Effect of ambient air pollution on tuberculosis risks and mortality in Shandong, China: A multi-city modelling study of the short- and long-term effects of pollutants

Yao Liu [a,1], Shi Zhao[b,c,1],Yifan Li[a], Wanmei Song[a], Qianyun Zhang[a], Lei Gao[d], Lili Su[a], Fei Long[a], Li Xu[a], Bin Liang[a], Xiaobin Ma[a], Ran Jinjun[f], Daihai He[b*] & Huaichen Li[a,e*]

Institution of authors:

a. Department of Respiratory Medicine, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China

b. Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong SAR, China

c. School of Nursing, Hong Kong Polytechnic University, Hong Kong SAR, China

d. NHC Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, and Center for Tuberculosis Research, Chinese Academy of Medical Sciences and Peking Union Medical College, 100730 Beijing, China.

e. Shandong University of Chinese Traditional Medicine, Jinan, Shandong, China

f. School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, China

1. These authors contributed equally to this work and should be considered as co-first authors.

Conflict of Interests:
All authors declare they have no actual or potential competing financial interest .

*Correspondence to: lihuaichen@163.com (H.L.) and daihai.he@polyu.edu.hk (D.H.)

Corresponding authors at: Huaichen Li: Department of Respiratory Medicine, Shandong Provincial Hospital Affiliated to Shandong University, No. 324 Jingwuweiqi Road, Jinan 250021, Shandong, China.

He Daihai: Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong SAR, China

ABSTRACT

Background: Few studies conducted in China have assessed the effects of ambient air pollution exposure on tuberculosis (TB) risk and mortality, especially with a multicity setting.

Objective: We evaluated the effect of short and long term ambient sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), and particulate matter$\leqslant$2.5 μm in aerodynamic diameter ($PM_{2.5}$) exposures on development and mortality of active TB in 7 Chinese cities in Shandong province from January 1, 2013 to December 31, 2017

Methods: We estimated the pollution-associated risk to new infection TB, recurrent TB and mortality in relation to 1μg/m^3 increases in air pollutants using the penalized multi-variate Poisson regression models.

Results: A total of 83,555 new infection TB and 3,060 recurrent TB including 997 deaths were recorded. Short and long term exposure to outdoor air pollutants (SO_2, NO_2, CO, O_3, and $PM_{2.5}$) was significantly associated with new infection TB, recurrent TB risk, and mortality. The dominant positive effects of SO_2, NO_2, CO, and $PM_{2.5}$ for new infection and recurrent TB risk was observed at long term (>30 days) exposure, whereas the dominant effects SO_2, CO, and $PM_{2.5}$ for mortality was observed at short term (≤30 days) exposures. Of the 5 air pollutants we assessed, SO_2, and $PM_{2.5}$ exhibited more consistently and strongly associations with TB related outcomes. We estimated an increase of 1.33% (95% CI: 1.29%, 1.37%), and 3.04% (95% CI: 2.98%, 3.11%) in new infection TB count for each 1μg/m^3 increase of SO_2 at lag 0–180 days, and $PM_{2.5}$ at lag 0–365 days, respectively.

Conclusions: This epidemiologic study in China shows that air pollution exposure is associated with increased risk of development of active TB and mortality. Control of ambient air pollution may benefit the control and decrease the mortality of TB disease.

***Keywords*:** Air pollution; Tuberculosis; Recurrent Tuberculosis; Mortality; China; Multi-city; Panelized regression.

1. Introduction

Despite improvements in recent years, tuberculosis (TB) remains a major infectious disease globally, and was the 9th leading cause of mortality worldwide, with the majority of which occur in the developing world (WHO, 2017). TB burden in China accounted for approximately 14% of the global total (WHO, 2016). Identification of potential risk factors for TB progression is necessary for reducing the disease burden, and smoking, diabetes, malnutrition, acquired immune deficiency syndrome (AIDS), and immunosuppressive treatment are well-known risk factors for TB progression (Lai et al., 2016; Lin et al., 2007; Lonnroth et al., 2009).

Air pollution is a substantial cause of morbidity and mortality worldwide. Numerous studies have reported the deleterious effects of air pollution on human health. Indoor air pollution, which primarily from biomass fuel combustion, was shown to be associated with TB disease in previous meta-analyses (Lin et al. 2007; Sumpter and Chandramohan 2013). Several ecologic and epidemiologic studies also suggests that ambient air pollution exposures may associated with the development of TB (Iwai et al. 2005; Smith et al. 2014; Tremblay 2007). Correlation was found between suspended particles in air and increased TB risk in previous ecologic studies (Iwai et al. 2005). However, present epidemiologic studies have provided inconsistent evidences linking outdoor air pollution to TB risks. For instance, several studies found significant associations between particulate matter$\leqslant$2.5 μm in aerodynamic diameter ($PM_{2.5}$) and positive TB status (Jassal et al., 2013; You et al., 2016). Whereas, other studies suggested no positive correlation between $PM_{2.5}$ and active TB (Lai et al., 2016; Smith et al., 2014, Hwang et al., 2014). In a nested case-control study, Smith et al (2014) showed that carbon monoxide (CO) and nitrogen dioxide (NO_2) were associated with increased risk of pulmonary TB. Another South Korea study reported that the interquartile increase in sulfur dioxide (SO_2) concentration but not CO, NO_2 or O_3, was associated with increased incidence of TB in males (Hwang et al., 2014). Whereas, a recent study conducted in Ningbo city in China reported negative correlation between ambient SO_2 exposure and daily TB patient visits.

The majority of previous studies were based on single city data (Popovic et al., 2019), and the generalizability of the findings was uncertain. Multicity studies were less prone to biases which might affect small studies and were believed to generate more stable results. In addition, most previous research were conducted in developed countries, and only limited data have been generated in China. In the view of the heterogeneities in population status, pollutant characteristics, and meteorological patterns between developed and developing countries, as well as the enormous TB disease burden in the latter, an urgent need for the multicity analysis about air pollution on the risk of active TB in China. Moreover, evidence for the association between ambient air pollution and the mortality of TB patients is limited. To our knowledge, up to now, only 1 study conducted in Shanghai city in China, has examined the effects of $PM_{2.5}$ exposure on TB mortality, which showed that long-term $PM_{2.5}$ exposure might increase the risk of death from TB and other diseases among TB patients (Peng et al., 2016). Further more comprehensive evaluation of ambient air pollution exposure and the mortality of TB is also needed.

The objectives of the present study were to present an extensive analysis of the effect of short and long term ambient SO_2, NO_2, CO, O_3 and $PM_{2.5}$ exposures on development and mortality of active TB, using data in 7 large Chinese cities in Shandong province from January 1, 2013 to December 31, 2017.We quantifies the associations between various air pollutants and new-infection TB, recurrent TB risks and mortality with a panelized regression approach.We also explore the spatial heterogeneities of the pollutants' effects on TB risks and mortality among 7 cities and compared the pollutant-associated risk rate by different sub-groups of population. Both short-term and long-term, instantaneously and cumulative lagged effects of air pollutants were studied.

2. Methods

2.1 Ethics

Ethics approval was obtained from the Ethics Committee of Shandong Provincial Hospital, affiliated with Shandong University, Shandong, China. Before analysis, patient records were anonymized and deidentified.

2.2 Study settings

Seven cities in Shandong Province were included in this study, including 6 inland cities Jinan, Weifang, Linyi, Jining, Liaocheng, and dezhou; and 1 coastal city Yantai (Fig. 1). Shandong peninsula located in the east of China, which is the third largest economic province and the second most populous province in China. Jinan, is the capital city of Shandong Province, with a resident population of approximately 7 million, and is 8,227 square kilometers. Weifang, Linyi, Jining, Liaocheng, dezhou and Yantai had 9.3, 11.2, 8.3, 6.0, 7.2 and 7.1 million residents, respectively. The 7 cities are more than half of the total population and area of Shandong Province and distributed in the eastern, western, southern, northern and central regions of Shandong Province. These cities have a typical temperate monsoon climate, with cold and dry winter, high temperature and rainy summer. The annual average temperature is 11-14 °C.

