



Long-term effect of exposure to ambient air pollution on the risk of active tuberculosis



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ABSTRACT

Objectives: To explore the long-term effect of exposure to ambient air pollution on the risk of active tuberculosis (TB).

Methods: We constructed a distributed-lag nonlinear model (DLNM) to evaluate the relatively long-term influence of outdoor PM_{2.5}, PM₁₀, SO₂ and NO₂ exposure on active TB risk in the city of Lianyungang in Jiangsu Province, China.

Results: There were 7,282 TB cases reported in the study area during 2014–2017, with annual median (interquartile range) concentrations of PM_{2.5}, PM₁₀, SO₂ and NO₂ at 45.86 (34.57–64.14) $\mu\text{g}/\text{m}^3$, 85.43 (62.86–116.14) $\mu\text{g}/\text{m}^3$, 22.00 (15.71–30.86) $\mu\text{g}/\text{m}^3$ and 30.00 (23.29–38.57) $\mu\text{g}/\text{m}^3$, respectively. The single-pollutant model showed that for each 10 $\mu\text{g}/\text{m}^3$ increase in concentration, the cumulative relative risk of TB was 1.12 (lag 0–24 weeks, 95% CI: 1.03–1.22) for PM_{2.5} with reference to 35 $\mu\text{g}/\text{m}^3$; 1.11 (lag 0–21 weeks, 95% CI: 1.06–1.17) for PM₁₀ with reference to 70 $\mu\text{g}/\text{m}^3$; 1.37 (lag 0–20 weeks, 95% CI: 1.16–1.62) for SO₂ with reference to 60 $\mu\text{g}/\text{m}^3$; and 1.29 (lag 0–22 weeks, 95% CI: 1.11–1.49) for NO₂ with reference to 40 $\mu\text{g}/\text{m}^3$. In the multipollutant model considering both PM₁₀ and NO₂, the association remained significant.

Conclusions: Our results revealed a potential association between outdoor exposure to PM_{2.5}, PM₁₀, SO₂, and NO₂ and active TB. Considering that people from developing countries continue to be exposed to both severe outdoor air pollution and high rates of latent TB infection, the association between worsening air pollution and active TB deserves further attention.

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Abbreviations: TB, tuberculosis; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; DLNM, distributed-lag nonlinear model; RR, relative risk; CI, confidence interval; M.tb, Mycobacterium tuberculosis; WHO, World Health Organization; CVD, cardiovascular disorders; GDP, Gross Domestic Product; PGDP, per capita GDP; PD, population density; NDP, number of doctors per 10,000 people; GAM, generalized additive model; WAT, weekly average temperature; WAP, weekly average air pressure; WAS, weekly average wind speed; WAH, weekly average relative humidity; WAST, weekly average sunshine time; ns, Natural cubic spline; df, degree of freedom; PACF, partial autocorrelation function; TNF, tumor necrosis factor; IFN- γ , interferon-gamma.

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Introduction

Worldwide, tuberculosis (TB) is the tenth leading cause of death (WHO, 2018). One-third of the global population is infected with the mycobacterium tuberculosis (M.tb) pathogen, but only 10% of them eventually develop active TB (Sgaragli and Frosini, 2016). Previous studies claimed that factors such as active and passive smoking, indoor air pollution, malnutrition or polymorphisms of immune-related genes were suggested to contribute to the increased risk of TB (Ferrara et al., 2012; Lin et al., 2007; Lonroth et al., 2009).

Since the 1990s, global economic development has begun to accelerate, but the accompanying environmental pollution has become increasingly serious (Chen and Kan, 2008). The WHO has estimated 2.4 million deaths due to air pollution-associated causes per year (Sierra-Vargas and Teran, 2012). An increasing number of

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epidemiological studies have shown the adverse effects of outdoor exposure to air pollution on human health. A prospective analysis in nine European countries revealed a positive relation between exposures to particulate matter (PM) with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM_{10}) and $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and lung cancer risk (Raaschou-Nielsen et al., 2013). In Hefei, China, Zhang et al. indicated that PM_{10} , sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) could significantly increase the cardiovascular disorders (CVD) mortality (Zhang et al., 2017). A systematic review found that ambient air pollution exposure might contribute to the occurrence and development of chronic respiratory diseases (Guan et al., 2016). Studies also indicated that outdoor exposure to air pollution might increase the risk of active TB. In Chengdu, China, Zhu et al. reported that people exposed to higher concentrations of PM_{10} , SO_2 and NO_2 in the short term were more likely to develop TB (Zhu et al., 2018). A study in Taiwan revealed a possible link between $\text{PM}_{2.5}$, CO, NO_2 and TB (Lai et al., 2016). Another study in North Carolina also suggested a potential correlation between particulate matter exposure and TB risk (Smith et al., 2014). In South Korea, Hwang et al. found that male TB patients were more susceptible to incremental concentrations of SO_2 than females (Hwang et al., 2014). Conversely, in a time-series analysis in Ningbo, China, Ge et al. reported that ambient SO_2 exposure might be a protective factor for TB (Ge et al., 2017). However, the above studies were mostly carried out in economically developed areas. Whether there is a similar relationship in economically underdeveloped regions requires further study.

