Associations of ambient air pollutants with regional pulmonary tuberculosis incidence in the central Chinese province of Hubei: a Bayesian spatial-temporal analysis

Fuqiang Liu¹, Zhixia Zhang², Hongying Chen³* and Shaofa Nie¹*

Abstract

Background: Air pollution and pulmonary tuberculosis (PTB) are still serious worldwide problems, especially in areas of developing countries. Whether there is an association between high ambient air pollutant concentrations and PTB has not been fully explored.

Methods: Bayesian spatial-temporal models were constructed to analyse the association between ambient air pollutants (particulate matter with aerodynamic diameters of ≤10 μm (PM₁₀), sulfur dioxide (SO₂) and nitrogen dioxide (NO₂)) and PTB incidence, adjusting for socioeconomic covariates. We collected data on pulmonary TB, ambient air pollution (PM₁₀, SO₂ and NO₂) concentrations and socioeconomic covariates from 17 prefectures in the central Chinese province of Hubei between Jan 1, 2006, and Dec 31, 2015.

Results: For every annual 10 μg/m³ increase in SO₂, the relative risk (RR) of PTB incidence was 1.046 (95% credible interval (CI), 1.038–1.054) in the study area. Moreover, we found positive associations with each annual 10 μg/m³ increase in ambient air pollutants (PM₁₀, SO₂ and NO₂) in females but only with SO₂ in males. A significant association for each 10 μg/m³ increase in SO₂ was observed in all the age groups, with a significant association for PM₁₀ only in children under 14 years of age. A significant response relationship was also observed at a 0–1 month moving average lag for each 10 μg/m³ increase in SO₂.

Conclusions: High ambient air pollution concentrations in areas of developing countries might increase the risk of regional PTB incidence, especially for women and young people. Precautions and protective measures and efforts to reduce ambient air pollutant concentrations should be strengthened in developing countries.

Keywords: Pulmonary tuberculosis, Air pollutants, Spatial-temporal analysis
Introduction

Although tuberculosis (TB) is likely to have emerged approximately 70,000 years ago, it remains a major health problem worldwide [1, 2]. In the past two centuries, almost one billion people have been killed by this infectious disease, with the top cause of death from a single infectious disease worldwide as human immunodeficiency virus (HIV) [3]. Currently, TB patients are mainly concentrated in developing areas, such as Southeast Asia, the Western Pacific (58%) and Africa (27%) [4]. Of the estimated 9.6 million people who developed tuberculosis globally in 2014, the top three countries with infections were India, Indonesia and China, accounting for 23, 10 and 10% respectively [4]. According to information recently published by the World Health Organization (WHO), the 20 countries with the highest TB burden based on the absolute number of incident cases and 10 countries with the highest TB burden based on the severity of the disease are all developing countries [5]. As a developing country with a high TB burden, China is currently facing a serious health problem due to the prevalence of tuberculosis [5, 6]. Despite a decrease in smear-positive TB cases, from 170 to 59 cases per 100,000 individuals during 1990–2010, TB has always ranked among the top five on the national list of notifiable infectious diseases in China [7]. Since TB can lead to substantial chronic lung disability, the loss of working ability and death among people in the most economically productive age groups [8], high TB incidences in developing countries will further aggravate the disease burden among low-income populations and hinder social and economic development.

Approximately one-third of the world's population is estimated to have been infected with Mycobacterium tuberculosis, and 5–10% of those infected may ultimately develop TB [9]. However, weakened immune systems may cause TB infection to reactivate [10]. Tumour necrosis factor (TNF)-α and interferon (IFN-γ) play a crucial role in inhibiting the growth of mycobacteria [11]. An experiment was conducted with animals to examine the effect of diesel exhaust particles on mycobacterial infection and found a decrease in the levels of TNF-α and IFN-γ [12]. Some ecological studies have also suggested that TB is associated with air pollution. In the USA, researchers found potential associations between long-term exposure to particulate matter and PTB disease in North Carolina residents during 1993–2007 [13]. They also observed positive associations between PTB and NO2 in a nested case-control study in northern California [14]. In South Korea, the interquartile increase in SO2 concentration was associated with a 7% increase in TB incidence in males [15]. In China, it has also been suggested that air quality is related to TB prevalence based on a geographically weighted regression model for the exploration of ecological factors [16].

All the regions of the world are affected by air pollution, but people in low-income countries are the most impacted. According to the latest global urban air pollution database from the WHO, 98% of cities in low- and middle-income countries with more than 100,000 inhabitants that monitored air pollution exceeded the WHO limits during 2008–2015 [9]. The levels of urban air pollution in low- and middle-income countries in the eastern Mediterranean and southeast Asia were highest in the world, with values five to ten times more than the WHO guidelines [17]. In more than two-thirds of the cities in these countries, air pollution levels increased more than 5% during the five-year period from 2008 to 2013. Due to the development of industrialization and rapidly growing number of transportation vehicles in China, air pollution caused by emissions of multiple pollutants and vehicle exhaust has become a major problem, threatening public health [18, 19]. To improve air quality levels, China has taken a series of actions to maintain the air pollution emission load within a permissible range, but the situation of air pollution with PM10, SO2, and NO2 is still very serious [20, 21].

