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Association between long-term exposure to ambient air pollutants and the risk of tuberculosis: A time-series study in Nantong, China

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A R T I C L E I N F O

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Tuberculosis
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A B S T R A C T

Background: Increasing evidence has shown that the risk of tuberculosis (TB) might be related to the exposure to air pollutants; however, the findings are inconsistent and studies on long-term air pollutant exposure and TB risk are scarce. This study aime to assess the relationship between monthly exposure to air pollution and TB risk in Nantong, China.
Methods: We collected the time series data on the number of TB cases, as well as environmental and socioeconomic covariates from January 2005 to December 2020. The impact of air pollutant exposure on TB risk was evaluated using the distributed lag nonlinear model (DLNM). Stratified analyses were conducted to examine the effect modifications of sex and age on the association between air pollutants and TB risk. Sensitivity analyses were applied to test the stability of the model.
Results: There were a total of 54,096 cases of TB in Nantong during the study period. In the single-pollutant model, for each 10 $\mu g/m^3$ increase in concentration, the pooled relative risks (RRs) of TB reached the maximum to 1.10 (95% confidence interval (CI): 1.04–1.16, lag 10 months) for particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), 1.05 (95% CI: 1.01–1.10, lag 9 months) for particulate matter with aerodynamic diameter less than 10 μm (PM_{10}), and 1.11 (95%CI: 1.04–1.19, lag 10 months) for nitrogen dioxide (NO_2). Ozone (O_3) did not show significant effect on TB risk. Effect modifications of sex and age on the association between air pollutants and TB risk were not observed. The multi-pollutant model results showed no significant variation compared with the single-pollutant model.
Conclusions: Our study suggests that air pollutants pose a substantial threat to the TB risk. Reducing air pollution might be crucial for TB prevention and control.

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1. Introduction

Tuberculosis (TB) is one of the oldest diseases in human history. It is caused by *Mycobacterium tuberculosis* (*M.tb*) and primarily affects the lungs, while it can also affect various other organs. As many as 9.9 million new cases of TB were reported globally in 2020. In China, newly diagnosed cases accounted for 8.5% of the global total, ranking second in global prevalence [1].

Air pollution is a significant contributor to multiple health problems affecting various systems of the body [2]. As the fifth leading cause of global mortality, it is a critical public health concern [3]. In recent years, a growing body of research has suggested that air pollutants are associated with TB. For example, an epidemiological study conducted in the United States found a significant correlation between particulate matter exposure of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) and TB risk [4]. Similarly, a study in South Korea showed that long-term exposure to sulfur dioxide (SO_2) was associated with increased TB risk among men, whereas other pollutants had no discernible effect [5]. Meanwhile, a study in Lianyungang city, China, found that exposure to nitrogen dioxide (NO_2), SO_2, particulate matter with aerodynamic diameter less than 10 μm (PM_{10}), and $PM_{2.5}$ were associated with increased TB risk [6].

Research on the link between air pollution exposure and TB risk remains limited. Owing to variations in environmental and socioeconomic covariates, the findings of different studies are not always consistent. Long-term exposure to air pollution has a chronic or sub-acute impact on the respiratory immune system. Few studies have examined the long-term effects of air pollution in existing literature. Evidence from several experiments indicates that the impact of air pollution to human health is nonlinear and exhibits a hysteresis effect. Therefore, a distributed lag nonlinear model (DLNM) was employed to examine the relationship between long-term air pollutant exposure and TB risk in Nantong city, China. In addition, this approach enables the simultaneous consideration of the nonlinear relationship between air pollutants and TB risk, as well as the lag effect of air pollutants on TB incidence [7]. The effects of sex and age on air pollutants and TB risk were also explored.