Nonlinear exposure-lag-response relationships have been demonstrated between outdoor air pollution and multiple health outcomes (Chen et al., 2017; Guo et al., 2017). The distributed-lag nonlinear model (DLNM) is an advanced time-series analysis method proposed by Gasparrini (Gasparrini, 2011; Gasparrini et al., 2010), that has been widely used to explore the relationships between meteorological factors and health outcomes (Buteau et al., 2018; Gasparrini, 2014; Neophytou et al., 2018), but has seldom been applied to evaluate the relationship between outdoor exposure to air pollution and active TB risk. Thus, we performed a time-series study using DLNM to explore the correlation between a relatively long-term exposure to outdoor air pollution and active TB risk in a Chinese population.

Materials and methods

Study area and study subjects

We selected the city of Lianyungang as the study site. It located in the northeastern region of Jiangsu Province, China, with an area of approximately 7.6 thousand square kilometers and 4.5 million permanent residents in 2017. Lianyungang is an economically underdeveloped city, where both the Gross Domestic Product (GDP) and per capita GDP (PGDP) rank 12th among the 13 cities in Jiangsu Province. TB cases reported from January 1, 2014, to December 31, 2017, were extracted through the Tuberculosis Management Information System. Diagnosis of active TB refers to the health industry standards of the People's Republic of China—diagnosis for pulmonary tuberculosis. Patient demographic characteristics and clinical records were also extracted. We divided the study period into 209 weeks and calculated the per-week number of cases. Because January 1, 2014, was a Wednesday, the first week was only five days. This study was approved by the ethics committee of Nanjing Medical University.

Air pollution and meteorological data

We collected daily concentrations of ambient $\text{PM}_{2.5}$, PM_{10} , NO_2 and SO_2 from the Lianyungang Environmental Monitoring

Terminal Station (<https://www.aqistudy.cn/>). CO and O_3 were excluded because of missing values in the database. Simultaneous meteorological data, including average temperature ($^{\circ}\text{C}$), pressure (hPa), wind speed (m/s), relative humidity (%), and sunshine time (h), were downloaded from the National Meteorological Data Sharing Center (<http://data.cma.cn/>). We calculated the weekly average air pollutants and meteorological factors for modeling.

Socioeconomic indicators

The socioeconomic indicators of Lianyungang including PGDP, population density (PD), and the number of doctors per 10,000 people (NDP), from 2014 to 2017, were collected from the Department of Statistics and entered into the model as covariates.

Statistics analysis

We used the Spearman correlation test to identify the correlations among four air pollutants and five meteorological factors. Considering the nonlinear exposure-lag-response relationship between outdoor exposure to air pollution and health (Chen et al., 2017; Guo et al., 2017), we adopted the DLNM to control the exposure-lag-response effect. The DLNM adds a lag dimension to the relationship between exposure and response and describes the variation of dependent variables in terms of both independent variable and lag dimensions. The core element of DLNM is the construction of a cross-basis function, which can be obtained by calculating the tensor product of functions. We constructed the model following the methods proposed by Gasparrini (Gasparrini, 2011; Gasparrini et al., 2010). Since the weekly reported active TB cases are generally considered to be rare and nonindependent events, we used the generalized additive model (GAM) based on the quasi-Poisson distribution (Zhu et al., 2018).

First, we constructed a basic model without air pollutants. We created a time variable of “week” (week = 1, 2, . . . , 209) to control the long-term patterns (including seasonal fluctuations) of the TB case reporting. Five meteorological factors, including weekly average temperature (WAT), weekly average air pressure (WAP), weekly average wind speed (WAS), weekly average relative humidity (WAH), weekly average sunshine time (WAST), and three socioeconomic indicators (PGDP, PD and NDP), were entered into the basic model as covariates. A natural cubic spline (ns) function was used to control the associations between the time-related variable of “week”, meteorological factors and active TB (Zhu et al., 2018). The degrees of freedom (df) of the ns were defined based on the principle of minimizing the sum of the absolute values of the partial autocorrelation function (PACF) of the residuals in the basic model (Wood, 2017). Then, we modeled the exposure-response relationship through a linear function and the lag-response relationship through an ns function to build a cross-basis function for each air pollutant (Zhu et al., 2018). We hypothesized that an increased concentration of four ambient air pollutants could increase the risk of M. tb infection and progression to active TB. The progression from M. tb infection to clinically observed symptoms takes several months to years, and some latent infections even last for life. The average incubation period of TB is estimated to be three months. In addition, the diagnosis and reporting of TB also require times that can cause a delay. Thus, if the increased concentration of ambient air pollutants contributes to TB, extra time is required for an infected individual to develop active disease, be diagnosed, and finally be reported by a health care institution (Murray et al., 2011; You et al., 2016). This type of lag was assumed to be over 2 months because the median time interval between infection and active disease was 7 weeks (Naranbat et al., 2009). Leung et al. recommended that the

maximum lag time was 6 months (Leung et al., 2005). Here, we set the maximum lag time as 25 weeks.