Since the levels of air pollution and PTB incidence are high in developing countries, if air pollution is indeed associated with the rates of TB disease, then high air pollution concentrations in developing countries will impact efforts of TB control. There is not a clear understanding of whether high concentrations of certain (or if any) air pollutants are impacting the risk of PTB incidence in developing countries. Moreover, there are variable gender and age-related differences in the effects of air pollution on PTB. On the other hand, data related to air pollution and notifiable PTB cases are often collected over space and time. The association between air pollutants and PTB incidences may vary spatiotemporally, and the relation can differ depending on location (in the spatial domain) or temporal patterns (in the spatial-temporal domain).

However, most previous studies used traditional regression models to determine the relationships between PTB disease and air pollution, which do not account for any residual spatial-temporal variation in the outcome that is not already captured by the exposures [13–15, 22–24]. Bayesian models, which have been widely applied in recent years, can fully utilize the temporal and spatial information of data and prior knowledge [25, 26]. In this study, using data from the central Chinese province of Hubei for 2006 to 2015, we aimed to assess the impact of air pollutants (SO2, NO2 and PM10) the only three air pollutants monitored by the Department of Hubei...
Environmental protection before 2012) on PTB incidence by Bayesian approaches that included spatial and temporal random effects.

Methods

Study area
Hubei Province is located between longitudes 108°21’ and 116°07’ east and latitudes 29°05’ and 33°20’ north in Central China, with a total area of 185,900 km² and a population of 58.16 million in 2015. Hubei Province is divided into 17 prefectures: 1 sub-provincial level city, 11 prefecture-level cities, 4 prefectures and 1 autonomous prefecture.

PTB incidence
Data, including the demographic information (e.g., gender, age, and address) from PTB case notifications, were available from the Hubei Centre for Disease Prevention and Control (CDC) through the Chinese information system for disease control and prevention. PTB cases were diagnosed using X-ray, pathogen detection, and pathological diagnosis, according to the diagnosis criteria recommended by the National Health and Family Planning Commission of the People’s Republic of China for the period from Jan 1, 2006, to Dec 31, 2015. Annual and monthly numbers of pulmonary TB case notifications in each city were retrieved from the system. PTB incidences were calculated as the number of PTB cases divided by the annual average population. Since the PTB data were secondary and properly anonymized and informed consent was obtained by the CDC at the time of data collection, ethical approval was not required.

Air pollutant exposure
Measurements of ambient air pollutant concentrations in 17 prefectures were obtained from the Hubei Environmental Monitoring Networks, which consisted of monitoring stations with the numbers from 17 in 2006 to 58 in 2015, scattered in each city and maintained by the Department of Hubei Environmental Protection. Each station provided daily concentrations of PM₁₀, NO₂, and SO₂ from 24-h continuous monitoring. The monitoring behaviour and data quality were evaluated and supervised each year, according to the Hubei Environmental Monitoring Quality Control Assessment Program. In the present study, for PM₁₀, NO₂, and SO₂, air pollutant exposure was defined as the yearly and monthly average of the 24-h measurements over all the monitors within the 17 cities in the entire study period.

Socioeconomic covariates
The socioeconomic covariates that were considered potential confounding factors in our analyses included the population density, proportion of the elderly population, per capita disposable income, per capita housing area, per capita Engel coefficient, per capita tobacco consumption, number of health technicians per thousand individuals, average temperature and humidity, and HIV incidence at the city level. The data were obtained from a Hubei population-based information sharing platform, Hubei Statistical Yearbook, the Hubei Tobacco Monopoly Bureau, and the Chinese information system for disease control and prevention.

Statistical analyses
Bayesian approaches use information from samples and prior distributions to estimate posterior distribution parameters, which can be done by using a Markov chain Monte Carlo (MCMC). Here, denote yᵢₜ and nᵢₜ as the number of TB cases and the population in city i at time t, respectively, for i = 1, ..., m cities and t = 1, ..., T years or months. Then, yᵢₜ ~ Poisson (Eᵢₜθᵢₜ), Eᵢₜ = nᵢₜνᵢₜ yᵢₜ/Σᵢₜ nᵢₜ, where Eᵢₜ is the expected number of TB cases and θᵢₜ is the relative risk (RR) of PTB in city i at time t. The Bayesian spatial-temporal regression models were constructed by a Poisson model with a log link, and the best fitting model was selected to quantify the associations between air pollutants and pulmonary TB incidence. Accounting for collinearity or potential interactions between the variables, all the socioeconomic covariates were entered into the linear regression model as potential confounders and were screened with backwards elimination and a 10% change-in-estimate criterion by the stepwise method. The covariates were then entered into the Bayesian models for further analysis.