2. Methods

2.1. Study area and study subjects

Nantong city (31°41′-32°42′N, 120°11′-121°54′E) is situated in Jiangsu Province, East China, covering an area of 8,001 square

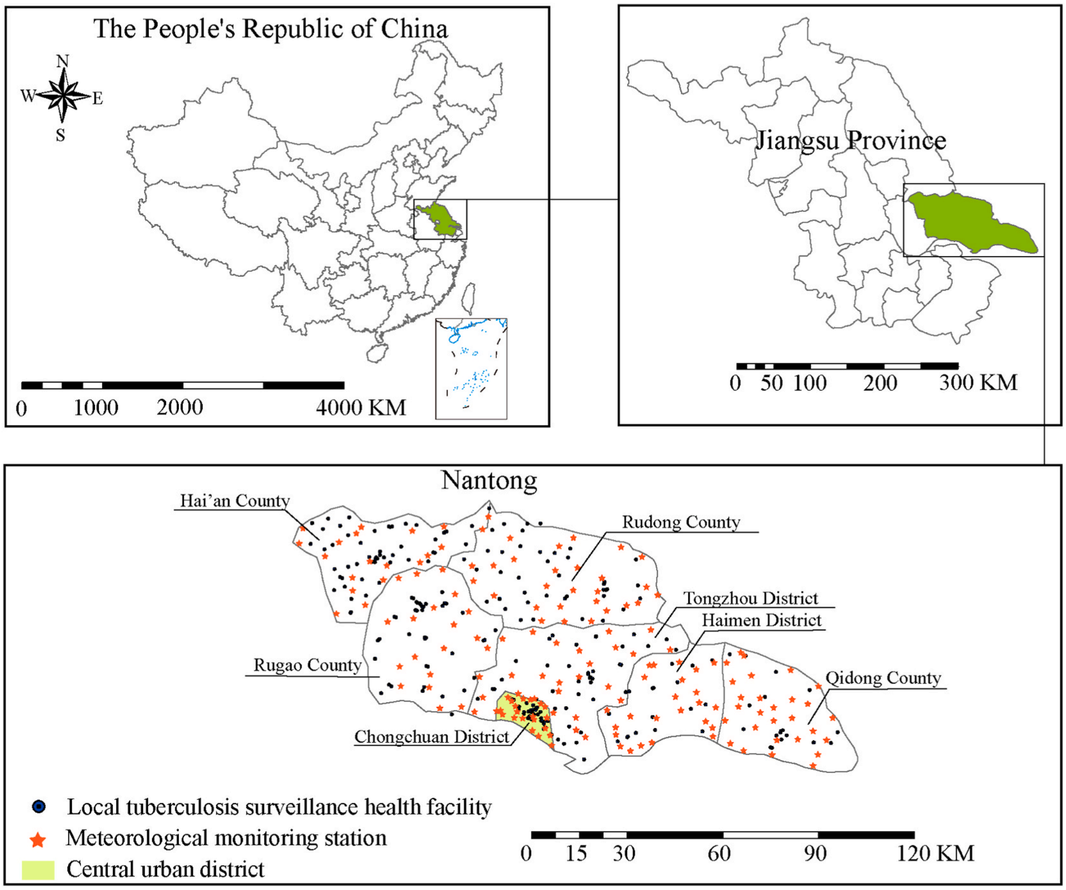

Fig. 1. Map of the distribution of tuberculosis surveillance health facilities and meteorological monitoring stations in Nantong city.

kilometers with a total population of 7,560,600 as of December 2020. Nantong is composed of three districts (Chongchuan, Tongzhou, and Haimen), four county-level cities (Qidong, Rugao, Rudong and Hai'an county) (Fig. 1). The climate in Nantong is mild with four distinct seasons, of which spring and autumn are relatively short. The TB case data from January 2005 to December 2020 were obtained from the Tuberculosis Management Information System. Fig. 1 shows all the TB surveillance health facilities in Nantong.

2.2. Environmental and socioeconomic covariates

Air pollution data were based on satellite-observed aerosol optical depth (AOD) retrievals. The PM_{10}, $PM_{2.5}$, and SO_2 were obtained from the Modern Retrospective Research and Applied Analysis, Second Edition (MERRA-2). The NO_2, carbon monoxide (CO) and ozone (O_3) data were obtained from the Copernicus Atmosphere Monitoring Service Global Reanalysis (EAC4). In particular, the MERRA-2 and EAC4 data were available at the 0.5° latitude × 0.625° longitude and 0.75° × 0.75° grid levels, respectively. The data was resampled to the 0.1° × 0.1° grid level using "interp.surface" bilinear interpolation function in "fields" package of R software. The concentrations of PM_{10} and $PM_{2.5}$ were calculated according to the adopted equations [8,9]. Ground-based pollution data were not utilized primarily because they were only available only after 2016.