2.3 Study Population

Daily TB case reports in the 7 cities were obtained from the Shandong Provincial Center for Disease Control and Prevention (Shandong CDC) from January 1, 2013 to December 31, 2017. China implements an online national infectious disease reporting system “China National Notifiable Disease Surveillance System”. According to the national guidelines on TB control, active or suspected TB cases detected in any health facilities should be reported through the reporting system within 24 hour. The system recorded patient’s demographic data, home address, diagnosis, names of the hospital for TB diagnosis and treatment, initial outpatient visit date for TB related symptom, and so on using a standard case report form (Wang et al., 2010). TB cases in the Shandong CDC database were diagnosed by isolation of *Mycobacterium tuberculosis* (*M. tb*) or in the absence of bacteriological confirmation, TB diagnosis were made in the light of clinical, radiologic evidence, and/or histologic grounds together with anti-tuberculosis treatment (prescription for at least 2 anti-tuberculosis medications including isoniazid, rifampin, ethambutol, and pyrazinamide).

2.4 Mortality data

Death information were also obtained from the infectious disease reporting system in the Shandong CDC. The treatment outcomes including cure or end of treatment, treatment failure or incomplete, loss of follow-up, death, or others were reported and documented in the reporting system. The death refer to all cause death.

2.5 Air pollutant data.

Air pollutant data included SO_2, NO_2, CO, O_3 and $PM_{2.5}$ concentration, in each city of Shandong Province from January 1, 2013 to December 31, 2017 were obtained from the department of Ecological Environment of Shandong Province. Air pollutants concentration were measured at the air monitoring stations in each of the 7 cities: 17 stations in Jinan, 10 stations in Weifang, 8 stations in Linyi, 7 stations in Jining, 5 stations in Liaocheng, 6 stations in dezhou, and 11 stations in Yantai. There are 5-17 fixed-site air monitoring stations in each city, which dispersed throughout the metropolitan areas. For SO_2, NO_2, CO and $PM_{2.5}$, daily data were 24-hour averages, and daily maximum of 8-hourly running average was used for O_3. The Chinese government mandated extensive quality assurance and quality control programs at the monitoring stations in order to provide reliable and comparable real-time hourly air pollutants concentrations. The monitoring measurements have been shown to be able to reflect urban air pollution levels (Chen et al., 2012).

2.6 Meteorological data.

Daily weather information were collected from the China Meteorological Science Data Sharing Service Network for the period from January 1, 2013 to December 31, 2017. The information including daily average temperature, relative humidity, wind speed, and so on was downloaded.

2.7 Statistical analysis

The penalized regression model is adopted to estimate the risk effects of pollution variants on the tuberculosis (TB) incidence and mortality rates (Goeman et al., 2010; Tibshirani et al., 1996). We treat the daily counts of the TB following a Poisson process that depends on many factors including demographic data, weather and pollution factors, and other seasonal factors. We model this Poisson process as a penalized multivariate regression against the pollutant variables and other co-variates. We also include dummy variables to offset the heterogeneities of different cities and detrend the unmeasurable temporal patterns. The regression model is given in Eqn (1).

$$\mathbf{E}[Y_t|\tau] = \exp\left[\sum_i \beta_{i,\tau} X_{i,t,\tau} + \sum_j \alpha_{j,\tau} X_{j,t,\tau} + \text{covariates} + \theta\right], \tag{1}$$

where $\beta_i > 0$ for all is. The function $\mathbf{E}[\cdot]$ represents the expectation, and θ is the interception term. The term Y_t denotes the TB counts at time t, and term $X_{i,t}$ denotes the i-th independent pollutant variable (i.e., predictor) at time t. The index i denotes the factor that is penalized, e.g., pollution factors, by forcing the coefficient to be positive. The index j is for those free factors, e.g., temporal and spatial dummy, demographic, weather variables. Thus, the regression parameter α can be unconstrained. The term τ is the lag term. To explore the lagged effects of the pollutants, the models in Eqn (1) are fitted to three types of TB risks with various lag terms (τ).

Single-day lag effect estimates may underestimate the cumulative correlations between air pollution levels and TB outcomes, therefore, we use two types of the lag effects

- the instantaneously lag effect; and
- the cumulative lag effect, which is the effect of the past number of days.

In this work, we consider the lag terms to be ranged from 0 to 365 days. We estimated the overall effects from lag0, lag15, lag30, lag90, lag180, to lag365 for the instantaneously lag effect. And similarly, the effects from lag0-1, lag0-15, lag0-30, lag0-90, lag0-180, and lag0-365 in the cumulative lag model, respectively. For the instantaneously lag effect, the lagged meteorological data are used in the model. And for the cumulative lag effect, the averages of the meteorological data in the past number of days are used in model. For the regression parameters under restriction (βi), we force the effects of all pollutants to be positive except for the O_3, of which a free (i.e., no penalty) effect is implemented. The effect estimates were presented as the percentage change (mean and 95%CIs), i.e., the excess rate, in daily mortality for each 1 μg/m^3 increase of daily PM2.5 concentrations.

Since the regression framework is based on "Y~exp(βX)", the term [exp(β)-1]*100% is the change rate, also known as the excess risk, of "Y" (i.e., the TB incidence or mortality risk in this work) when there is one unit increase in "X" (i.e., one of the pollution factors). We also explore the relative risk (i.e., risk ratio, RR) between different groups of population. The population are divided according to the genders, age groups, and sputum smear tests. Age group was classified into two levels: 4-64 years and 65 years or above; sputum smear status was grouped into smear positive cases and smear negative cases. We estimation the RRs of each pollution variants to the TB risk of the new infection, recurrent, and death respectively.

We avoid to smooth the variable time series, and instead, we directly use raw data to fit the penalized regression model. Therefore, the models could be noisy so that it may be difficult to provide apparent shape of curve of the effect (β) versus lag (τ). To be able to recognize a clear shape of the curve, it is preferable to restrict the coefficients to vary smoothly with lag terms. Inspired by previous study (Zanobetti et al., 2003), we restrict the effect terms to a natural cubic spline of the lag terms. Hence, for the *i*-th variable, we have $\beta_{i,\tau} = \beta_i(\tau) = \mathrm{ns}_i(\tau)$, where “ns” represents the natural cubic spline function. Here, we consider τ ranging from 0 to 365 days, and set up 5 knots, which are evenly distributed in one year period (i.e., from 0 to 365 days), to develop the spline function of each effect function for all *i*s in Eqn (1).

To check the fitting performance of the penalized regression model, the likelihood ratio (LR) test is adopted to verify the significance of the full model in Eqn (1) against the null model. To further investigate the spatial heterogeneity in the seven different cities, we employ the Cochran's Q test to exam the heterogeneity of the pollutant effect estimates in different places (Lin et al., 2016).

All data process and analysis are conducted by using **R** (version 3.4.3) (Team et al., 2013). **R** package ‘penalized’ is used for fitting the penalized regression models (Goeman et al., 2018). **R** package ‘Epi’ is used for developing the natural spline function of the effect (β) versus lag (τ) (Carstensen et al., 2008). **R** package ‘metafor’ is used for conducting the Cochran's Q tests (Viechtbauer et al., 2010).

3. Results

3.1 Descriptive results

Table 1 summarizes the incidence of new infection TB, recurrent TB, and death in the seven cities in Shandong province from 1st January 2013 to 31st December 2017. During the study period, a total of 83555 new infection TB cases, and 3060 recurrent TB cases, including 997 deaths were recorded in the seven cities. The daily incidence of new infection TB and recurrent TB (per 100,000 population) varied among the cities and ranged from 24.3 to 48.5, and from 0.5 to 1.7, respectively. The daily incidence rates of death in all TB cases range from 0.2 to 0.6 (per 100000 population) and from 6.2 to 15.7 (per 1000 infection) respectively. There was an overall decreasing trend of new infection TB incidence in the seven cities over the period. Six of seven cities have decreasing trends of the recurrent TB except Yantai. However, we also found increasing trends of mortality rates in the TB cases in Shandong. Yantai has a highest mortality rate and Liaocheng has the lowest.