To avoid a multiple collinearity problem, we screened variables by setting the inclusion criteria of $|r| < 0.7$ (Zhu et al., 2018). Since there was a high correlation between the WAT and WAP ($r = -0.93$), we removed the WAP from the basic model. We further added the constructed cross-basis function to the basic model. The final single-pollutant model was $Y_t = \text{quasiPoisson}(\mu_t)$, where $\mu_t = \alpha + W_X^T \eta + ns(\text{week}, df_1 * 4) + ns(\text{WAT}, df_2) + ns(\text{WAS}, df_3) + ns(\text{WAH}, df_4) + ns(\text{WAST}, df_5) + \beta_1 \text{PGDP} + \beta_2 \text{PD} + \beta_3 \text{NDP}$. Y_t and μ_t were the observed and expected number of TB cases on week t , respectively; α was an intercept; $W_X^T \eta$ was a cross-basis function of each air pollutant; df_1 was the annual df of the time variable "week"; $df_2 - df_5$ were the df s of meteorological factors; $\beta_1 - \beta_3$ were the coefficients of PGDP, PD and NDP, respectively. For $\text{PM}_{2.5}$ and PM_{10} , $df_1 - df_5$ were defined as 1, 4, 5, 4, and 1, respectively. For SO_2 and NO_2 , df_1 was defined as 2, while $df_3 - df_5$ were defined as 1, 4, and 1, respectively. df_2 was missing because the WAT was highly correlated with both SO_2 ($r = -0.79$) and NO_2 ($r = -0.72$), and the WAT was not involved in the single-pollutant model of SO_2 and NO_2 .

By referring to the annual average concentration threshold of each air pollutant specified by the National Ministry of Ecology and Environmental Protection (GB3095-2012), we defined the reference values as $35 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, $70 \mu\text{g}/\text{m}^3$ for PM_{10} , $60 \mu\text{g}/\text{m}^3$ for SO_2 and $40 \mu\text{g}/\text{m}^3$ for NO_2 . We calculated the cumulative relative risk (RR) and 95% confidence interval (CI) to express the strength of association between every $10 \mu\text{g}/\text{m}^3$ increase in each air pollutant concentration and active TB risk (Zhu et al., 2018).

We further assessed whether the effects of air pollutants were modified by gender or age. We calculated the 95% CI to identify the difference between subgroup effects using the following formula:

$(\hat{Q}_1 - \hat{Q}_2) \pm 1.96 \sqrt{(\hat{SE}_1)^2 + (\hat{SE}_2)^2}$. In this formula, \hat{Q}_1 and \hat{Q}_2 are the point estimates of the RRs, and \hat{SE}_1 and \hat{SE}_2 are their standard errors. If the 95% CI contained a value of zero, there was no evidence showing modification by gender or age (Huang et al., 2018; Schenker and Gentleman, 2001). Since $\text{PM}_{2.5}$ and SO_2 were highly correlated with the other three air pollutants, we constructed the multipollutant model only for PM_{10} and NO_2 in order to evaluate the stability of the effects.

All analyses were performed with the "dlnm", "mgcv" and "splines" packages in R software version 3.5.3 (<https://www.r-project.org/>). The significance level was set at 0.05.

Results

Characteristics of TB cases

There were 7,282 active TB cases reported in the study area from 2014 to 2017, with an annual incidence of $34.39/10^5$. As shown in Table 1, 74.43% of TB cases were males and 60.24% were younger than 60 years old. Most cases (82.00%) were manual workers and were of Han nationality (99.71%). Only 3.17% were migrant populations. Figure 1 shows the number of weekly reported TB cases from 2014 to 2017.

Characteristics of air pollutants and meteorological factors

The weekly average concentration of air pollutants is also shown in Figure 1. The range of weekly average concentrations was $15.29-156.71 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, $29.43-234.60 \mu\text{g}/\text{m}^3$ for PM_{10} , $4.43-79.60 \mu\text{g}/\text{m}^3$ for SO_2 , and $10.86-65.57 \mu\text{g}/\text{m}^3$ for NO_2 . The annual median (interquartile range) concentration of each air pollutant was 45.86 ($34.57-64.14$) $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, $85.43 \mu\text{g}/\text{m}^3$

Table 1

Characteristics of newly reported active tuberculosis cases in Lianyungang, 2014–2017.