Monthly meteorological data, including mean temperature (MT, °C), precipitation (mm), sunlight (h), relative humidity (RH, %), and wind speed (WS, m/s), were obtained from the Nantong Municipal Statistics Bureau (http://tjj.nantong.gov.cn/).

Data on several socioeconomic status (SES) indicators, which included population density (PD), gross domestic product (GDP) per capita, and medical technical personnel (MTP) per 1000 population were also collected from the Nantong Municipal Statistics Bureau.

2.3. Time series analysis

The seasonality of TB incidence was analyzed using the time-series decomposition method (X-11). The seasonal index was calculated as the ratio of the mean number of observed TB cases in the same month of the study period to the mean number of TB cases for the entire study period. Significant seasonal variation was determined by the seasonal index which was greater or less than 1 for the particular month [10].

2.4. Construction of non-linear models with distributional lags

Spearman's rank correlation analysis was used to investigate the correlations between the variables. Variables significantly related to TB incidence were selected for further evaluation in the DLNM model. To ensure model stability, only correlations ($|r|<0.7$) were selected for inclusion in the DLNM to avoid multicollinearity [11].

The DLNM was used to investigate the association between air pollutants and TB incidence, as well as the lag effect. As the occurrence of TB is a small-probability event, its distribution is approximately a Poisson distribution, with excessively discrete data, and a quasi-Poisson function with a log connection was selected for the connection function in this model [12]. First, a basic model without air pollutants was developed. Meteorological factors, binary variable "Spring-Festival," and socioeconomic indicators were added as covariates [13]. The time variable was fitted with a natural cubic spline function (ns), and the degree of freedom (df) of the time variable was defined based on the principle of minimizing the sum of the absolute values of the partial autocorrelation function (PACF) of the basic model residuals [6]. Meteorological factors were fitted using the ns function with three df [14]. Second, a cross-basis function was developed for each air pollutant, and a linear function was used to fit the exposure-response relationship between air pollutants and TB risk. The ns function was used to model the lag-response relationship [6,12]. The maximum lag time observed in this study was 18 months, because the delay between air pollution exposure and TB cases may be as long as 18 months [15]. Finally, a cross-basis function was integrated into the basic model to construct a single-pollutant model. The final model is shown in ((1):

$$
\begin{aligned}
&Y_t \sim quasiPoisson\ (\mu_t), \\
&log(\mu_t) = \alpha + w_x^T\eta + ns(time, \mathrm{d}f * 16) + \sum ns(M,3) + \sum \beta SES \\
&\qquad\qquad + \varepsilon Sping - Festival
\end{aligned}
\tag{1}
$$

Where the Y_t and μ_t are the actual and expected number of TB cases in month t, respectively; α was an intercept; $w_x^T\eta$ represents the cross-basis function of each air pollutant; the df of the time variable was set to 1; M is the monthly average of five meteorological factors with an empirical value of 3df; β is the regression coefficients of the three socioeconomic covariates, and ε is the regression coefficient of the binary variable "Spring-Festival."

The Class II concentration limits of the National Environmental Quality Standard (GB3095-2012) were used as reference values for each air pollutant. The relative risk (RR) and 95% confidence interval (CI) of TB risk were calculated for each 10 $\mu g/m^3$ increase in air pollutant concentration.

To investigate whether the associations between air pollutants and TB risk were modified by sex and age, we conducted stratified analyses by sex (male, female) and age (<65 years old, ≥65 years old). The Z-test was used to analyze whether there was a difference in the effect modifications between the two groups. (2):

$$Z = \frac{E_1 - E_2}{\sqrt{(\widehat{SE}_1)^2 + (\widehat{SE}_2)^2}} \tag{2}$$

where E_1 and E_2 are the point estimates for both subgroups and $\widehat{SE}_1$ and $\widehat{SE}_2$ are their corresponding standard errors [12].