We constructed four Bayesian models with socioeconomic covariates. The first Bayesian model was a non-spatial model, built as: log (θᵢₜ) = β₀ + βₖXᵢₜ + μᵢ. In this model, Xᵢₜ is the independent variable in city i at time t and includes the concentrations of ambient air pollutants and socioeconomic covariates. β₀ represents the intercept of all the cities and times with a flat distribution (β₀ ~ dflat()), βₖ represents the coefficients of the parameters, assigned as non-informative normal priors (βₖ ~ normal (0, 100)), and μᵢ is a non-spatially structured random effect caused by other non-spatial factors, following a normally distributed prior with a zero mean and precision equal to 0.001. The second model was a spatial model, which considered non-spatial and spatial random effects: log (θᵢₜ) = β₀ + βₖXᵢₜ + μᵢ + νᵢ. In this model, νᵢ is a random effect that is spatially structured by prefecture to account for spatial autocorrelation, which was assumed to be a conditionally autoregressive (CAR) prior, in which the weights were derived from an adjacency-based first-order spatial proximity matrix. A uniform prior was specified for νᵢ (νᵢ ~ normal (0, σᵣ²)), where σᵣ² is the variance of νᵢ. The third model was a
spatiotemporal model, which included nonspatial, spatial and temporal random effects: $\log(\theta_t) = \beta_0 + \beta_k X_{it} + \mu_t + \nu_t + g_t$. Here, $g_t$ is explained as the temporal variations, considering the spatial effects to be independent at different times, following an autoregressive (AR) prior with a normal distribution ($g_t \sim \text{normal}(0, \sigma^2_g)$), where $\sigma^2_g$ is the variance of $g_t$. The fourth model was a spatiotemporal interactive model, in which the spatiotemporal interactive effects were added to the spatiotemporal model, resulting in the form $\log(\theta_{it}) = \beta_0 + \beta_k X_{it} + \mu_t + \nu_t + g_t + \psi_{it}$. In this equation, $\psi_{it}$ is a spatial-temporal interaction effect, assuming random spatial effects in each time as a conditionally autoregressive process, with the non-informative prior $\psi_{it} \sim \text{normal}(0, 1000)$. The model with the smallest deviance information criterion (DIC) value was considered the most appropriate model. Additionally, to explore the lag response relationship of ambient air pollutants on regional TB incidence, we also analysed the lag elapses in various months by the Bayes action effect, assuming random spatial effects in each active model among the four Bayesian models. There- further analysis.

Table 2 shows the deviance information criterion (DIC) value was lowest in the spatial-temporal inter-
active model among the four Bayesian models. Therefore, the spatiotemporal interactive model was used for further analysis.

Table 4 shows the estimated RR and 95% confidence intervals (CIs) based on the spatiotemporal interactive model, adjusting for socioeconomic covariates. Every 10 $\mu g/m^3$ increase in SO$_2$ concentration increases the risk of regional TB incidence by 4.6% (RR = 1.046; 95% CI, 1.038–1.054). However, PM$_{10}$ and NO$_2$ were not significantly associated with regional PTB case notifications. When the model analysis was stratified by gender, positive associations were observed among females, with a 1.0, 2.0 and 1.5% increase in the risk of regional PTB for every 10 $\mu g/m^3$ increase in PM$_{10}$, SO$_2$ and NO$_2$, respectively. Among males, positive associations were found only for SO$_2$, with a 5.4% increase in the risk of PTB for each 10 $\mu g/m^3$ increase. To test whether associations of air pollutants and regional PTB differed by age, the analysis was also stratified into three age groups (<15, 15–59 and ≥60 years). The results showed that PM$_{10}$ was positively associated with regional PTB only in children under 15 years of age (RR = 1.018; 95% CI, 1.007–1.030). Positive associations were also observed for SO$_2$, with a 2.2, 6.4 and 1.8% increase in the PTB risk of individuals <15, 15–59 and ≥60 years old, respectively. However, the observed increased risk was not statistically significant for NO$_2$.

### Results

During the study period, there were 91,83 total average PTB case notifications per 100,000 individuals, decreasing from 108.23 per 100,000 individuals in 2006 to 78.14 per 100,000 individuals in 2015 (Table 1). The risk of PTB increased with age, with the lowest PTB incidence in children under 14 years old. From a gender perspective, rates of reported PTB incidence were lower for women in all the age groups, with an average male-to-female sex ratio of 2.08 (Fig. 1). The total average concentrations of the air pollutants (PM$_{10}$, SO$_2$ and NO$_2$) were 90.7, 30.4 and 25.2 $\mu g/m^3$, respectively (Table 2). Of these, the annual averages of PM$_{10}$ were higher than the current Ambient Air Quality Standard of China [27]. A moderate rise in the annual concentrations of PM$_{10}$ and NO$_2$ was found; the mean values of PM$_{10}$ increased from 93 in 2006 to 99 $\mu g/m^3$ in 2015, and the mean values of NO$_2$ increased from 20 in 2006 to 28 $\mu g/m^3$ in 2015. There was a relatively steady decline in the annual concentrations of SO$_2$, from 33 in 2006 to 18 $\mu g/m^3$ in 2015 (Fig. 2). To visualize the spatial-temporal trends, we plotted the spatial distributions of the air pollutants and PTB incidence among the 17 prefectures in Hubei Province (Fig. 3).

Table 3 shows that the deviance information criterion (DIC) value was lowest in the spatial-temporal interactive model among the four Bayesian models. Therefore, the spatiotemporal interactive model was used for further analysis.