Characteristics	N (%)
Gender	
Male	5420 (74.43)
Female	1862 (25.57)
Age group	
<60 years old	4387 (60.24)
≥60 years old	2895 (39.76)
Occupation	
Students	354 (4.86)
Manual workers	5971 (82.00)
Office workers	92 (1.26)
Unemployed	518 (7.11)
Retired	179 (2.46)
Others	168 (2.31)
Race	
Han nationality	7261 (99.71)
Others	21 (0.29)
Household register	
Local residents	7051 (96.83)
Other cities residents	231 (3.17)
Type of TB	
Pulmonary TB	7281 (99.99)
Extrapulmonary TB	1 (0.01)

($62.86-116.14$) for PM_{10} , $22.00 \mu\text{g}/\text{m}^3$ ($15.71-30.86$) for SO_2 and 30.00 ($23.29-38.57$) $\mu\text{g}/\text{m}^3$ for NO_2 . The information on five meteorological factors is also listed in Table 2.

The four air pollutants were positively associated with each other ($P < 0.01$). $\text{PM}_{2.5}$, PM_{10} and SO_2 were positively associated with WAP and negatively associated with WAT and WAH ($P < 0.01$), while NO_2 was positively associated with WAP ($P < 0.01$) and negatively associated with WAT, WAS, WAH and WAST ($P < 0.05$) (Table 3).

$\text{PM}_{2.5}$ and TB

As shown in Figure 2 (A1 and A2), for the single-pollutant model, the association between a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration and active TB was significant (with reference to $35 \mu\text{g}/\text{m}^3$). The cumulative RR reached its maximum at a lag of 24 weeks (RR: 1.12, 95% CI: 1.03–1.22) (Table 4). After stratification by gender and age, the association remained significant in males (RR: 1.13, 95% CI: 1.03–1.24) and young groups (RR: 1.13, 95% CI: 1.02–1.24). The effect was not altered by gender or age ($P > 0.05$) (Table S1).

PM_{10} and TB

As shown in Figure 2 (B1 and B2), for the single-pollutant model, the association between a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} concentration and active TB was significant (with reference to $70 \mu\text{g}/\text{m}^3$). The cumulative RR reached its maximum at a lag of 21 weeks (RR: 1.11, 95% CI: 1.06–1.17) (Table 5). After stratification by gender and age, the associations remained significant in each subgroup. In the multipollutant model, the association was still significant, with a cumulative RR of 1.07 (95% CI: 1.02–1.13) at a lag of 0 to 21 weeks (Table 5). The associations remained significant in males (1.07, 95% CI: 1.02–1.14), young (1.06, 95% CI: 1.00–1.13) and old groups (1.09, 95% CI: 1.01–1.17). The effect was not altered by gender or age ($P > 0.05$) (Table S2).

SO_2 and TB

As shown in Figure 2 (C1 and C2), for the single-pollutant model, the association between a $10 \mu\text{g}/\text{m}^3$ increase in SO_2 concentration and active TB was significant (with reference to $60 \mu\text{g}/\text{m}^3$). The cumulative RR reached a maximum at a lag of 20