Sensitivity analyses were conducted to evaluate the robustness of the model results by building multi-pollutant models and changing the dfs (1, 2, 4, and 5) of meteorological factors. The "dlnm" and "splines" packages in R (version 3.2.3) were utilized to conduct all the analyses. p-value<0.05 were defined as statistically significant.

3. Results

3.1. Characteristics of the study samples

During the study period from 2005 to 2020, 54,096 TB cases were identified in Nantong, of 69.8% were male, and 67.0% were young people (Table 1). Table 1 lists the mean and quartile distributions of the environmental and socioeconomic covariates.

Fig. 2A showed the time series of TB cases during the study period. Fig. 2B illustrated an overall downward trend in the number of TB cases since 2005, The time-series seasonal decomposition analysis of TB cases showed a clear seasonal cycle, and also displayed that March was the peak of the epidemic, with the seasonal index value of 1.18 (95%CI: 1.10-1.36) (Fig. 2C and E). Fig. 2D showed the residual data after excluding seasonal and long-term trends.

Boxplots of TB cases, meteorological factors, and air pollutants suggested significant seasonal variations. The number of TB cases was the highest in spring (Fig. 3A). Among the meteorological factors, sunlight and WS were higher in spring, whereas MT, precipitation, and RH were higher in summer (Fig. 3B). The $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO concentrations were higher in winter, and the O_3 concentrations were higher in summer (Fig. 3C).

3.2. Association between TB cases, air pollutants, and meteorological factors

The Spearman rank correlation matrix (Table 2) was used to investigate the relationships among monthly TB cases, air pollutants, and meteorological factors. Two of the six air pollutants (SO_2 and CO), as well as the precipitation variables in the meteorological factors, showed no significant correlation with TB cases ($p > 0.05$) and were therefore excluded from the DLNM. During multivariate model construction, the $PM_{2.5}$ and PM_{10} could not be included in the model simultaneously because of their strong correlation ($r = 0.80$).

Table 1
Descriptive statistics for TB cases, air pollutants, meteorological factors, and socioeconomic covariates in Nantong, 2005–2020.

Variables	Number (%)	Mean ± SD	Centiles				
			Min	P_{25}	P_{50}	P_{75}	Max
TB cases	54096 (100.00)	281.75 ± 109.21	92.00	200.00	265.50	349.50	551.00
Male	37761 (69.80)	196.67 ± 75.17	71.00	140.00	184.50	246.50	389.00
Female	16335 (30.20)	85.08 ± 35.30	21.00	58.50	79.00	106.50	171.00
<65 years old	36245 (67.00)	188.78 ± 72.07	63.00	134.00	179.50	239.00	366.00
≥65 years old	17851 (33.00)	92.97 ± 38.98	29.00	62.00	85.50	115.50	206.00
Pollutant concentration							
$PM_{2.5}$ (μg/m^3)	/	39.30 ± 9.01	18.41	32.78	39.20	45.36	70.37
PM_{10} (μg/m^3)		65.91 ± 12.01	44.72	57.41	64.12	73.43	118.65
SO_2 (μg/m^3)	/	34.79 ± 8.36	12.47	29.11	35.04	39.00	72.98
NO_2 (μg/m^3)	/	31.43 ± 5.63	19.64	27.89	31.49	35.74	52.25
CO (mg/m^3)		0.70 ± 0.18	0.39	0.57	0.69	0.81	1.27
O_3 (μg/m^3)	/	97.91 ± 25.09	39.68	77.33	100.80	117.53	176.28
Meteorological factors							
Mean temperature (°C)	/	16.29 ± 8.69	−0.40	7.80	17.00	23.75	31.20
Precipitation (mm)	/	103.44 ± 98.37	1.10	35.65	69.90	123.80	475.80
Sunlight (h)	/	154.97 ± 47.07	35.20	124.80	152.30	185.50	301.10
Relative humidity (%)	/	77.06 ± 6.06	59.00	73.00	77.00	81.50	92.00
Wind speed (m/s)	/	2.73 ± 0.54	0.90	2.50	2.80	3.10	4.30
Socioeconomic covariates							
population density	/	956.56 ± 4.17	947.31	953.97	956.51	958.84	965.29
GDP per capita (10000 CNY)	/	5.31 ± 2.19	2.04	3.25	5.12	7.39	8.93
MTP per 1000	/	4.28 ± 0.61	3.69	3.80	4.08	4.60	5.66