Table 4 shows the estimated RR and 95% confidence intervals (CIs) based on the spatiotemporal interactive model, adjusting for socioeconomic covariates. Every 10 $\mu g/m^3$ increase in SO$_2$ concentration increases the risk of regional PTB incidence by 4.6% (RR = 1.046; 95% CI, 1.038–1.054). However, PM$_{10}$ and NO$_2$ were not significantly associated with regional PTB case notifications. When the model analysis was stratified by gender, positive associations were observed among females, with a 1.0, 2.0 and 1.5% increase in the risk of regional PTB for every 10 $\mu g/m^3$ increase in PM$_{10}$, SO$_2$ and NO$_2$, respectively. Among males, positive associations were found only for SO$_2$, with a 5.4% increase in the risk of PTB for each 10 $\mu g/m^3$ increase. To test whether associations of air pollutants and regional PTB differed by age, the analysis was also stratified into three age groups (<15, 15–59 and ≥60 years). The results showed that PM$_{10}$ was positively associated with regional PTB only in children under 15 years of age (RR = 1.018; 95% CI, 1.007–1.030). Positive associations were also observed for SO$_2$, with a 2.2, 6.4 and 1.8% increase in the PTB risk of individuals <15, 15–59 and ≥60 years old, respectively. However, the observed increased risk was not statistically significant for NO$_2$.

### Table 1: Demographic characteristic of PTB incidence (per 100,000 population) in Hubei Province, 2006–2015

| Age  | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Total |
|------|------|------|------|------|------|------|------|------|------|------|-------|
| 0- year | 6.50 | 5.30 | 4.42 | 3.84 | 3.56 | 4.13 | 4.63 | 4.01 | 4.05 | 4.41 | 4.52 |
| 15- year | 115.84 | 112.35 | 106.83 | 91.12 | 86.62 | 89.32 | 89.43 | 84.02 | 78.18 | 71.21 | 93.09 |
| 30- year | 108.62 | 103.83 | 95.12 | 78.79 | 73.89 | 71.88 | 73.69 | 70.87 | 67.77 | 64.27 | 81.88 |
| 45- year | 179.63 | 186.59 | 173.28 | 131.11 | 120.07 | 122.80 | 111.89 | 103.90 | 99.71 | 98.29 | 128.78 |
| 60- year | 326.75 | 339.31 | 305.74 | 225.42 | 213.81 | 199.83 | 200.51 | 188.56 | 184.75 | 190.92 | 231.90 |
| 75- year | 234.92 | 281.80 | 293.64 | 219.31 | 192.80 | 179.88 | 166.51 | 158.47 | 146.27 | 150.27 | 192.70 |

| Sex   | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Total |
|-------|------|------|------|------|------|------|------|------|------|------|-------|
| Male  | 142.28 | 148.18 | 141.33 | 120.28 | 113.61 | 118.75 | 119.24 | 112.53 | 107.72 | 106.14 | 122.96 |
| Female | 72.60 | 73.54 | 70.89 | 58.62 | 53.41 | 55.71 | 54.29 | 52.21 | 50.11 | 49.11 | 58.98 |
| Total  | 108.23 | 112.43 | 107.55 | 90.70 | 84.75 | 88.11 | 87.67 | 83.14 | 79.58 | 78.14 | 91.83 |
Figure 4 shows the lag associations between the ambient air pollutant concentrations and regional PTB based on the spatial-temporal interactive model, adjusting for socioeconomic covariates. We observed a significant response relationship, with a 0–1 month moving average lag for each 10 μg/m$^3$ increase in SO$_2$. However, no significant associations were observed in PM$_{10}$ and NO$_2$.

**Discussion**

Previously, the relationships between air pollutants and TB were explored by many traditional methods, including linear models, conditional logistic regression models, Poisson regression models and hierarchical Bayesian methods [14–16, 21, 28]. However, few studies have considered spatial or spatial-temporal interactive effects at the population level. Considering the goodness of fit based on the DIC value, we adopted a Bayesian spatial-temporal interactive model in our study. This model could identify spatial differences and solve problems such as spatial autocorrelation, which is difficult for most traditional statistical methods. Hubei Province is one of the most serious tuberculosis epidemic areas in China. The rates of PTB incidence as well as the annual air pollutant concentrations of PM$_{10}$, SO$_2$ and NO$_2$ in our study are higher than those in developed countries [4, 20, 21]. Our findings showed that SO$_2$ was positively associated with PTB incidence, with a 4.6% increase in PTB incidence rates per 10 μg/m$^3$ increase in SO$_2$. When stratified by gender, positive associations were noted with exposure to all three air pollutants in females but only to SO$_2$ in males. When stratified by age, positive associations were observed for SO$_2$ in all the age groups and for PM$_{10}$ only in children under 15 years. Moreover, a significant lag response relationship was also found, with a lag of 0–1 month for SO$_2$.