Table 1 also summarizes the air pollutants concentration, and meteorological variables in the seven cities. The daily mean concentrations of SO_2 in the cities ranged from 23.2 to 56.0 μg/m^3, NO_2 ranged from 34.6 to 51.3 μg/m^3, CO ranged from 0.8 to 1.7 μg/m^3, O_3 ranged from 106.9 to 129.3 μg/m^3, and $PM_{2.5}$ ranged from 44.2 to 97.7 μg/m^3. Jinan had the highest levels of SO_2 and NO_2, whereas Liaocheng showed the highest concentrations of CO and $PM_{2.5}$. Yantai, the only coastal city, showed the lowest concentrations of SO_2, NO_2, CO and $PM_{2.5}$. The mean temperature of the seven cities ranged from 13.1 °C to 15.4 °C. Table 2 shows the the mean values for the Spearman correlation coefficients between air pollutants in seven cities from 2013 to 2017. SO_2, $NO_{2,}$ CO, and $PM_{2.5}$ was positively correlated with each other, whereas O_3 had negative correlation with other pollutants.

3.2. Regression results

Table 3 shows results from the single-lag day (L0, L15, L30, L90, L180, L365) and cumulative lag days (L0-1, L0-15, L0-30, L0-90, L0-180, L0-365) using multi-pollutants models for the percent increase (mean and 95%CIs) in daily new infection TB,and recurrent TB counts per 1μg/m^3 in pollution in seven cities during 2013–2017.

New infection TB In single-day lag models, statistically significant effects on new infection TB counts were observed for SO_2 (L0, L15, L30, L180, L365), NO_2 (L180), O_3 (L0, L15, L30, L365), CO (L30), and $PM_{2.5}$ (L0, L15, L30, L90) exposure (all p-value < 0.05). In the cumulative exposure models, high exposure to SO_2 (L0-1, L0-15, L0-30, L0-180), NO_2 (L0-15, L0-30, L0-90, L0-365), O_3 (L0-1, L0-15, L0-30, L0-365), CO (L0-15, L0-30) and $PM_{2.5}$ (L0-1, L0-15, L0-30, L0-180, L0-365) were all significantly associated with increased incidence of new infection TB (all p-value < 0.05). For instance, we estimated an increase of 1.33% (95% CI: 1.29%, 1.37%), 1.58% (95% CI: 1.54%, 1.62%), and 3.04% (95% CI: 2.98%, 3.11%) in new infection TB count for each 1μg/m^3 increase of SO_2 at lag 0–180 days, NO_2 at lag 0–90 days, and $PM_{2.5}$ at lag 0–365 days, respectively. The effect estimates of the 5 pollutants in multi-day exposure models generally produced larger estimates compared with the single-day lag models, suggesting the cumulative effects of SO_2, NO_2, O_3, CO, and $PM_{2.5}$ on new infection TB. The effect estimates achieved highest at lag 0-180 for SO_2, at lag 0–90 for NO_2, at lag 0-15 for O_3, at lag 0-30 for CO, at lag 0-365 for $PM_{2.5}$, respectively. Thus, we used these lags for each pollutant in the following analyses.We show the estimated percentage change rates of new infection TB of all lags from 0 to 365 days in the Figure S1.

Recurrent TB In single-day lag models, statistically significant relationships were observed for recurrent TB incidence with SO_2 (L0, L15, L30, L180, L365), NO_2 (L90), O_3 (L0, L15, L30, L365), CO (L15, L30, L180), and $PM_{2.5}$ (L0, L15, L90, L180) (P< 0.05). In cumulative exposure models, exposure to SO_2 (L0-1, L0-15, L0-30, L0-365), NO_2 (L0-90, L0-365), O_3 (L0-1, L0-15, L0-30, L0-365), CO (L0-15, L0-30, L0-90, L0-180, L0-365) and $PM_{2.5}$ (L0-90, L0-180, L0-365) were also significantly associated with increased incidence of recurrent TB (p-value < 0.05). We estimated an increase of 0.59% (95% CI: 0.50%, 0.67%), 0.49% (95% CI: 0.43%, 0.54%), 1.47% (95% CI: 1.41%, 1.53%) and 0.55% (95% CI: 0.52%, 0.57%) in recurrent TB count for each 1 μg/m^3 increase of SO_2 at lag 0–180 days, NO_2 at lag 90 days, O_3 at lag 0-365 days and $PM_{2.5}$ at lag 0–365 days, respectively. We show the estimated percentage change rates of recurrent TB of all lags from 0 to 365 days in the Figure S1.

Mortality Statistically significant effects on mortality were observed for exposure to SO_2 (L15, L30, L180), NO_2 (L180, L365), O_3 (L180), CO (L15, L30), and $PM_{2.5}$ (L15, L30, L90) in the single-day lag models. In cumulative-day lag models, SO_2 (L0-1, L0-15, L0-30), NO_2 (L0-90), O_3 (L0-180), CO (L0-15, L0-30) and $PM_{2.5}$ (L0-15, L0-30, L0-90) were significantly associated with increased incidence of mortality. An increase of 1μg/m^3 in SO_2 (L0-1), NO_2 (L365), O_3 (L0-180), and $PM_{2.5}$ (L0-30) were associated with a 0.12% (95% CI: 0.11%, 0.14%), 0.07% (95% CI: 0.03%, 0.11%), 0.38% (95% CI:0.34%, 0.41%) and 0.20% (95% CI: 0.19%, 0.22%) increase of mortality, respectively. The cumulative effect estimates of SO_2 and $PM_{2.5}$ were larger than the single day exposures. We also show the percentage change rate estimate of the TB mortality in the Figure S1.

Fig. 2 illustrates the percentage increase of new infection TB incidence associated with a 1μg/m^3 increase of air pollutants concentrations in the seven cities. In the multi-pollutants models, statistically significant effects of SO_2 (L180), NO_2 (L90), O_3 (L30), CO (L15), and $PM_{2.5}$ (L365) with new infection TB incidence were observed in most of the cities we studied. However, the associations of the five pollutants with new infection TB varied by cities (Fig. 2), and Q-tests showed that the heterogeneity was statistically significant for meta-analyses (all p-value < 0.05). For instance, we observed that Yantai, which with lowest concentrations of SO_2, NO_2, CO and $PM_{2.5}$ among the seven cites, showed higher effect estimates per unit increase of SO2, CO and PM2.5 concentrations (Fig. 2). The percentage change estimation results of TB risks to different pollutants in different cities of all lags from 0 to 365 days were shown in Figure S2.

3.3. Stratified analyses

Table 4 shows the effect estimates of stratified analyses by age group, sex, and sputum smear tests. For new infection TB, the effect estimates of SO_2 and O_3 were higher among the females, the young population (4-64 years old), and among smear positive cases; whereas, the effect estimates of NO_2 and $PM_{2.5}$ were higher among the males, the elderly aged 65 years or more, and also among smear positive cases. For recurrent TB, high exposure to NO_2, CO, and $PM_{2.5}$ was associated with increased risk of recurrent TB among men and smear positive cases, but not among women and smear negative cases. For different age groups, the effect estimates of O_3 and $PM_{2.5}$ among the young population were found higher than those among the elderly, whereas a higher risk of recurrent TB was observed among the elderly exposed to higher levels of NO_2. We also showed the effect estimates of stratified analyses by age group, sex, and sputum smear tests of all lags from 0 to 365 days in the Figure S3-S8.

4. Discussion

To the best of our knowledge, this is the largest epidemiologic study and the first multicity study to date on the association between ambient air pollution and TB outcomes in China. Using data from seven cities in the Shandong province, our study provided evidence that short and long term exposure to outdoor air pollutants (SO_2, NO_2, O_3, CO, and $PM_{2.5}$) was significantly associated with new infection TB,recurrent TB incidence, and mortality using multi-pollutants models. SO_2, and $PM_{2.5}$ exhibited more consistently and strongly associations with TB risks among the 5 air pollutants. Moreover, the health effects implicated different lag structures for various pollutants in our study. Specifically, the positive effects of SO_2, NO_2, O_3 and $PM_{2.5}$ for new infection TB and recurrent TB were observed at both short (≤30 days) and long term (with the length of lag from 31 to 365 days) exposure. The significant effects of CO for new infection TB were observed at within 30 days exposure only, and for recurrent TB were found at both short- and long-term exposure. Additionally, the dominant positive effects of SO_2, CO, and $PM_{2.5}$ for mortality was observed at short term (≤30 days) exposures.