SD: standard deviation; Min: minimum; P_{25}: 25th percentile; P_{50}: median; P_{75}: 75th percentile; Max: maximum; TB: tuberculosis; $PM_{2.5}$: particulate matter with aerodynamic diameter <2.5 μm; PM_{10}: particulate matter with aerodynamic diameter <10 μm; SO2: sulfur dioxide; NO_2: nitrogen dioxide; CO: carbon monoxide; O3: ozone; GDP: gross domestic product; MTP: medical technical personnel.

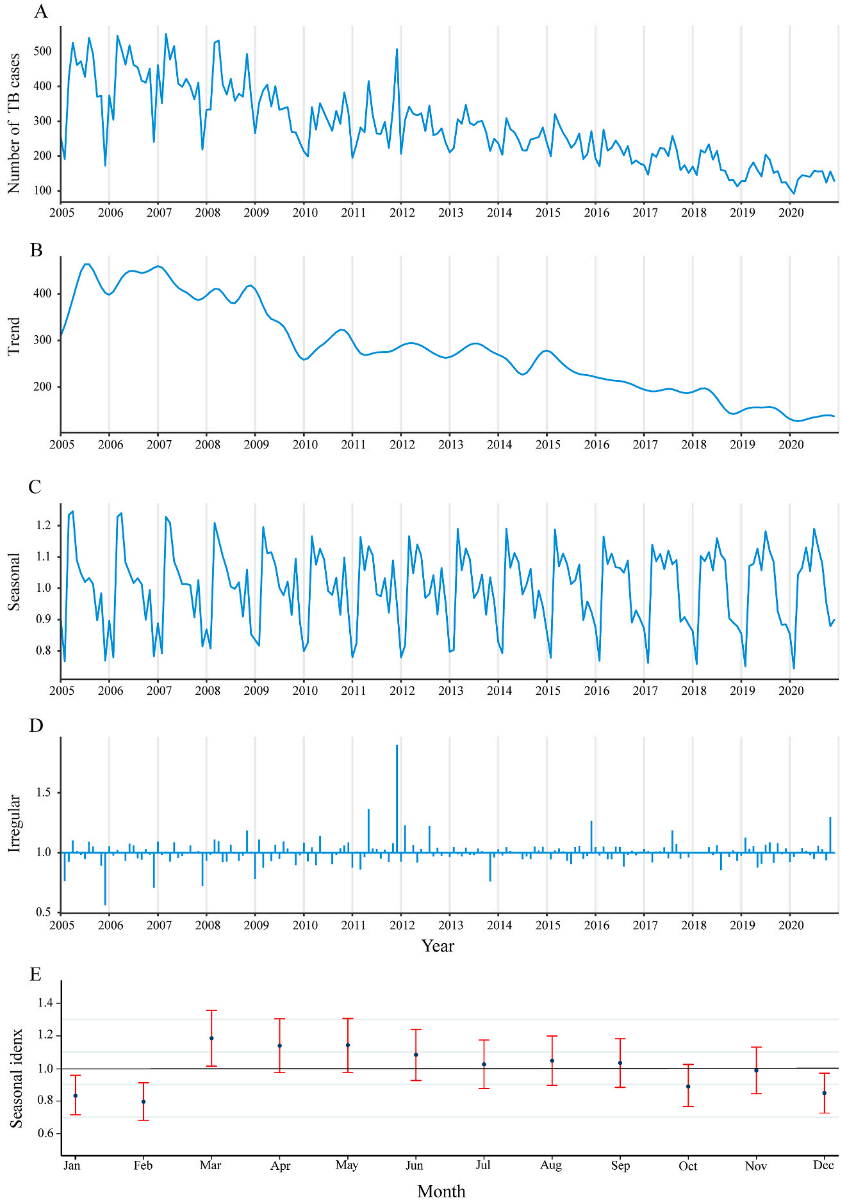

Fig. 2. Temporal distribution of reported TB cases in Nantong city from 2005 to 2020. (A) Time-series of monthly TB cases; (B) a long-term trend was decomposed from the time-series of TB cases; (C) a seasonal trend was decomposed from the time-series of TB cases; (D) the residual data after excluding seasonal and long-term trends; (E) the seasonal index of 12 months.