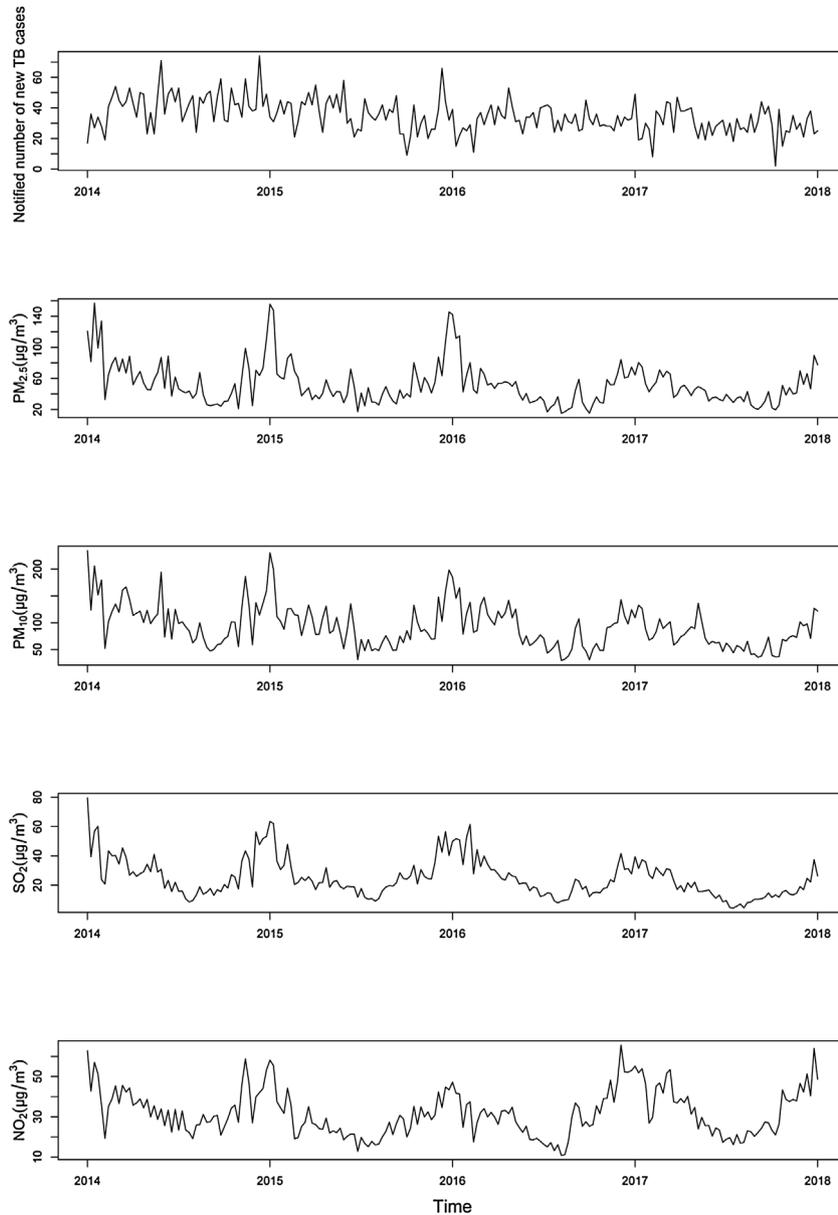


Figure 1. Weekly reported numbers of new TB cases and weekly average air pollution concentrations in Lianyungang, 2014–2017.

TB: tuberculosis; PM_{2.5}: particulate matter with aerodynamic diameter of $\leq 2.5 \mu\text{m}$; PM₁₀: particulate matter with aerodynamic diameter of $\leq 10 \mu\text{m}$; SO₂: sulfur dioxide; NO₂: nitrogen dioxide.

Table 2

Weekly average air pollutant and meteorological indicators in Lianyungang, 2014–2017.

Variables	Minimum	Q ₂₅	Median	Mean	Q ₇₅	Maximum
Pollutant concentration						
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	15.29	34.57	45.86	52.30	64.14	156.71
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	29.43	62.86	85.43	92.54	116.14	234.60
SO ₂ ($\mu\text{g}/\text{m}^3$)	4.43	15.71	22.00	24.83	30.86	79.60
NO ₂ ($\mu\text{g}/\text{m}^3$)	10.86	23.29	30.00	31.84	38.57	65.57
Meteorological indicator						
Temperature ($^{\circ}\text{C}$)	-4.24	5.64	16.19	14.79	22.94	31.00
Air pressure (hPa)	1001.00	1009.00	1017.00	1017.00	1025.00	1034.00
Wind speed (m/s)	1.57	2.14	2.47	2.50	2.80	4.27
Relative humidity (%)	46.71	66.00	74.71	73.90	82.29	92.00
Sunshine time (h)	0.91	4.93	6.30	6.20	7.60	11.17

Q₂₅: 25% quartile; Q₇₅: 75% quartile; PM_{2.5}: particulate matter with aerodynamic diameter of $\leq 2.5 \mu\text{m}$; PM₁₀: particulate matter with aerodynamic diameter of $\leq 10 \mu\text{m}$; SO₂: sulfur dioxide; NO₂: nitrogen dioxide.

Table 3
Spearman rank correlation coefficients between weekly average air pollutant concentrations and meteorological factors in Lianyungang, 2014–2017.

Variables	PM _{2.5}	PM ₁₀	SO ₂	NO ₂	Temperature	Air pressure	Wind speed	Relative humidity	Sunshine time
PM _{2.5}	1	0.92**	0.79**	0.74**	−0.64**	0.55**	−0.09	−0.45**	−0.09
PM ₁₀		1	0.81**	0.67**	−0.59**	0.48**	0.03	−0.51**	0.04
SO ₂			1	0.73**	−0.79**	0.72**	−0.04	−0.59**	−0.04
NO ₂				1	−0.72**	0.71**	−0.30**	−0.47**	−0.14*
Temperature					1	−0.93**	0.03	0.52**	0.30**
Air pressure						1	−0.19**	−0.48**	−0.28**
Wind speed							1	−0.13	0.10
Relative humidity								1	−0.46**
Sunshine time									1

PM_{2.5}: particulate matter with aerodynamic diameter of ≤2.5 μm; PM₁₀: particulate matter with aerodynamic diameter of ≤10 μm; SO₂: sulfur dioxide; NO₂: nitrogen dioxide; **: P < 0.01; *: P < 0.05.