In the present study, we found a consistently positive correlation between SO_2 exposure and increased incidence of new infection TB, recurrent TB, and mortality rate. Mixed findings were reported in previous studies investigating the effects of SO_2 exposure on TB incidence. A recent time-series study by Zhu et al. (2018) and a previous Korea study by Hwang et al. (2014) which both explored short-term exposure effects, showed that SO_2 exposure led to an increased risk of TB incidence. But the study by Hwang et al. (2014) only used single pollutant models, with no adjustment made for possible confounding pollutants. Other 2 epidemiological studies suggested no significant associations between TB and SO_2 level in Taiwan (Lai et al., 2016) and in northern California (Smith et al., 2016). Interestingly, a recent study conducted in Ningbo, China, suggested short-term SO_2 exposure contributed to decreased risk of initial TB outpatient visits. China is one of the few countries with highest SO_2 levels in the world (Su et al., 2011). Shandong and its surrounding Beijing-Tianjin-Yi areas have gathered electricity, iron and steel, chemical and other high-energy industries, with a large amount of coal and other energy consumption. Especially after the winter heating season, the emission of pollutants from coal burning increased, the emission of SO_2 increased nearly 50% and $PM_{2.5}$ emission increased by 30%. For example, the mean SO_2 concentrations in the seven cities in our study ranged from 23.2 $\mu g/m^3$ (Yantai) to 56.0 $\mu g/m^3$ (Jinan). In contrast, Sunyer et al. reported that the mean SO_2 levels in 7 European cities varied from 5 $\mu g/m^3$ (Stockholm) to 21 $\mu g/m^3$ (London) (Sunyer et al., 2003b). SO_2 concentrations in Ningbo were also lower than most cities in China with a daily average of 25 $\mu g/m^3$, and the counter-intuitive protective effects of SO_2 reported by Ge et al. (2017) is observed based on single city data with less than one week lag time window. In contrast, our results are based on the recent 5 years data from seven cities that are broadly representative of the Northern China population and with one year observation time lag window. Moreover, we use multi-pollutants models to adjust for potential confounding effects of co-pollutants. After adjusting for $PM_{2.5}$, NO_2, CO and O_3, the current analysis suggests that short and long term SO_2 exposure was independently related with TB outcomes in the 7 cities in Shandong province. The heterogeneity of various findings may reflect differences in the characteristics of local air pollution or patterns of exposure among local residents.

In the present study, exposure to $PM_{2.5}$ was found to be significantly associated with an increased risk of new infection and recurrent TB as well as mortality. Similarly, in previous research, $PM_{2.5}$

was also shown to be more strongly and frequently associated with TB related outcomes than other pollutants. Four of prior six studies analyzing $PM_{2.5}$ and TB prevalence or mortality, reported statistically significant effects (Jassal et al., 2013; Peng et al., 2016; Smith et al., 2014; You et al., 2016). Different lag structures of $PM_{2.5}$ for TB incidence and mortality were observed in our analysis. Statistically significant effects on TB incidence (new infection TB and recurrent TB) were seen ranging from lag0 to one year, with the largest effect estimates of $PM_{2.5}$ obtained at long-term cumulative time lags (365 days). In particular, it suggests that the adverse response to $PM_{2.5}$ for increased TB risks persists to a year or even longer after exposure. Whereas, a shorter lagged effects were seen for mortality. The longer lagged effects for TB incidence may be explained by the latent period of TB which varied from several weeks to years. Moreover, previous evidence suggested there were also several months delay in the diagnosis and notification of TB disease. The median patient-related delay (from symptoms onset to first contact with health services) was between 34.5 and 54 days and median health care-related delay (from first contacting with health services to initiate treatment) was 29.5 days. On the other hand, death for TB cases showed an acute response to trigger agents. The deleterious effects of $PM_{2.5}$ on TB outcomes could be explained by several potential mechanisms. Firstly, increased $PM_{2.5}$ exposure could modify or impair the immunology of the human respiratory system so as to increase host's susceptibility to TB. Existing studies showed that $PM_{2.5}$ exposure could adversely impact lung immunology by inducing nitrosative stressors and oxidative (Kappos et al., 2004; Nel, 2005). It also has been documented that inhaled PM could weaken mucociliary clearance function and alveolar macrophage activity which are critical defense mechanisms against M. tb (D'amato et al., 2010; Smith et al., 2010). Moreover, elevated $PM_{2.5}$ level was shown to be consisted of high levels of transition metals which may increase iron availability so as to aid in *M. tb* proliferation (Ghio, 2014; Zelikoff et al., 2002). Iron acquisition is needed for microbial growth, and exogenous iron accumulation in the host due to $PM_{2.5}$ exposure creates a favourable environment for invading M. tb (Banerjee et al., 2011; Ratledge, 2004; Weinberg, 2009).Further investigations to explore the mechanisms of the deleterious effects of $PM_{2.5}$ on TB are still required.

Our study showed NO_2 was also positively associated increased risk of new infection and recurrent TB incidence in both short and long term exposure time. Inconsistent results were reported in previous studies exploring exposure effects of NO_2. A long term exposure studies by Smith et al (2016) showed significant associations with ambient NO_2 pulmonary TB risk in a case-control study in California. In another time-series study (Zhu et al. 2018) which investigated short-term exposure effects, positive associations between NO_2 and the incidence of TB at lag 0-2 days were also observed in Chengdu, China (Zhu et al. 2018). The other three studies showed no significant effects of NO_2 (Lai et al. 2016; Hwang et al., 2014; Chen et al., 2016). NO_2 is primarily produced from combustion sources, such as electric generating units, and motor vehicle exhaust. There is skepticism on whether the adverse effects of NO_2 are reflecting other traffic pollutants effects such as PM with which NO_2 are highly correlated. However, the statistically significant effects of NO_2 for TB outcomes observed in the present analysis after adjusting for $PM_{2.5}$, SO_2, and other pollutants suggesting an independent effect.

The present analysis suggested O_3 was contributed independently to increased TB risks in analyses that controlled for other pollutants. Previous studies exploring ozone exposure with TB incidence have been inconsistent. Most of previous studies reported no evidence of significant association between O_3 exposure and TB outcomes, but the findings were based on limited sample size. However, in the case-control study by Smith et al. (2016), an inverse correlation was seen between O_3 exposure and pulmonary TB, with O_3 exposures above the lowest quintile level resulted in decreased pulmonary TB risk. Evidences from prior large cohort studies demonstrated O_3 exposure was significantly associated with death from respiratory disease. And there is biologic plausibility for a respiratory effect of O_3. O_3 was shown to increase airway inflammation, worse pulmonary function and gas exchange in laboratory studies (Bell et al. 2014). However, the extent to which the biological mechanisms be relevant to TB infection is unknown. Given the relatively small sample size and mixed findings of prior studies, future more research is advocated to address the effect of ambient O_3 on TB outcomes.

We observed between-city heterogeneity in the associations of ambient air pollution and TB outcomes in the seven cities. The heterogeneity may be related to differences in air pollution levels, components of pollutants especially $PM_{2.5}$, climate conditions, indoor air pollution, sensitivity of local residents to the environmental exposures (e.g., age, smoking, socioeconomic status).

Our study has several limitations. Firstly, a proportion of TB cases identified from Shandong CDC were diagnosed based on clinical and radiologic evidence without of pathogenic proof. Also the traditional methods (smear microscopy and bacterial culture) may cause underdiagnoses of TB-positive cases due to testing procedures. This might lead to diagnosis misclassification. Secondly, we did not investigate several covariates that could also have affected study outcomes, such as smoking history, body mass index (BMI), and indoor air pollutants exposure. Indoor air pollutants including $PM_{2.5}$ as well as nitrogen oxides produced by incomplete combustion of solid fuels have been proved to be risk factors for both initial TB infection and TB progression. The lack of indoor pollutants' assessment might lead to estimation biases of the pollutants' effects.

In summary, our study suggests that ambient air pollution is significantly associated with increased risk of active TB development and mortality in 7 Chinese cities. SO_2 and $PM_{2.5}$ exhibited more consistently and strongly associations with TB related outcomes. These findings support the Chinese government efforts in reducing high levels of air pollution, in order to reduce TB incidence and mortality.

Declarations

Ethics approval and consent to participate: Since no personal data were collected, ethical approval and individual consent were not applicable.

Funding: This work was partly supported by Department of Science and Technology of Shandong Province (CN) (No.2007GG30002033; No.2017GSF218052) and Jinan Science and Technology Bureau (CN) (No.201704100).