3.3. Effects of air pollutants on TB risk

In the single-pollutant model, the RR range from 2005 to 2020 was 0.85–1.38 for $PM_{2.5}$ (Fig. 4A), 0.88–1.29 for PM_{10} (Figs. 4B), 0.82-1.13 for NO_2 (Fig. 4C), and 0.90-1.10 for O_3 (Fig. 4D).

The pooled RRs and cumulative RRs of $PM_{2.5}$, PM_{10}, NO_2, and O_3 exposure as well as the TB risk in the single-pollutant model were shown in Fig. 5. A 10 μg/m^3 increase in $PM_{2.5}$ concentration significantly affected TB risk from lag 3 to lag 18 months, peaking in month 10 (RR:1.10, 95%CI: 1.04–1.16). The cumulative TB risk for 18 months was 3.12 (95%CI:1.58–6.18) (Fig. 5A and E). Fig. 5B showed that TB risk was positively associated with a 10 μg/m^3 increase in PM_{10} concentration during the 5–16 months lag. On the ninth month of lag, the lag-specific RR was a maximum of 1.05 (95%CI: 1.01–1.10). The cumulative RR increased with increasing lag months and reached a maximum at a cumulative lag of 18 months (RR:1.73, 95% CI: 1.03–2.92) (Fig. 5F). For a 10 μg/m^3 increase in NO_2 concentration, the effect of NO_2 on TB was significant from lag 3 to lag 18 months. The cumulative RR of TB reached its maximum when the cumulative lag was 18 months (RR: 3.69, 95%CI: 1.62–8.40) (Fig. 5C and G). Neither the lag-specific effect nor cumulative effect models for O_3 were statistically significant (Fig. 5D and H).