In our study, the risk of PTB was not significantly associated with exposure to PM$_{10}$. We noticed that in previous experimental studies, exposure to PM$_{10}$ was found to enhance intracellular *Mycobacterium tuberculosis* growth by inducing senescence and downregulating the expression of the antimicrobial peptides human β-defensin2 (HBD-2) and HBD-3, which are important in the early control of TB infection [29, 30]. However, experimental studies cannot reflect the actual association between ambient PM$_{10}$ and TB incidence at the population level. Although one previous epidemiological study in North Carolina found that exposure to particulate air pollution increased the risk of TB during 1993–2007 [13], the study was based on Poisson regression models with low ambient PM$_{10}$ levels (19.39–24.63 μg/m$^3$) as

![Fig. 1 Total PTB incidence by gender and age in Hubei Province, China](image)

**Table 2** Annual ambient air pollutant concentrations of 17 cities in Hubei Province, China, 2006–2015

| Pollutant | Mean | SD  | Min  | 5%  | Median | 95%  | Max  | IQR  |
|-----------|------|-----|------|-----|--------|------|------|------|
| PM$_{10}$ (μg/m$^3$) | 90.7 | 20.0 | 31.0 | 44.1 | 93.5   | 117.8| 150.0| 24.0 |
| SO$_2$ (μg/m$^3$)  | 30.4 | 15.3 | 8.0  | 11.6 | 29.0   | 56.9 | 95.0 | 19.0 |
| NO$_2$ (μg/m$^3$)  | 25.2 | 12.1 | 3.0  | 9.0  | 23.0   | 54.0 | 60.0 | 16.0 |

Ambient air quality standards set by Ministry of Ecology and Environment of the people’s Republic of China [27]

PM$_{10}$ ≤ 70 μg/m$^3$ (annual), NO$_2$ ≤ 40 μg/m$^3$ (annual), SO$_2$ ≤ 60 μg/m$^3$ (annual)

PM$_{10}$: particulate matter with aerodynamic diameter of ≤10 μm; SO$_2$: sulfur dioxide; NO$_2$: nitrogen dioxide; SD: standard deviation; Min: minimum; Max: maximum; 5%, IQR: interquartile range.
well as a low rate of PTB disease incidence (4.41 per 100,000 persons/year); in contrast, in our research, there were high levels of air pollutant concentrations and PTB incidence. However, most recent epidemiologic studies have found no significant associations between PM$_{10}$ and TB, which is consistent with our results [13–15]. To elucidate the possible associations between PM$_{10}$ and PTB, more research needs to be done in the future.

The associations observed for SO$_2$ were significantly positive, similar to the findings of other studies. Shilova and Glumnaia found that atmospheric pollutants (including SO$_2$) were significantly associated with TB incidence in Russia [31]. Hwang et al. reported that the interquartile increase in the SO$_2$ concentration in outdoor air pollutants could result in a 7% increase in TB incidence in South Korea [15]. The reason for this association may be attributed to the effect of exposure to SO$_2$ on pulmonary defences. A previous study showed that a 30-min exposure to 12.5 ppm SO$_2$ induced 62% death of alveolar macrophages and led to a decrease of 63% in the release of reactive oxygen species, which are crucial for inhibiting or killing *Mycobacteria tuberculosis* [32]. The researchers also found that exposure to SO$_2$ caused a significant decrease in the production or release of TNF-$\alpha$ and interleukin-1, which can defend against *Mycobacterium tuberculosis* by regulating the activity of other cytokines and chemokines in early TB infections [27, 33]. Using TNF-neutralizing therapies increases the risk of developing tuberculosis and induces frequent reactivation of latent TB in patients [34–36]. However, compared with other studies, the effect size of SO$_2$ in our study seems very small. For example, the interquartile range (IQR = 0.3 ppb) increase in SO$_2$ concentration was associated with a 7% increase in TB incidence rate in South Korea, but only a 4.6% increase in TB incidence rates per 10 $\mu$g/m$^3$ increase in SO$_2$ concentration was observed in our study. There may be several reasons for these findings. First, the average SO$_2$ concentrations and IQRs in our study were higher than those in other studies, which caused a smaller variation with the same scale change in concentrations. Second, a higher TB incidence may result in a smaller change in the TB incidence rate ratio if the effect caused the same change size in TB incidence. Third, some potential confounders, which influenced regional TB epidemiology [37], may disturb the effect of SO$_2$, and no adjustments were made for this disturbance in the previous study.

No association was observed between NO$_2$ and PTB, consistent with the findings of some studies. After exploring the impact of outdoor air pollution on TB in South Korea, researchers found that the concentrations of ambient NO$_2$ were not associated with TB incidence [15]. Another study also showed no significant association between the daily initial TB outpatient visits and daily average concentration of NO$_2$ [38]. However, a recent nested case–control study in northern California found a positive association between TB and NO$_2$ [14]. One thing to note is that the study in northern California assessed average individual-level concentrations of NO$_2$ for only 2 years before the diagnosis of TB; the
individual-level exposure depending on only outdoor concentrations may be altered by smoking or using gas appliances indoors.