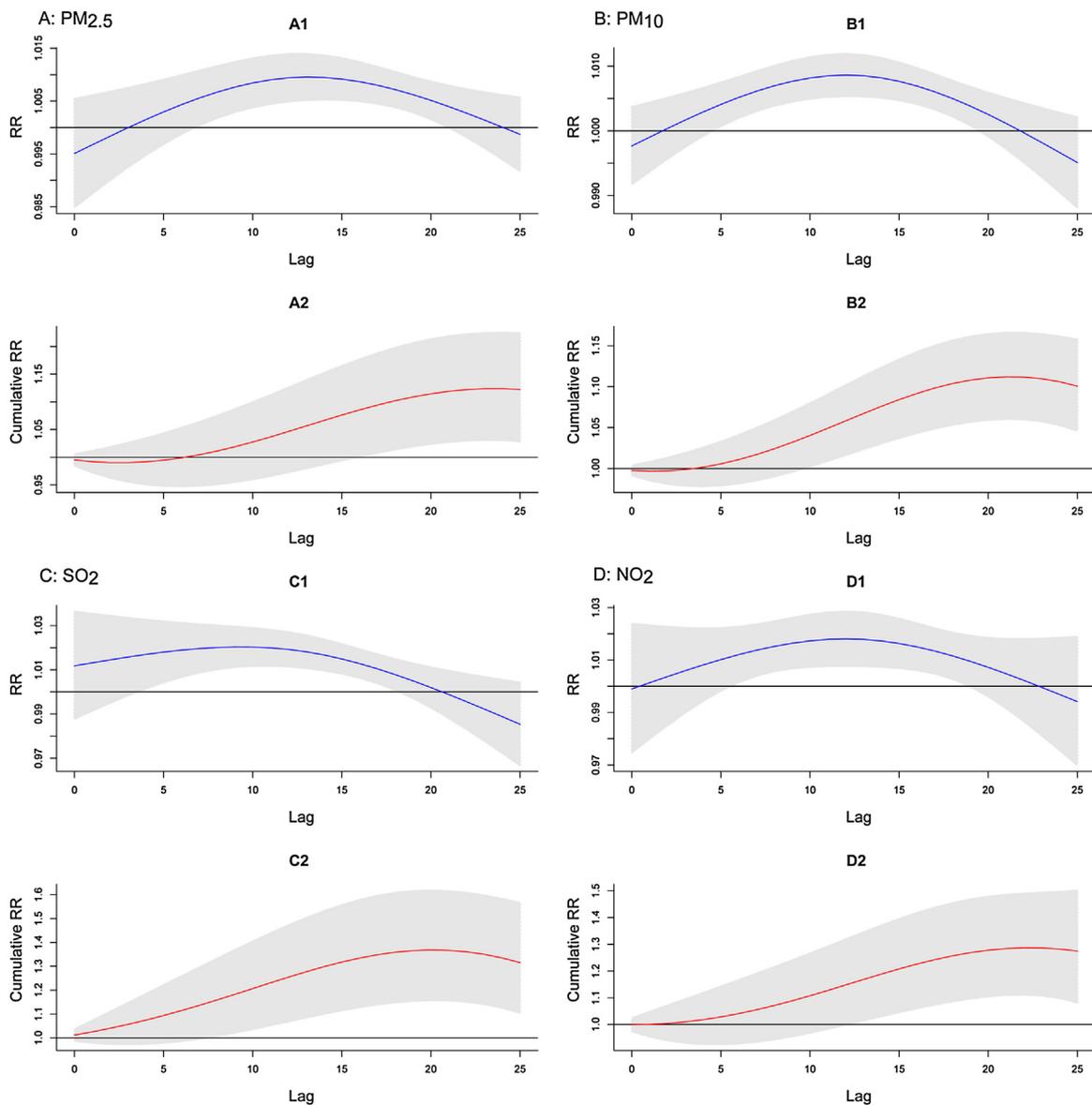


Figure 2. The relative risk of a 10 μg/m³ increase in four air pollutants on active TB cases at different lag weeks, based on the single-pollutant model. RR: relative risk; CI: confidence interval; PM_{2.5}: particulate matter with aerodynamic diameter of ≤2.5 μm; PM₁₀: particulate matter with aerodynamic diameter of ≤10 μm; SO₂: sulfur dioxide; NO₂: nitrogen dioxide; TB: tuberculosis; Pooled RRs (A1, B1, C1 and D1); Cumulative RRs (A2, B2, C2 and D2).

weeks (RR: 1.37, 95% CI: 1.16–1.62) (Table 6). After stratification by gender and age, the associations remained significant in each subgroup. The effect was not altered by gender or age (P > 0.05) (Table S3).

NO₂ and TB

As shown in Figure 2 (D1 and D2), for the single-pollutant model, the association between a 10 μg/m³ increase in NO₂

Table 4

Cumulative RR and 95% CI for the association between a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration and active TB cases at a lag of 0 to 24 weeks in Lianyungang, 2014–2017.

Variables	Single-pollutant model ^a
All cases	1.12 (1.03–1.22)
Sex	
Male	1.13 (1.03–1.24)
Female	1.11 (0.97–1.26)
Age group	
<60 years old	1.13 (1.02–1.24)
≥ 60 years old	1.11 (0.98–1.25)

RR: relative risk; CI: confidence interval; $\text{PM}_{2.5}$: particulate matter with aerodynamic diameter of $\leq 2.5 \mu\text{m}$; TB: tuberculosis.

^a Adjusted for long-term trend, meteorological factors (temperature, wind speed, relative humidity and sunshine time) and socioeconomic indicators (per capita gross domestic product, population density and the number of doctors per 10,000 people).

Table 5

Cumulative RR and 95% CI for the association between a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} concentration and active TB cases at a lag of 0 to 21 weeks in Lianyungang, 2014–2017.