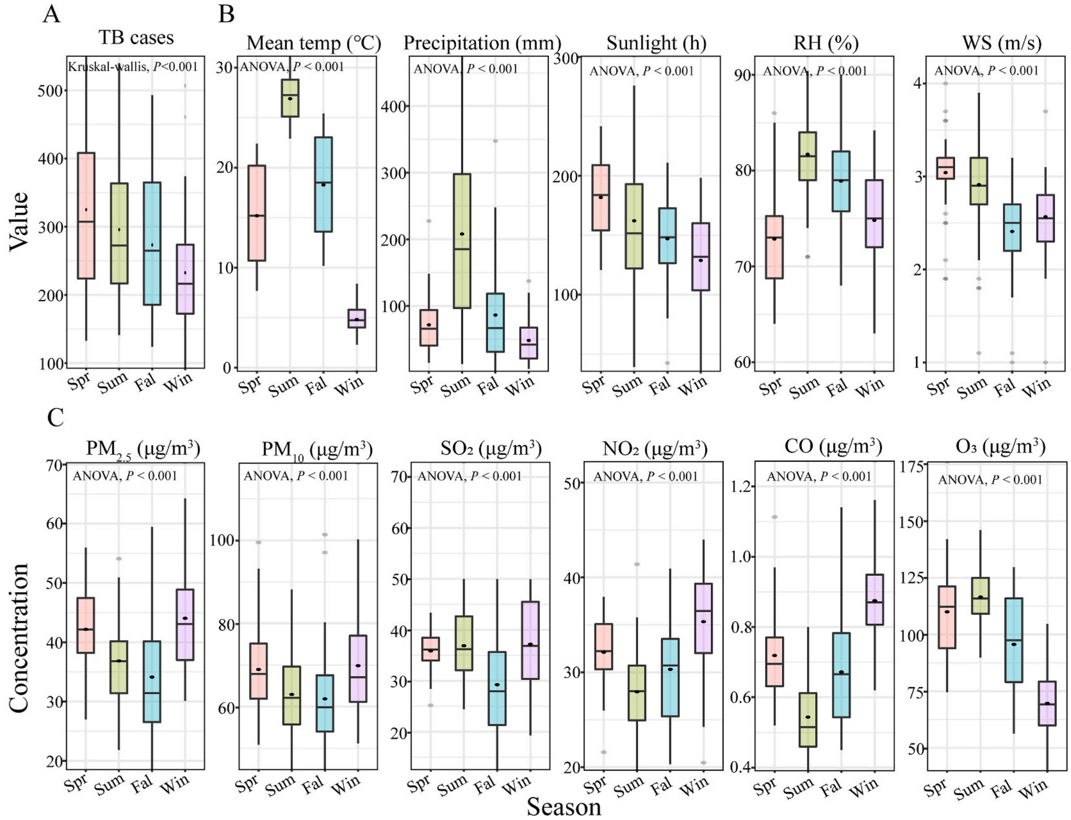

Fig. 3. Boxplots of the number of TB cases, five meteorological factors and six air pollutants in four seasons from 2005 to 2020. (A) The seasonal pattern of TB cases. (B) The seasonal pattern of Meteorological factors. (C) The seasonal pattern of air pollutants. An analysis of variance (ANOVA) test is applied to examine the values or concentrations among the four seasons. A Kruskal-Wallis test is used to examine the TB cases among the four seasons: spring (March to May), summer (June to August), autumn (September to November), and winter (December to February). TB: tuberculosis; RH: Relative humidity; WS: Wind speed; $PM_{2.5}$: particulate matter with aerodynamic diameter <2.5 μm; PM_{10}: particulate matter with aerodynamic diameter <10 μm; SO_2: sulfur dioxide; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone.

3.4. Effect modifications

The $PM_{2.5}$ was positively associated with the TB risk in all subgroups. There was a strong trend towards a risk effect in the older adult subgroup, with a significant increase in TB risk for each 10 μg/m^3 increase in $PM_{2.5}$ concentration, with cumulative RR of 5.16 (95%CI: 2.16–12.33) versus 2.44 (95%CI: 1.23–4.84). The PM_{10} was significantly associated with the TB risk of the male subgroup and the older adult subgroup, with cumulative RR of 1.92 (95%CI: 1.14–3.24) and 2.64 (95%CI:1.35–5.15), respectively. In contrast, no association was found in the female (RR: 1.35, 95%CI: 0.71–2.60) and the non-older adult subgroups (RR: 1.42, 95%CI: 0.85–2.39). Furthermore, in the subgroup analysis of NO_2 and TB risk, there was still a strong trend toward a risk effect in the older adult subgroup, with cumulative RR of 6.37 (95%CI: 2.22–18.30) versus 2.81 (95%CI: 1.24–6.40) for each 10 μg/m^3 increase in NO_2 concentration. However, the results of the z-test did not show any modifying effects of sex and age on the association between air pollutants and TB risk (Table 3).

3.5. Sensitivity analyses

A multi-pollutant model was developed for each air pollutant to assess the sensitivity of our results. The multi-pollutant model results showed no significant variation compared with the single-pollutant model (Table 4). In addition, the stability of the model was evaluated by varying the dfs of the meteorological factors in the DLNM. No significant changes were observed in the key findings (Tables S1–S4). Therefore, we conclude that the model performed well, and the results were reliable and stable.

4. Discussion

The number of TB cases in Nantong showed a downward trend and a clear seasonal cycle between 2005 and 2020. After adjusting for long-term trends, Spring-Festival, meteorological factors, and socioeconomic covariates, increased concentrations of $PM_{2.5}$, PM_{10}, and NO_2 were associated with increased TB risk. No significant effect of O_3 exposure on TB risk was identified. The effects of the air

Table 2
Spearman correlation analysis between the number of tuberculosis cases, air pollutants and meteorological factors in Nantong.