Acknowledgments: Not applicable.

Authors' Contributions:

D He and H Li conceived and supervised this study. Y Liu and H Li collected the data. S Zhao processed the data and carried out the analyses in this study. Y Liu, S Zhao, D He and H Li discussed the results. Y Liu and S Zhao drafted the first manuscript. Y Liu and S Zhao revised the manuscript. All authors read the manuscript and gave final approval for publication.

References

Banerjee, S., Farhana, A., Ehtesham, N.Z., Hasnain, S.E., 2011. Iron acquisition, assimilation and regulation in mycobacteria. Infect Genet Evol 11 (5), 825–838.

Bell, M.L., Zanobetti, A., Dominici, F., 2014. Who is more affected by ozone pollution? A systematic review and meta-analysis. Am J Epidemiol. 180(1), 15±28.

Carstensen, B., Plummer, M., Laara, E., Hills, M., 2008. Epi: A package for statistical analysis in epidemiology. R package version 1(8).

Chen, R., Kan, H., Chen, B., Huang, W., Bai, Z., Song, G., Pan, G., 2012. Association of particulate air pollution with daily mortality: the China air pollution and health effects study. Am. J. Epidemiol. 175, 1173–1181.

Goeman, J., Meijer, R., Chaturvedi, N., Lueder, M., Goeman, M.J., Rcpp, I., Rcpp, L., 2018. Package 'penalized'.

Goeman, J.J., 2010. L1 penalized estimation in the Cox proportional hazards model. Biometrical journal 52(1), 70-84.

D'amato, G., Cecchi, L., D'amato, M., Liccardi, G., 2010. Urban air pollution and climate change as environmental risk factors of respiratory allergy: an update. J. Investig. Allergol. Clin. Immunol. 20, 95e102.

Ge, E., Fan, M., Qiu, H., Hu, H., Tian, L., Wang, X., Wei, X., 2017. Ambient sulfur dioxide levels associated with reduced risk of initial outpatient visits for tuberculosis: A population based time series analysis. Environ. Pollut 228, 408–415. https://doi.org/10.1016/j.envpol.2017.05.051.

Ghio, A.J., 2014. Particle exposures and infections. Infection 42 (3), 459–467. https://doi.org/10.1007/s15010-014-0592-6.

Hwang, S.S., Kang, S., Lee, J.Y., Lee, J.S., Kim, H.J., Han, S.K., et al., 2014. Impact of outdoor air pollution on the incidence of tuberculosis in the Seoul metropolitan area, South Korea. Korean J. Intern. Med. 29, 183–190. https://doi.org/10.3904/kjim.2014.29.2.183.

Iwai, K., Mizuno, S., Miyasaka, Y., Mori, T., 2005. Correlation between suspended particles in the environmental air and causes of disease among inhabitants: cross-sectional studies using the vital statistics and air pollution data in Japan. Environ Res. 99, 106-117.

Jassal, M.S., Bakman, I., Jones, B., 2013. Correlation of ambient pollution levels and heavily-trafficked roadway proximity on the prevalence of smear-positive tuberculosis. Public Health 127 (3), 268–274. https://doi.org/10.1016/j.puhe.2012.12.030.

Lai, T.C., Chiang, C.Y., Wu, C.F., Yang, S.L., Liu, D.P., Chan, C.C., Lin, H.H., 2016. Ambient air pollution and risk of tuberculosis: A cohort study. Occupational and Environmental Medicine 73 (1), 56–61.

Lin, H.H., Ezzati, M., Murray, M., 2007. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. Plos Med. 4, 173–89.

Lin, H., Liu, T., Xiao, J., Zeng, W., Li, X., Guo, L., Zhang, Y., Xu, Y., Tao, J., Xian, H,.2016. Mortality burden of ambient fine particulate air pollution in six Chinese cities: results from the Pearl River Delta study. Environment international 96, 91-97.

Lonnroth, K., Jaramillo, E., Williams, B.G., et al., 2009. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med. 68, 2240–6.

Nel, A., 2005. Air pollution-related illness: effects of particles. Science 308, 804e806.

Peng, Z., Liu, C., Xu, B., Kan, H., Wang, W., 2016. Long-term exposure to ambient air pollution and mortality in a Chinese tuberculosis cohort. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv. 2016.12.128.

Popovic, I., Soares Magalhaes, R.J., Ge, E., Marks, G.B., Dong, G.H., Wei, X., Knibbs, L.D.,2019. A systematic literature review and critical appraisal of epidemiological studies on outdoor air pollution and tuberculosis outcomes. Environ Res. 170, 33-45.

Ratledge, C., 2004. Iron, mycobacteria and tuberculosis. Tuberculosis 84 (1), 110–130.

https://doi.org/10.1016/j.tube.2003.08.012.

Smith, L.A., Paszkiewicz, G.M., Hutson, A.D., Pauly, J.L., 2010. Inflammatory response of lung macrophages and epithelial cells to tobacco smoke: a literature review of ex vivo investigations. Immunol. Res. 46, 94e126.

Smith, G.S., Schoenbach, V.J., Richardson, D.B., Gammon, M.D., 2014. Pulmonary Tuberculosis Disease in North Carolina: an Ecological Study. Int J Environ Health Res. 24, 103-112.

Smith, G.S., Van Den Eeden, S.K., Garcia, C., Shan, J., Baxter, R., Herring, A.H., Gammon, M.D., 2016. Air Pollution and pulmonary tuberculosis: a nested case-control study among members of a Northern California health plan. Environ. Health Perspect. 124 (6), 761–768.

https://doi.org/10.1289/ehp.1408166.

Su, S.s., Li, B.G., Cui, S., and Tao, S., 2011.Sulfur Dioxide Emissions from Combustion in China: From 1990 to 2007. Environ. Sci. Technol. 45, 8403–8410.

Sumpter, C., Chandramohan, D., 2013. Systematic review and meta-analysis of the associations between indoor air pollution and tuberculosis. Trop Med Int Health. 18, 101-108.

Sunyer, J., et al., 2003b. The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (The Aphea-II study). Eur. Heart J. 24, 752–760.

Team, R.C., 2013. R: A language and environment for statistical computing.

Tibshirani, R., 1996. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society Series B (Methodological) 267-288.

Tremblay, G.A., 2007. Historical statistics support a hypothesis linking tuberculosis and air pollution caused by coal. Int J Tuberc Lung Dis. 11, 722-732.

You, S., Tong, Y.W., Neoh, K.G., Dai, Y., Wang, C.H., 2016. On the association between outdoor PM2.5 concentration and the seasonality of tuberculosis for Beijing and Hong Kong. Environ. Pollut. 218, 1170–1179. https://doi.org/10.1016/j.envpol.2016.08.071.

Kappos, A.D., Bruckmann, P., Eikmann, T., Englert, N., Heinrich, U., Heoppe, P., Koch, E., Krause, G.H., Kreyling, W.G., Rauchfuss, K., 2004. Health effects of particles in ambient air. Int. J. Hyg. Environ. Health 207, 399e407.

Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J Stat Softw 36(3), 1-48.

Weinberg, E.D., 2009. Iron availability and infection. Biochim. Biophys. Acta 1790 (7), 600–605. https://doi.org/10.1016/j.bbagen.2008.07.002.

World Health Organisation, 2016. Global Tuberculosis Report 2016. Retrieved from ⟨http://www.who.int/tb/publications/global_report/en/⟩.

World Health Organisation, 2017. Global Tuberculosis Report 2017. Retrieved from ⟨http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf?ua = 1⟩.

Zanobetti, A., Schwartz, J., Samoli, E., Gryparis, A., Touloumi, G., Peacock, J., Anderson, R.H., Le Tertre, A., Bobros, J., Celko, M., 2003. The temporal pattern of respiratory and heart disease mortality in response to air pollution. Environmental health perspectives 111(9), 1188-1193.

Zhu, S., Xia, L., Wu, J., Chen, S., Chen, F., Zeng, F., Zhang, J., 2018. Ambient air pollutants are associated with newly diagnosed tuberculosis: A time-series study in Chengdu, China. Sci. Total Environ. 631-632, 47–55. https://doi.org/10.1016/j.scitotenv.2018.03.017.

Table 1. Summary statistics of the trends of tuberculosis (TB), air pollutant concentrations and meteorological factors in the seven cities of Shandong Province of China, (2013–2017).