To investigate the sex-specific associations between air pollution and PTB, the analysis was stratified by gender. Positive relationships were observed for PM$_{10}$ and NO$_2$ in females but not in males. This result suggested that the effects of PM$_{10}$ and NO$_2$ on PTB may differ by gender. Other epidemiological studies also found that the effects of air pollutants on respiratory health are much more marked in females [39]. Clougherty et al. also found that increased impact of air pollution on respiratory health in females was linked to their social or behavioural and biological differences [40]. The reason may be that some sex-linked traits impact the biological transport of environmental chemicals, while gender-linked activities (i.e., where and what people spend time doing) determine the distribution of air pollution exposure. The biological sex of females leads to the inhalation of more doses of air pollution, greater deposition and absorption of air pollution and higher gas–blood barrier permeability in the respiratory tract [41, 42]. Another important reason for the sex-specific associations between air pollution and PTB may be related to a prominent feature of smoking habits in China and the substantial male/female difference in the rates of smoking. For example, a recent nationally representative survey showed that the male/female ratio of smoking was 22 in 2010 [43]. The increased relative risk degree of PTB incidence by air pollution exposure may be obscured or weaken partially by heavy smoking in men. Further stratifying the analysis by age, we observed positive associations for PM$_{10}$ in individuals aged 0–14 years but not in those aged 15 years or older. Evidence from epidemiological studies also found that the effects of air pollution on respiratory health in females was linked to their social or behavioural and biological differences [40].

Table 3 The deviance information criterion (DIC) for Bayesian models

| Bayesian Model               | DIC    |
|-----------------------------|--------|
| Non-spatial model           | 22,983.2|
| Spatial model               | 22,144.5|
| Spatial-temporal model      | 19,501.5|
| Spatial-temporal interactive model | 1887.6 |

Fig. 3 Spatial distributions of air pollutants and pulmonary TB incidence in Hubei Province, 2006–2015
Table 4 Every 10 μg/m³ increase in ambient air pollutant concentration on PTB incidence by spatial-temporal interactive model

|            | PM₁₀ | SO₂  | NO₂  |
|------------|------|------|------|
| All        | 1.002| 1.046| 1.008|
|            | 95% CI| 95% CI| 95% CI|
|            | 0.988–1.019| 1.038–1.054| 0.986–1.028|
| Stratified by gender | | | |
| Male       | 0.994| 1.054| 0.998|
|            | 95% CI| 95% CI| 95% CI|
|            | 0.971–1.017| 1.045–1.063| 0.981–1.016|
| Female     | 1.010| 1.020| 1.015|
|            | 95% CI| 95% CI| 95% CI|
|            | 1.002–1.017| 1.017–1.023| 1.006–1.025|
| Stratified by age | | | |
| < 15 years | 1.018| 1.022| 0.998|
|            | 95% CI| 95% CI| 95% CI|
|            | 1.007–1.030| 1.008–1.036| 0.979–1.019|
| 15–59 years| 0.988| 1.064| 1.010|
|            | 95% CI| 95% CI| 95% CI|
|            | 0.964–1.011| 1.050–1.078| 0.989–1.022|
| ≥ 60 years | 1.006| 1.018| 1.005|
|            | 95% CI| 95% CI| 95% CI|
|            | 0.993–1.035| 1.010–1.027| 0.980–1.031|

Abbreviations: CI Credible interval; PTB Pulmonary tuberculosis; PM₁₀ Particulate matter with aerodynamic diameter of ≤10 μm; SO₂ Sulfur dioxide; NO₂ Nitrogen dioxide; RR Relative risk

Fig. 4 The RRs and 95% CIs of a 10 μg/m³ increase in ambient air pollutants on PTB at different lag months by spatial-temporal interactive model in Hubei Province. RR, relative risk; CI, credible interval; PTB, pulmonary tuberculosis; PM₁₀, particulate matter with aerodynamic diameter of ≤10 μm; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; IRR, incidence rate ratio
pollution on respiratory health are much more marked in children [44–46]. This may be due to the differences in breathing pattern and lung structure between children and adults. The dose of air pollutants deposited in the respiratory systems of children is higher than that of adults if they are exposed to the same levels of air pollutants [47, 48]. By spending more time on activities outdoors, children also increased their ventilation rates and exposure to air pollutants [49]. Therefore, we supposed that the gender- and age-related effects of air pollutants on pulmonary TB in our study may be due to some interplay between the above mentioned factors.

As with any statistical modelling study, our study also has some limitations. First, despite the biologic plausibility of a possible association between air pollutants and PTB, our results should be interpreted cautiously, with the inherent limitations of an ecological study design that used population-level data. Second, some key potential confounders to the relationship between air pollution and regional PTB, including household air pollution from the burning of solid fuel and more detailed information on smoking, should be accounted for in future investigations, although city-level tobacco consumption data were collected. Third, exposure to ambient PM\textsubscript{2.5} is arguably an equally relevant indicator of air pollution exposure, but is not included given the unavailability of PM\textsubscript{2.5} estimates from the Hubei monitoring network before 2012. Last but not least, due to the implementation of the Chinese TB control project and policy shifts, there are also potential issues with the identification of TB, including changes in active TB screening, access to or use of TB treatment, case registration report rate, and others. Future epidemiological cohort studies are needed for the assessment of cause-specific TB disease, especially in females and young people.