	Single-pollutant model ^a	Multipollutant model ^b
All cases	1.11 (1.06–1.17)	1.07 (1.02–1.13)
Sex		
Male	1.12 (1.06–1.18)	1.07 (1.02–1.14)
Female	1.10 (1.02–1.18)	1.08 (0.99–1.17)
Age group		
<60 years old	1.12 (1.06–1.18)	1.06 (1.00–1.13)
≥ 60 years old	1.10 (1.03–1.18)	1.09 (1.01–1.17)

RR: relative risk; CI: confidence interval; PM_{10} : particulate matter with aerodynamic diameter of $\leq 10 \mu\text{m}$; TB: tuberculosis.

^a Adjusted for long-term trend, meteorological factors (temperature, wind speed, relative humidity and sunshine time) and socioeconomic indicators (per capita gross domestic product, population density and the number of doctors per 10,000 people).

^b Adjusted for long-term trend, meteorological factors (wind speed, relative humidity and sunshine time), socioeconomic indicators (per capita gross domestic product, population density and the number of doctors per 10,000 people) and NO_2 .

Table 6

Cumulative RR and 95% CI for the association between a 10 $\mu\text{g}/\text{m}^3$ increase in SO_2 concentration and active TB cases at a lag of 0 to 20 weeks in Lianyungang, 2014–2017.

	Single-pollutant model ^a
All cases	1.37 (1.16–1.62)
Sex	
Male	1.39 (1.16–1.66)
Female	1.33 (1.03–1.72)
Age group	
<60 years old	1.36 (1.13–1.63)
≥ 60 years old	1.37 (1.08–1.74)

RR: relative risk; CI: confidence interval; SO_2 : sulfur dioxide; TB: tuberculosis.

^a Adjusted for long-term trend, meteorological factors (wind speed, relative humidity and sunshine time) and socioeconomic indicators (per capita gross domestic product, population density and the number of doctors per 10,000 people).

concentration and active TB was significant (with reference to 40 $\mu\text{g}/\text{m}^3$). The cumulative RR reached its maximum at a lag of 22 weeks (RR: 1.29, 95% CI: 1.11–1.49) (Table 7). After stratification by gender and age, the association remained significant in each subgroup. In the multipollutant model, the association was still significant, with a cumulative RR of 1.30 (95% CI: 1.11–1.53) at a lag of 0 to 22 weeks (Table 7). After stratification by gender and age, the associations remained significant in each subgroup. The effect was not altered by gender or age ($P > 0.05$) (Table S4).

Table 7

Cumulative RR and 95% CI for the association between a 10 $\mu\text{g}/\text{m}^3$ increase in NO_2 concentration and active TB cases at a lag of 0 to 22 weeks in Lianyungang, 2014–2017.

	Single-pollutant model ^a	Multipollutant model ^b
All cases	1.29 (1.11–1.49)	1.30 (1.11–1.53)
Sex		
Male	1.28 (1.09–1.50)	1.29 (1.08–1.54)
Female	1.32 (1.06–1.65)	1.35 (1.05–1.72)
Age group		
<60 years old	1.30 (1.11–1.52)	1.30 (1.09–1.55)
≥ 60 years old	1.26 (1.02–1.55)	1.35 (1.08–1.69)

RR: relative risk; CI: confidence interval; NO_2 : nitrogen dioxide; TB: tuberculosis.

^a Adjusted for long-term trend, meteorological factors (wind speed, relative humidity and sunshine time) and socioeconomic indicators (per capita gross domestic product, population density and the number of doctors per 10,000 people).

^b Based on a single-pollutant model, adjusted with PM_{10} .

Discussion

In this time-series study performed in a northeastern region of Jiangsu Province, China, we observed a potential correlation between relatively long-term outdoor exposure to $\text{PM}_{2.5}$, PM_{10} , SO_2 and NO_2 , and active TB. Ambient PM_{10} and NO_2 remained significant in the multipollutant models, and the association was not altered in subgroups of different genders and ages. To date, this is the first DLNM-based time-series study exploring the role of relatively long-term outdoor air pollution on active TB risk.

A study in Chengdu, China also reported exposure to ambient PM_{10} , NO_2 and SO_2 in relation to increased morbidity of TB (Zhu et al., 2018). However, the maximum lag time in their model was 28 days for PM_{10} and 5 days for SO_2 and NO_2 , which could only estimate the short-term effects. Progression from infection with M. tb to the clinically observable immunological response usually takes a few months or even several years, and the diagnosis and reporting of TB also require some time; this lag time should be included in the time-series model (Murray et al., 2011; You et al., 2016). The commonly used lag time in TB modeling was two months though sometimes, up to six months was used (Leung et al., 2005). Therefore, we set the maximum lag time as 25 weeks, which was rational and could be applied to evaluate a relatively long-term effect caused by air pollution exposure.