City	Dezhou	Jinan	Jining	Liaocheng	Linyi	Weifang	Yantai
Outcomes* (per 100,000 population)							
New infection	26.9; -12.1%	25.9; -4.7%	25.6; -9.4%	48.5; -2.4%	41.7; -8.4%	24.3; -8.6%	28.3; -10.0%
Recurrent	0.8; -61.5%	0.5; -10.1%	1.1; -26.3%	1.2; -14.8%	1.7; -16.6%	1.1; -4.4%	1.4 ; 1.3%
Death	0.2; 30.2%	0.2; 43.2%	0.3 ; 13.7%	0.3; 0.9%	0.6 ; -7.0%	0.3; 6.9%	0.5 ; -6.4%
Death (per 1000 infection)	10.0; 55.1%	8.8; 50.2%	11.9; 27.9%	6.2 ; 4.5%	14.1 ; 2.2%	13.8 ; 16.7%	15.7 ; 4.7%
No. of Air Monitors	6	17	7	5	8	10	11
Air pollution, μg/m^3; (mean±SD)							
SO_2	44.3±34.3	56.0 ± 46.8	55.8±38.1	41.3 ±35.9	42.8 ±34.3	48.1±41.2	23.2 ±16.4
NO_2	46.0±19.7	51.3 ±21.1	44.3 ±17.3	45.9 ±19.7	50.0 ±22.7	40.6 ±17.4	34.6 ±15.2
CO	1.6±0.6	1.3 ±0.7	1.3 ±0.5	1.7 ±0.7	1.6 ±0.8	1.0±0.5	0.8 ±0.4
O_3	120.1 ±61.5	123.1 ±63.1	126.8± 61.5	107.8 ±60.9	106.9±54.2	129.3 ±57.2	113.8 ±42.6

$PM_{2.5}$	96.3 ±67.2	85.3 ±53.9	85.3 ±59.3	97.7±64.9	80.4 ±60.1	74.6 ±48.1	44.2 ±32.7
Meteorologic measures (24-h average)							
Temperature (°C)	14.7 ±10.7	15.1 ±10.5	15.4 ±10.3	14.0 ±10.4	14.5 ± 10.1	14.0 ±10.7	13.1 ±10.0
Humidity (%)	60.6±17.5	56.0 ±19.4	64.0 ±16.1	71.2 ±16.1	66.6 ±16.3	63.5 ±16.3	64.2 ±16.8

Table 2. Spearman's correlation between air pollutants in seven cities in Shandong, from 2013 to 2017.

	SO_2	NO_2	$PM_{2.5}$	O_3	CO
SO_2	-	0.717*	0.684*	-0.310	0.639*
NO_2	-	-	0.706*	-0.373	0.699*
$PM_{2.5}$	-	-	-	-0.183	0.794*
O_3	-	-	-	-	-0.351
CO	-	-	-	-	-

* $P<0.05$

Table 3. Percentage change (mean and 95% confidence intervals) of new infection TB, and re-refection TB associated with a 1 μg/m^3 increase of air pollutants along different lag days in the instantaneously and cumulative lag model in the seven cities of China, (2013–2017).

Pollutant	Lag 0 days	Lag 15 days	Lag 30 days	Lag 90 days	Lag180 days	Lag365 days	Lag 0-1 days	Lag 0-15 days	Lag 0-30 days	Lag 0-90 days	Lag 0-180 days	Lag 0-365days
New infection												
SO_2	0.28 (0.24-0.33)	0.30 (0.28, 0.32)	0.28 (0.25, 0.30)	0.01 (-0.01, 0.03)	0.05 (0.03, 0.07)	0.08 (0.05, 0.11)	0.68 (0.61, 0.74)	0.51 (0.48, 0.54)	0.32 (0.28, 0.35)	0.02 (-0.02, 0.05)	1.33 (1.29, 1.37)	0.01 (-0.04, 0.06)
NO_2	0.02 (-0.05, 0.08)	-0.01 (-0.04, 0.03)	-0.01 (-0.05, 0.03)	-0.00 (-0.04, 0.04)	0.20 (0.16, 0.24)	-0.02 (-0.07, 0.03)	-0.08 (-0.16, -0.01)	0.04 (0.01, 0.08)	0.05 (0.01, 0.09)	1.58 (1.54, 1.62)	0.004 (-0.04-0.04)	0.116 (0.065-0.166)
O_3	0.24 (0.19, 0.29)	0.30 (0.28, 0.33)	0.32 (0.29, 0.35)	-0.08 (-0.11, 0.05)	-0.31 (-0.33, 0.28)	0.11 (0.07, 0.14)	0.42 (0.34, 0.51)	0.72 (0.68,0.76)	0.71 (0.66, 0.75)	-0.56 (-0.51, -0.52)	-0.95 (-0.99, -0.90)	0.35 (0.30,0.41)
CO	-0.001 (-0.003, 0.000)	0.001 (-0.00, 0.002)	0.002 (0.001, 0.003)	-0.00 (-0.001, 0.001)	0.001 (-0.00, 0.002)	0.00 (-0.001, 0.001)	-0.00 (-0.01, 0.004))	0.004 (0.001, 0.007)	0.007 (0.003, 0.01)	0.003 (-0.001, 0.01)	-0.01 (-0.02,-0.01)	-0.001 (-0.001,-0.004)
$PM_{2.5}$	0.03 (0.01, 0.04)	0.01 (0.00, 0.02)	0.01 (0.001, 0.02)	0.16 (0.15, 0.17)	0.002 (-0.007, 0.012)	0.00 (-0.01, 0.01)	0.14 (0.04, 0.23)	0.14 (0.10, 0.18)	0.22 (0.17, 0.28)	-0.01 (-0.06, 0.04)	0.100 (0.05, 0.15)	3.04 (2.98, 3.11)
Re-infection												
SO_2	0.20 (0.15, 0.26)	0.19 (0.17, 0.22)	0.16 (0.12, 0.19)	0.00 (-0.03, 0.03)	0.12 (0.09, 0.16)	0.17 (0.13,0.21)	0.59 (0.50, 0.67)	0.29 (0.25, 0.33)	0.06 (0.01, 0.10)	-0.004 (-0.05, 0.04)	0.02 (-0.03, 0.07)	0.30 (0.24, 0.36)
NO_2	0.01 (-0.09-0.01)	0.00 (-0.06,0.05)	-0.01 (-0.07,0.05)	0.49 (0.43,0.54)	0.02 (-0.03,0.08)	0.02 (-0.06, 0.09)	0.17 (0.01, 0.32)	-0.11 (-0.18,-0.03)	0.05 (-0.04, 0.13)	0.23 (0.14, 0.32)	0.003 (-0.0.8, 0.09)	0.39 (0.28, 0.51)
O_3	0.19 (0.11-0.27)	0.17 (0.14,0.21)	0.15 (0.11,0.20)	-0.11 (-0.15,-0.06)	-0.19 (-0.24,-0.15)	0.13 (0.08,0.19)	0.30 (0.21,0.38)	0.40 (0.36,0.44)	0.44 (0.39,0.49)	-0.23 (-0.27,-0.18)	-0.40 (-0.45,-0.36)	1.47 （1.41,1.53）