Conclusions

This study shows that long-term exposure to high ambient air pollutant concentrations in areas of developing countries increased the risk of regional PTB, especially for women and young people. Precautions and protective measures and efforts to reduce ambient air pollutant concentrations should be strengthened in developing countries.

Abbreviations

CDC: Centre for disease prevention and control; CI: Credible interval; DIC: Deviance information criterion; HIV: Human immunodeficiency virus; RR: Relative risk; NO\textsubscript{2}: Nitrogen dioxide; PM\textsubscript{10}: Particulate matter with aerodynamic diameter of ≤ 10 μm; PTB: Pulmonary tuberculosis; SO\textsubscript{2}: Sulfur dioxide; TB: Tuberculosis

Acknowledgements

We would like to thank Hubei Centre for Disease Prevention and Control for the information they have collected, which made the study possible.

Authors’ contributions

FL designed the study and drafted the initial manuscript. FL and ZZ collected and analyzed the data. SN and HC contributed to the interpretation of the results and critical revision of the manuscript and approved the final version of the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by grants from the Health and Family Planning Scientific Research Project of Hubei Province (WJ2016JT-002).

Availability of data and materials

The data can be accessed from the Hubei CDC and Department of Hubei Environmental Protection with permission via direct request.

Ethics approval and consent to participate

Data from Department of Hubei Environmental Protection, Population-based Information Sharing Platform and Statistical Yearbook are publicly available. Data of PTB and HIV were secondary without any personal information, which properly anonymized and informed consent was obtained by the Hubei CDC at the time of original data collection. We confirm that no member of our research team named in the author list of the paper had access to identifying patient information when analyzing the data. Our exemption from approval has been granted by Ethics Committee of Huazhong University of Science and Technology.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

1Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430000, Hubei, People’s Republic of China. 2Wuchang University of Technology, Wuhan 430000, Hubei, People’s Republic of China. 3Hubei Centre for Disease Prevention and Control, Wuhan 430000, Hubei, People’s Republic of China.

Received: 21 August 2019 Accepted: 24 April 2020

Published online: 14 May 2020

References

1. Comas I, Coscolla M, Luo T. Out-of-Africa migration and Neolithic coexpansion of mycobacterium tuberculosis with modern humans. Nat Genet 2013;45:1176–1182. https://doi.org/https://doi.org/10.1038/ng.2744.
2. Dheda K, Barry CE, Maartens G. Tuberculosis. Lancet. 2016;387:1211–1226. https://doi.org/https://doi.org/10.1016/S0140-6736(15)00151-8.
3. Ortblad KE, Lozano R, Murray CJ. The burden of HIV: insights from the global burden of disease study 2010. AIDS. 2013;27:2003–17.
4. World Health Organization. Global Tuberculosis Report 2015. Geneva; 2015. http://www.who.int/tb/publications/global_report/en/.
5. World Health Organization. Global Tuberculosis Report 2017. Geneva; 2017. http://www.who.int/tb/publications/global_report/en/.
6. Bei C, Fu M, Zhang Y, et al. Mortality and associated factors of patients with extensive drug-resistant tuberculosis: an emerging public health crisis in China. BMC Infect Dis 2018;18(1):261. https://doi.org/https://doi.org/10.1186/s12879-018-2617-y.
7. Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990–2010: a longitudinal analysis of national survey data. Lancet. 2014;383:2057–2064. https://doi.org/https://doi.org/10.1016/S0140-6736(13)62639-2 (2014).
8. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006;367:174–1757.
9. World Health Organization. WHO Global Urban Ambient Air Pollution Database (update 2016). 2018. http://www.who.int/peh/health_topics/outdoorair/databases/cities/en/.
10. World Health Organization. WHO Report 2010. Geneva: Global Tuberculosis Control 2010, 2010.
11. Freemond C, Allie N, Dambua i, et al. Membrane TNF confers protection to acute mycobacterial infection. Respir Res 2005;6:136. https://doi.org/10.1186/1465-9921-6-136.

12. Hirai-Matsui K, Saito Y, Sakakibara K, et al. The effects of inhalation of diesel exhaust on murine mycobacterial infection. Exp Lung Res. 2005;31:405–15.

13. Smith GS, Schoenbach VJ, Richardson DB, Gammon MD. Particulate air pollution and susceptibility to the development of pulmonary tuberculosis in North Carolina: an ecological study. Int J Environ Res Public Health 2014; 24:103–112. https://doi.org/10.3390/ijerph12031209.380599.

14. Smith GS, Van Den Eeden SK, Garcia C, et al. Air pollution and pulmonary tuberculosis: a nested case-control study among members of a northern California health plan. Environ Health Perspect 2016;124:761–767. https://doi.org/10.1289/ehp.1408166.

15. Hwang SS, Kang S, Lee JY, et al. Impact of outdoor air pollution on the incidence of tuberculosis in the Seoul metropolitan area, South Korea. Korean J Intern Med 2014;29:183–190. https://doi.org/10.3904/kjm.2014.29.2.183.

16. Sun W, Gong J, Zhou J, et al. A spatial, social and environmental study of tuberculosis in China using statistical and GIS technology. Int J Environ Res Public Health 2015;12:1452–1448. https://doi.org/10.3390/ijerph12061452.