The particle diameter of $\text{PM}_{2.5}$ is fine enough to reach the pulmonary alveoli along the respiratory tract. $\text{PM}_{2.5}$ and some toxic compounds attached to it may contribute to a variety of diseases (Chen and Kan, 2008; Guan et al., 2016; Raaschou-Nielsen et al., 2013). In a systematic review, the pollutant most frequently associated with TB outcomes was $\text{PM}_{2.5}$, where 4 out of 6 studies demonstrated a significant association (Popovic et al., 2019). However, previous studies have shown inconsistent conclusions on the relationship between ambient PM_{10} and SO_2 exposure and active TB risk (Popovic et al., 2019).

A study in Taipei found that increased concentration of PM_{10} increased the incidence of culture-positive TB, which is consistent with our results (Chen et al., 2016). However, the effect of PM_{10} did not appear to be associated with TB in other studies in northern California (Smith et al., 2016) and South Korea (Hwang et al., 2014). This inconsistency may be partly attributed to a disparity in air pollutant levels. For example, the median concentration of PM_{10} was 20.6 $\mu\text{g}/\text{m}^3$ in northern California and 62.8 $\mu\text{g}/\text{m}^3$ in South Korea, which were lower than the value of our study at 85.4 $\mu\text{g}/\text{m}^3$. In addition, other factors such as meteorological conditions and socioeconomic levels may also differ in ways that impact the exposure-response effect (Zhu et al., 2018).

SO_2 , a dominant air pollutant, is released into the atmosphere through the combustion of fossil fuels for energy conversion. A

study in South Korea reported that an increased concentration of SO₂ might increase the morbidity of TB in males but not in females (Hwang et al., 2014). Conversely, a study in Ningbo, China, found that exposure to SO₂ might function as a protective factor against TB (Ge et al., 2017). This counterintuitive protective effects may be attributed to the antimicrobial properties of SO₂. It is noteworthy that these studies explored the effects of SO₂ on TB in the context of short-term exposure.

Since inhaling high concentrations of NO₂ can irritate the respiratory tract, people living in environments with high concentrations of NO₂ may be more susceptible to respiratory infections. An increased concentration of NO₂ contributed to the increased morbidity of active TB in Taiwan (Lai et al., 2016) and northern California (Smith et al., 2016). Our results also indicated a positive link between NO₂ exposure and TB risk. The cumulative RR reached its maximum at a lag of 22 weeks, and this association was not altered by gender or age.

The potential role of outdoor exposure to air pollution in active TB may be explained by the following reasons. First, the mucous lining of the human nasal and respiratory tract surface is the first line of defense in combating M.tb infection by stopping it from entering the pulmonary alveoli. Exposure to ambient air pollutants may weaken the clearance of respiratory secretions, resulting in M.tb escaping the first line of host defense (Zhu et al., 2018). Second, particulate matter, particularly PM_{2.5}, can reach the pulmonary alveoli and impair the defense function of alveolar macrophages (Ni et al., 2015). Additionally, both NO₂ and SO₂ are easily soluble in water, which makes them able to damage the upper respiratory tract mucosa. Third, during the early phase of infection, alveolar macrophages can inhibit the proliferation of M.tb by phagocytosis and the formation of granulomas in the lungs (Palanisamy et al., 2011), while SO₂ can affect the macrophage function and the ability of alveolar clearance and mucociliary transport (Hwang et al., 2014). Exposure to SO₂ at a concentration of 12.5 ppm in vitro can cause the death of 62% of alveolar macrophages within 30 minutes (Kienast et al., 1993). Fourth, continuous exposure to SO₂ and NO₂ might decrease the production of tumor necrosis factor (TNF)-α and interferon-gamma (IFN-γ) (Saito et al., 2002a,b), which are essential for combating M.tb infection (Dutta and Karakousis, 2014; Flad et al., 1995; Fremont et al., 2005).

Our study has several limitations. First, our data on ambient pollutant concentrations came from local environmental monitoring terminal stations and might not provide precise exposure estimates for the entire city. Second, we assumed that all the inhabitants of this study were exposed to similar weekly average levels of ambient air pollutants. There may exist an ecological fallacy, and the misclassification of exposure is inevitable. Due to missing data, other air pollutants such as CO and O₃ were not included in our study.

Conclusions

Our results indicate that exposure to ambient PM_{2.5} (lag 0–24 weeks), PM₁₀ (lag 0–21 weeks), SO₂ (lag 0–20 weeks) and NO₂ (lag 0–22 weeks) can increase the risk of active TB. Reducing the concentration of ambient air pollutants is likely to bring about health benefits in TB-endemic areas.

Author contributions

ZL, XM and JW conceived and designed the study. ZL, XM, QL, HS, YJ, DX, BQ and DT were involved in the data analysis and collection. ZL and XM conducted the data analysis and interpretation. ZL, XM and JW drafted and wrote the article and all authors provided critical revisions. All authors approved the final version of the article.

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Competing interests

The authors declare no competing financial interest.

Patient consent for publication

Not required.

Data sharing statement

All data generated or analyzed during this study are included in this published article.

Ethical approval

This study was approved by the ethics committee of Nanjing Medical University.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2019.07.027>.

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