CO	0.001 (-0.002-0.004)	0.008 (0.006-0.009)	0.01 (0.009,0.01)	0.00 (-0.002, 0.002)	0.02 (0.00,0.004)	0.001 (-0.002,0.003)	0.004 (-0.003,0.010)	0.02 (0.02,,0.022)	0.02 (0.02, 0.03)	0.01 (0.00, 0.01)	0.09 (0.08, 0.09)	0.12 (0.11, 0.12)
$PM_{2.5}$	0.06 (0.03, 0.10)	0.02 (0.01, 0.03)	–0.002 (-0.02, 0.01)	0.02 (0.00, 0.03)	0.01 (0.00, 0.02)	0.001 (-0.02, 0.02)	0.03 (-0.01, 0.07)	0.02 (-0.00, 0.03)	0.00 (-0.02, 0.02)	0.02 (0.00, 0.04)	0.02 (0.003, 0.04)	0.55 (0.52, 0.57)
Death												
SO_2	0.02 (-0.01,0.05)	0.04 (0.03,0.06)	0.06 (0.04, 0.07)	-0.001 (-0.02, 0.02)	0.04 (0.03, 0.06)	0.01 (-0.01, 0.03)	0.12 (0.11, 0.14)	0.09 (0.08, 0.09)	0.05 (0.04, 0.06)	-0.00 (-0.00, 0.10)	-0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.101)
NO_2	0.01 (-0.04,0.06)	0.01 (-0.03,0.02)	-0.00 (-0.03, 0.03)	0.02 (-0.01, 0.05)	0.06 (0.03, 0.09)	0.07 (0.03, 0.11)	-0.002 (-0.01, 0.01)	-0.00 (0.00, 0.01)	-0.00 (0.00, 0.01)	0.01 (0.00, 0.10)	0.00 (-0.004, 0.01)	-0.00 (-0.01, 0.01)
O_3	-0.11 (-0.16,-0.06)	-0.12 (-0.14,-0.09)	-0.10 (-0.13,-0.07)	0.004 (-0.03, -0.03)	0.08 (0.05, 0.11)	-0.009 (-0.05, 0.03)	-0.26 (-0.32,-0.19)	-0.13 (-0.17,-0.10)	-0.03 (-0.06, 0.01)	-0.06 (-0.10,-0.03)	0.38 （0.34,0.41）	-0.60 （-0.6, 0.56）
CO	-0.001 (-0.002,0.001)	0.001 (0.001,0.002)	0.003 (0.002,0.004)	0.001 (-0.001,0.002)	0.00 (-0.001,0.001)	0.002 (-0.000,0.003)	-0.001 (-0.003,-0.001)	0.001 (0.000, 0.002)	0.003 (0.001, 0.004)	0.00 (-0.001,-0.001)	-0.002 （-0.003,-0.001）	0.00 （-0.001,0.002）
$PM_{2.5}$	-0.002 (-0.02,-0.02)	0.01 (0.00,0.02)	0.02 (0.01,0.03)	0.01 (0.003,0.02)	0.01 (-0.00,0.02)	0.02 (-0.00,0.03)	-0.11 (-0.14,-0.08)	0.08 (0.06,0.09)	0.20 (0.19,0.22)	0.05 (0.04, 0.07)	-0.00 （-0.02,0.01）	-0.00 （-0.02,0.02）

Table 4. Sex, age, suptum smear status specific risk ratio (RR and 95%CI) in TB outcomes associated with a 1 μg/m3 increase in air pollutants in the seven cities of China, (2013–2017). Here, the *p*-values are from the Cochran's Q tests.

		SO_2 (Lag 0-180 days)		NO_2 (Lag 0-90 days)		CO (Lag 0-15 days)		O_3 (Lag 0-30 days)		$PM_{2.5}$ (Lag 0-365 days)	
New infection		**RR (95%CI)**	**p-Value**	**RR (95%CI)**	**p-Value**	**RR (95%CI)**	**p-Value**	**RR (95%CI)**	**p-Value**	**RR (95%CI)**	**p-Value**
Sex	Male	1.38 (1.33-1.42)	<0.05	2.37 (2.31-2.44)	<0.05	0.00 (-0.00-0.00)	0.77	0.59 (0.55, 0.63)	<0.05	3.26 (3.17-3.35)	<0.05
	Female	1.62 (1.56-1.68)		1.82 (1.71-1.94)		0.00 (-0.00-0.00)		0.69 (0.62, 0.75)		1.46 (1.37-1.56)	
Age	4-64	1.51 (1.47-1.54)	<0.05	1.43 (1.34-1.51)	<0.05	0.01 (0.00, 0.01)	0.06	0.75 (0.70, 0.80)	<0.05	3.50 (3.38-3.62)	0.12
	≧65	1.25 (1.16-1.35)		2.99 (2.83-3.16)		0.00 (-0.00-0.00)		0.60 (0.53, 0.66)		3.64 (3.51-3.78)	
Suptum smear	Positive	0.11 (0.00-0.23)	0.06	1.21 (1.00-1.42)	<0.05	0.02 (0.01-0.02)	<0.05	0.30 (0.22-0.37)	<0.05	1.78 (1.64, 1.93)	<0.05
	Negative	0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)	
Re-infection											
Sex	Male	0.02 (-0.02-0.06)	0.09	0.62 (0.58-0.66)	<0.05	0.01 (0.01, 0.02)	<0.05	0.32 (0.28, 0.37)	<0.05	0.38 (0.35, 0.41)	<0.05
	Female	1.82		-0.01		0.00		0.06		0.00	

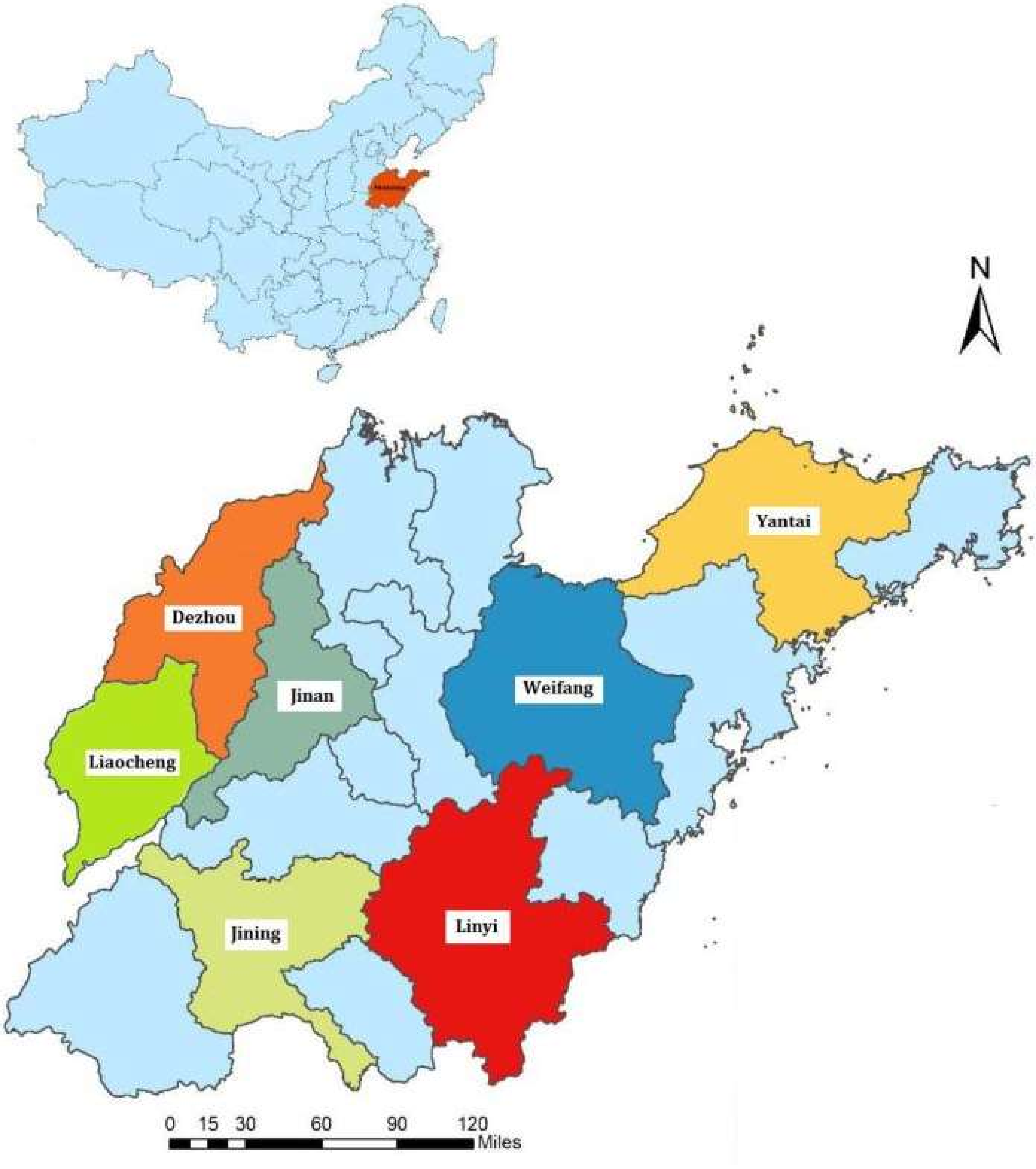
		(1.71-1.94)		(-0.07-0.04)		(0.00-0.00)		(0.04, 0.07)		(-0.00-0.00)	
Age	4-64	0.02 (-0.02-0.05)	0.45	0.02 (-0.10-0.15)	<0.05	0.01 (0.01, 0.02)	0.65	0.32 (0.29, 0.35)	<0.05	0.05 (0.02, 0.08)	<0.05
	≧65	0.00 (-0.01-0.01)		0.35 (0.30-0.39)		0.01 (0.01, 0.01)		0.05 (0.02, 0.08)		0.00 (-0.00-0.00)	
Suptum smear	Positive	0.01 (-0.03-0.05)	0.57	0.31 (0.25-0.37)	<0.05	0.02 (0.02-0.03)	<0.05	0.40 (0.36-0.44)	<0.05	0.68 (0.66-0.71)	<0.05
	Negative	0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)	
Death											
Sex	Male	-0.00 (-0.02-0.01)	<0.05	0.01 (-0.01-0.02)	0.15	0.01 (0.00, 0.01)	<0.05	-0.14 (-0.17--0.12)	<0.05	0.00 (-0.02--0.02)	0.98
	Female	0.07 (0.00-0.02)		-0.01 (-0.02-0.01)		0.00 (-0.00-0.00)		0.00 (-0.00-0.00)		-0.00 (-0.01--0.01)	
Age	4-64	-0.00 (-0.00-0.00)	0.88	0.01 (0.00-0.02)	0.17	0.01 (0.01, 0.01)	<0.05	-0.03 (-0.05--0.02)	<0.05	-0.00 (-0.02--0.02)	0.99
	≧65	0.00 (-0.00-0.00)		-0.00 (-0.00-0.00)		0.00 (-0.00, 0.00)		-0.11 (-0.13--0.09)		-0.00 (-0.01--0.01)	
Suptum smear	Positive	-0.00 (-0.01-0.01)	0.78	-0.00 (-0.00-0.00)	0.97	0.00 (-0.00-0.00)	0.08	-0.08 (-0.10--0.06)	<0.05	0.00 (-0.02--0.02)	0.99
	Negative	0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)		0.00 (0.00-0.00)	