17. United Nations. UN health agency warns of rise in urban air pollution. 2016. https://www.un.org/sustainabledevelopment/blog/2016/05/un-health-agency-warns-of-rise-in-urban-air-pollution-with-poorest-cities-most-at-risk/.

18. Wang H, Zhang Y, Zhao H, et al. Trade-driven relocation of air pollution and health impacts in China. Nat Commun 2017;8:1738. https://doi.org/10.1038/s41467-017-00918-5.

19. Kan H, Chen B, Hong C. Health impact of outdoor air pollution in China: current knowledge and future research needs. Environ Health Perspect 2009;117:1A187. https://doi.org/10.1289/ehp.12737.

20. Song C, Wu L, Xia Y, et al. Air pollution in China: status and spatiotemporal variations. Environ Pollut 2017;227:334–347. https://doi.org/10.1016/j.envpol.2017.04.075.

21. Jin Y, Andersson H, Zhang S. Air pollution control policies in China: a retrospective and prospective. Int J Environ Res Public Health 2016;13:1219. https://doi.org/10.3390/ijerph13011219.

22. Peng Z, Liu C, Xu B, Kan H, Wang W. Long-term exposure to ambient air pollution and mortality in a Chinese tuberculosis cohort. Sci Total Environ 2017;580:1483–1488. https://doi.org/10.1016/j.scitotenv.2016.12.128.

23. Garcia-Sancho MC, Garcia-Garcia L, Baez-Saldana R, et al. Indoor pollution as an occupational risk factor for tuberculosis among women: a population-based, gender oriented, case-control study in southern Mexico. Rev Invest Clin. 2009;61(5):392–8.

24. Lin HH, Enatti M, Murray M, Tobacoo smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med 2007;4(10): e20. https://doi.org/10.1371/journal.pmed.0040020.

25. Liu Y, Wang X, Pang C, et al. Spatio-temporal analysis of the relationship between climate and human, food, and mouth disease in Shandong province, China, 2008-2012. BMC Infect Dis 2015;15:146. https://doi.org/10.1186/s12879-015-0901-4.

26. Hossain MM, Lawerson AB. Space-time Bayesian small area disease risk models development and evaluation with a focus on cluster detection. Environ Ecol Stat 2010;17:73–95. https://doi.org/10.1007/s10651-008-0102-2.

27. Ministry of Ecology and Environment of the people’s Republic of China (MEE). Ambient air quality standards. 2012. http://gks.mep.gov.cn/hjbhbz/s10651-008-0102-z.

28. Mohan VP, Scanga CA, Yu K, et al. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. Infect Immun 2001;69(3):1847–1855. https://doi.org/10.1128/IAI.69.3.1847-1855.2001.

29. Keane J. TNF-blocking agents and tuberculosis: new drugs illuminate an old topic. Rheumatology (Oxford) 2005;44(7):714–720. https://doi.org/10.1093/rheumatology/keh167.

30. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098–104.

31. Millet JP, Moreno A, Fina L, et al. Factors that influence current tuberculosis epidemiology. Eur Spine J 2013; 4:539–548. https://doi.org/10.1007/s00586-012-2334-8.

32. Ge E, Fan M, Qu H, et al. Ambient sulfur dioxide levels associated with reduced risk of initial outpatient visits for tuberculosis: a population based time series analysis. Environ Pollut 2017;228:408–15.

33. Rumchev K, Spickett JT, Brown HL, Mkhwebi B. Indoor air pollution from biomass combustion and respiratory symptoms of women and children in a Zimbabwean village. Indoor Air 2007;17:468–474. https://doi.org/10.1111/j.1600-0668.2007.0094x.

34. Clougherty JE. A growing role for gender analysis in air pollution epidemiology. Environ Health Perspect 2010;118:167–176. https://doi.org/10.1289/ehp.0909994.

35. Brauner EV, Motersen J, Moller F, et al. Effects of ambient air particulate exposure on blood-gas barrier permeability and lung function. Inhaled Toxicol 2009;21(1):38–47. https://doi.org/10.1080/0895837080234735.

36. Jones AY, Lam PK. End-expiratory carbon monoxide levels in healthy subjects living in a densely populated urban environment. Sci Total Environ 2006;354:150–156. https://doi.org/10.1016/j.scitotenv.2005.02.018.

37. Li Q, Hsa J, Yang G. Prevalence of smoking in 2010. NEJM. 2011; 364:269–70.

38. Sacks JD, Rappold AG, Davis JA, et al. Influence of urbanicity and county characteristics on the association between ozone and asthma emergency department visits in North Carolina. Environ Health Perspect 2014;122:506–512. https://doi.org/10.1289/ehp.1306940.

39. Schuepp K, SIl PD. The developing respiratory tract and its specific needs in limiting pathology. Infect Immun 2001;69(3):1847–1855. https://doi.org/10.1128/IAI.69.3.1847-1855.2001.

40. Moya J, Bearer CF, Etzel RA. Children’s behavior and physiology and how it affects exposure to environmental contaminants. Pediatrics. 2004;113:996–1006.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.