% CI) of per 10-unit increase in the daily concentrations of O_3 on pulmonary TB. The impact of O_3 exposure on different genders and age groups.



suspended particles, $PM_{2.5}$ could carry harmful substances in the environment and external impurities such as benzopyrene, heavy metals, pathogenic microorganisms, metal ions and minerals into the respiratory tract, and may even reach bronchioles and alveoli [1]. Harmful substances entering the alveoli were cleared by the phagocytosis of macrophages, but some would still deposit in the lungs and caused local inflammatory reaction. As *Mycobacterium tuberculosis* was an obligate aerobic bacterium, its growth and reproduction could not be separated from metal elements such as iron, while $PM_{2.5}$, which carried high-level transition metals in the environment, increased the content of iron, which may create a good environment for the growth and reproduction of *Mycobacterium tuberculosis* [23,24]. In vitro evidence from human alveolar cells showed that when alveolar cells were exposed to simulated $PM_{2.5}$ environment, the survival rate of *Mycobacterium tuberculosis* was higher than that of the unexposed group, which indicated that $PM_{2.5}$ exposure may improve the survival rate of *Mycobacterium tuberculosis* and accelerate the incidence of TB [25]. In addition, a study also explained the relevant reasons from the perspective of immunology [26]. They found that exposure to $PM_{2.5}$ inhibited the expression of TNF-α factor in peripheral blood mononuclear cells before an individual was infected with *Mycobacterium tuberculosis*. It is worth noting that TNF-α factor inhibited the proliferation of tubercle bacillus in human body by mediating the formation and maintenance of granuloma. Therefore, the above reasons explained that the exposure of $PM_{2.5}$ may reduce human immunity and provide a favorable environment for the growth and reproduction of *Mycobacterium tuberculosis*, which may accelerate the process of pulmonary TB. In this study, we also found that there may be a certain lag effect in the adverse effects of $PM_{2.5}$ exposure, which may be because most people infected with *Mycobacterium tuberculosis* did not have obvious clinical symptoms and the onset was not rapid. Thus, patients might not seek medical treatment immediately after a certain mild symptom, but choose to take medicine for remission. Therefore, this might also have a lag effect on the correlation between them.

This study also found that there was a statistical correlation between the increase of PM_{10} exposure and the increasing risk of TB, and the correlation had a certain lag effect. A case-control study conducted in Taiwan showed that exposure to PM_{10} increased the risk of positive sputum test in patients with pulmonary TB [27]. It is worth noting that in this study, we found that the exposure effect of PM_{10} was similar to that of $PM_{2.5}$, and the lag period was also concentrated in 13-14 days. This may be because $PM_{2.5}$ was included in the monitored PM_{10}. Therefore, the main harmful substances in PM_{10} may be $PM_{2.5}$ and its related toxic substances and external impurities. The results of correlation analysis also showed that the correlation between PM_{10} and $PM_{2.5}$ was strong, and the correlation coefficient reached 0.96 (Supplementary Table 1), which may be one of the reasons why the effects of PM_{10} and $PM_{2.5}$ were similar. Relevant in vitro experimental results showed that, as with $PM_{2.5}$, the exposure of PM_{10} would also make the colony count of *Mycobacterium tuberculosis* higher than that of the unexposed group [25]. The results of cellular experiments using alveolar type II epithelial cells also showed that the levels of important inflammatory factors involved in the immune response of epithelial cells exposed to PM_{10} were also significantly decreased [28].

Stratified analysis of particulate matter showed that PM_{10} and $PM_{2.5}$ still showed a high degree of similarity in subgroup analysis. The results showed that the increase of $PM_{2.5}$ and PM_{10} exposure was related to the increased risk of male and 15–60-year-old age group, which may be because compared with female and minors, male and adults were more likely to work outdoors, which increased the exposure frequency of particulate matter, thereby increasing the risk of pulmonary TB. In addition, compared to females, males were more likely to be affected by unhealthy lifestyles such as smoking and drinking, which were risk factors for TB [29]. Studies have shown that nicotine in alcohol and cigarettes can inhibit the cellular immune function and the production of TNF-α factor, thus affecting human immunity [30]. For the middle-aged and elderly TB population, particle exposure was more likely to reduce their immune level, and caused the corresponding inflammatory reaction and respiratory symptoms, thereby increasing the incidence risk [31].