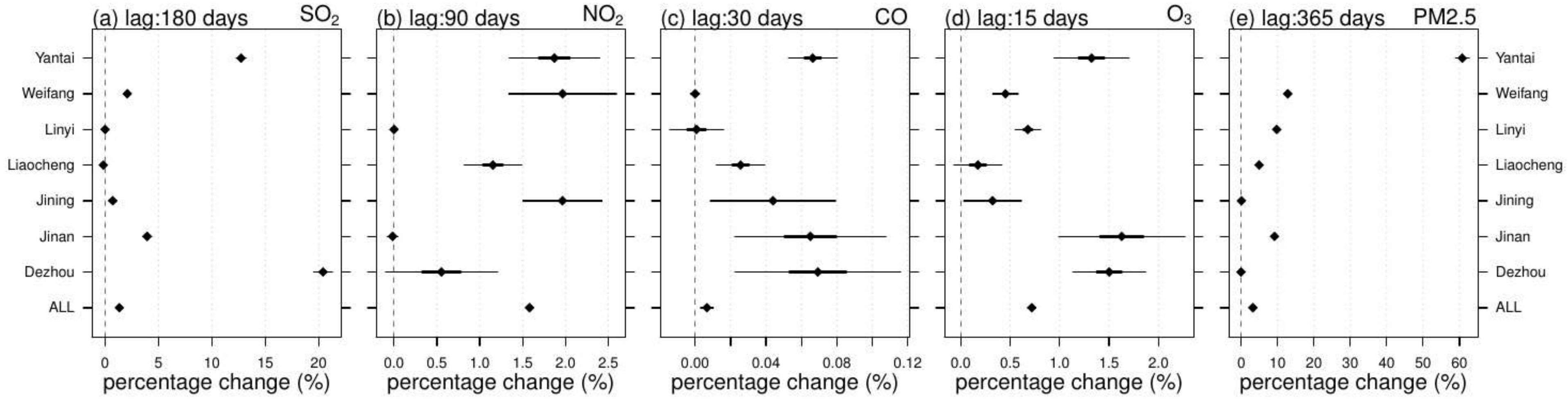
Figure legends

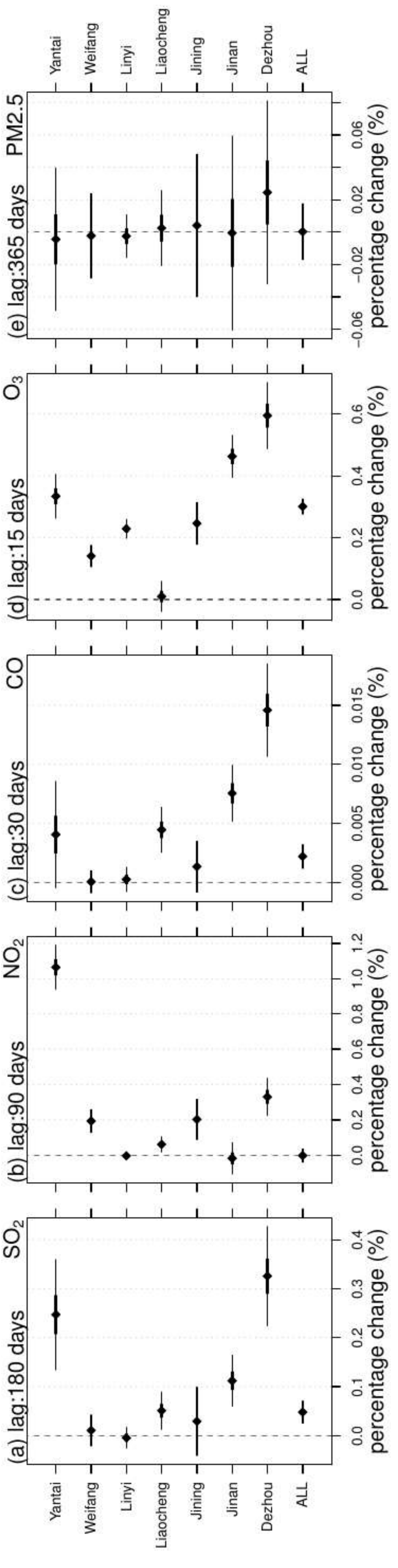
Figure 1 The map of the seven cities, i.e., Dezhou, Jinan, Jining, Liaocheng, Linyi, Weifang and Yantai, in Shandong, China. The upper panel show the location of Shandong province in China. The lower panel highlights the locations of the seven cities in Shandong.

Figure 2. The percentage change estimation results of pollutants and TB new infection risks in different cities. Note that the lag term in the panel label is the cumulative lag, i.e., lag x means lag 0-x days. The dots are the point estimations and the bars are the 95%CIs.

Figure 3. The percentage change estimation results of pollutants and TB new infection risks in different cities. Note that the lag term in the panel label is the lag of instantaneously effect. The dots are the point estimations and the bars are the 95%CIs.


N
Yantai
Dezhou
Jinan
Weifang
Liaocheng
Linyi
Jining
0 15 30 60 90 120
Miles


(a) lag:180 days
SO_2
(b) lag:90 days
NO_2
(c) lag:30 days
CO
(d) lag:15 days
O_3
(e) lag:365 days
PM2.5
Yantai
Weifang
Linyi
Liaocheng
Jining
Jinan
Dezhou
ALL
0
5
10
15
20
0.0
0.5
1.0
1.5
2.0
2.5
0.00
0.04
0.08
0.12
0.0
0.5
1.0
1.5
2.0
0
10
20
30
40
50
60
percentage change (%)
percentage change (%)
percentage change (%)
percentage change (%)
percentage change (%)


(a) lag:180 days
SO$_2$
(b) lag:90 days
NO$_2$
(c) lag:30 days
CO
(d) lag:15 days
O$_3$
(e) lag:365 days
PM2.5
Yantai
Weifang
Linyi
Liaocheng
Jining
Jinan
Dezhou
ALL
percentage change (%)
0.0
0.1
0.2
0.3
0.4
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.000
0.005
0.010
0.015
0.0
0.2
0.4
0.6
−0.06
−0.02
0.02
0.06