This study also explored the relationship between O_3 and the incidence of pulmonary TB. The results showed that the increase of O_3 exposure was related to the acute increase of the incidence risk of TB, and the correlation was statistically significant with delay of 2 days. Previous studies showed that O_3 exposure was associated with mortality, stroke, myocardial infarction and even appendicitis [32–37]. However, no positive association between O_3 and tuberculosis has been found [8,9,27,38–40]. The positive correlation found in this study can be explained from the following aspects: O_3, as a gas with strong oxidation, could undergo oxidation reaction at low temperature and participate in a variety of chemical reactions in the atmospheric environment. After being inhaled by human body, O_3 with strong oxidation would cause cough, dyspnea and decline of pulmonary function, which might aggravate the condition of TB patients and increase the risk of disease [41]. In addition, O_3 could also participate in the reaction of unsaturated fatty acids, amino acids and other proteins in organisms, causing fatigue, cough, chest tightness, chest pain, skin wrinkles, nausea and headache, accelerated pulse, memory decline, decreased vision and other symptoms in people who had been directly exposed to high concentration O_3 for a long time, which might accelerate the process of pulmonary TB and increase the incidence risk [42]. After the exposure effect of O_3 was stratified by age and gender, the incidence risk of TB in male, 0-15 years old and 15-60 years old age groups was statistically correlated with the increase of O_3 concentration. Compared to females, males had a higher chance of exposure to O_3 in outdoor work, which increased the frequency of O_3 exposure. There was little evidence about the sensitivity of different age groups to O_3.

However, this study also had some limitations. First, the exposure index of air pollutants was considered by calculating the average value of all detection stations in Chongqing, without considering the spatial heterogeneity of air pollution in different districts and counties. Secondly, this study was limited to Chongqing, which meant that our research results should be carefully extended to other places. Finally, we did not consider the impact of other confounding factors, such as economic status and smoking history.

Conclusions

This study found that there was a positive lag effect between the exposure to $PM_{2.5}$, PM_{10}, O_3 and the incidence risk of pulmonary TB in Chongqing. The risk of being male was higher than that of female, while the short-term exposure to $PM_{2.5}$, PM_{10} was riskier for the 15-60-year-old age group. The disease burden caused by a large number of people exposed to air pollution and the cumulative effect of air pollution was worthy of attention. Therefore, in order to protect patients with TB and save medical and social resources, it is necessary for government departments to formulate targeted publicity and preventive measures according to the quality of local air.

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Annex – Supplementary Items

Supplementary Table 1. Spearman rank correlation coefficients between daily concentration of air pollutants and meteorological factors in Chongqing from 2014 to 2020.

	TEM	**PRE**	**HUM**	**SUN**	**$PM_{2.5}$**	**PM_{10}**	**SO_2**	**CO ($\mu g/m^3$)**	**NO_2**	**O_3**
TEM	1.00									
PRE	-0.01	1.00								
RUH	-0.39	0.62	1.00							
SSD	0.56	-0.38	-0.69	1.00						
$PM_{2.5}$	-0.42	-0.38	-0.06	-0.12	1.00					
PM_{10}	-0.30	-0.47	-0.20	0.01	0.96	1.00				
SO_2	-0.17	-0.45	-0.29	0.07	0.66	0.73	1.00			
CO ($\mu g/m^3$)	-0.39	-0.25	0.19	-0.23	0.72	0.69	0.63	1.00		
NO_2	-0.25	-0.38	-0.15	0.04	0.65	0.70	0.50	0.56	1.00	
O_3	0.75	-0.20	-0.65	0.77	-0.23	-0.11	-0.04	-0.35	-0.10	1.00

TEM: temperature; PRE: precipitation; HUM: humidity; SUN: sunshine hours.