Variables	TB cases	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3	Mean Temperature	Precipitation	Sunlight	Relative Humidity	Wind speed
TB cases	1.000											
$PM_{2.5}$	0.329**	1.000										
PM_{10}	0.326**	0.800**	1.000									
SO_2	−0.133	0.623**	0.451**	1.000								
NO_2	0.309**	0.564**	0.352**	0.684**	1.000							
CO	−0.125	0.648**	0.421**	0.490**	0.755**	1.000						
O_3	0.238**	−0.398**	−0.368**	−0.290**	−0.563**	−0.653**	1.000					
Temperature	0.176*	−0.408**	−0.285**	−0.122	−0.548**	−0.729**	0.700**	1.000				
Precipitation	−0.009	−0.216**	−0.187**	−0.003	−0.358**	−0.407**	0.370**	0.555**	1.000			
Sunlight	0.237**	0.062	0.228**	0.123	−0.048	−0.122	0.286**	0.321**	−0.221**	1.000		
Humidity	−0.203**	−0.501**	−0.422**	−0.245**	−0.435**	−0.463**	0.261**	0.452**	0.585**	−0.434**	1.000	
Wind speed	−0.174*	−0.163*	−0.005	0.038	−0.183*	−0.270**	0.269**	0.147*	0.176*	0.115	0.168*	1.000

TB: tuberculosis; $PM_{2.5}$: particulate matter with aerodynamic diameter less than 2.5 μm; PM_{10}: particulate matter with aerodynamic diameter less than 10 μm; SO_2: sulfur dioxide; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone.
*$p < 0.05$, **$p < 0.01$.

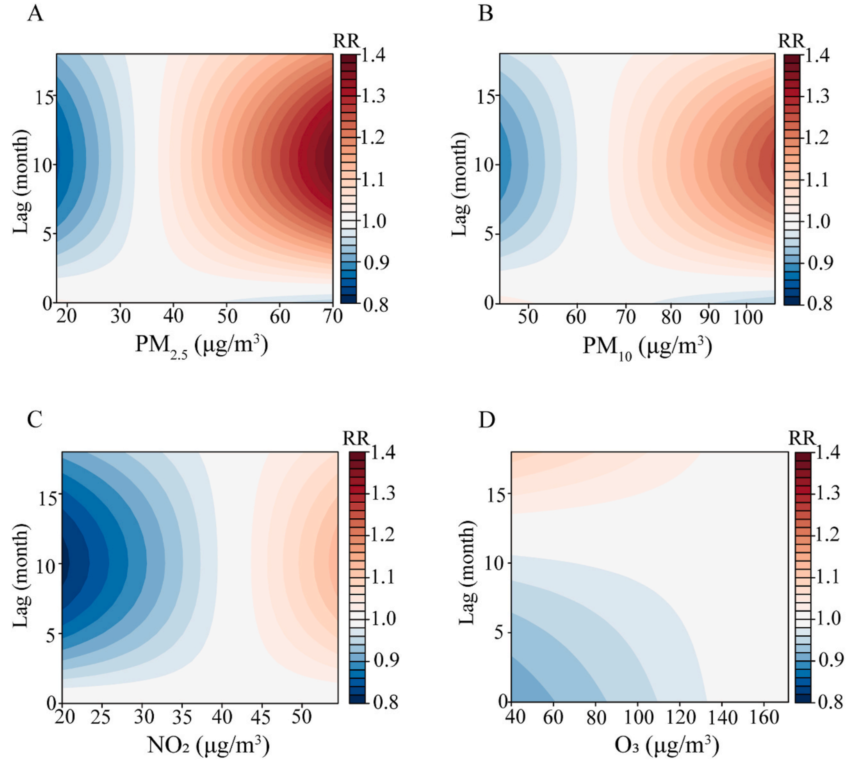

Fig. 4. Contour plots of the exposure-response relationship for the association between TB cases and air pollutants in the single-variable model. (A–D) Four air pollutants from 2005 to 2020. In the single-variable model, we further adjust the temporal trend, meteorological factors, Spring-Festival, and socioeconomic covariates. The Y-axis is the lag month ranging from 0 to 18. The X-axis is the range of the observed values of each variable. The color gradient represents the relative risk (RR). The red color gradient represents higher strength of RR, above 1, and the blue gradient represents lower strength of RR, below 1. The white color represents no difference, at RR = 1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

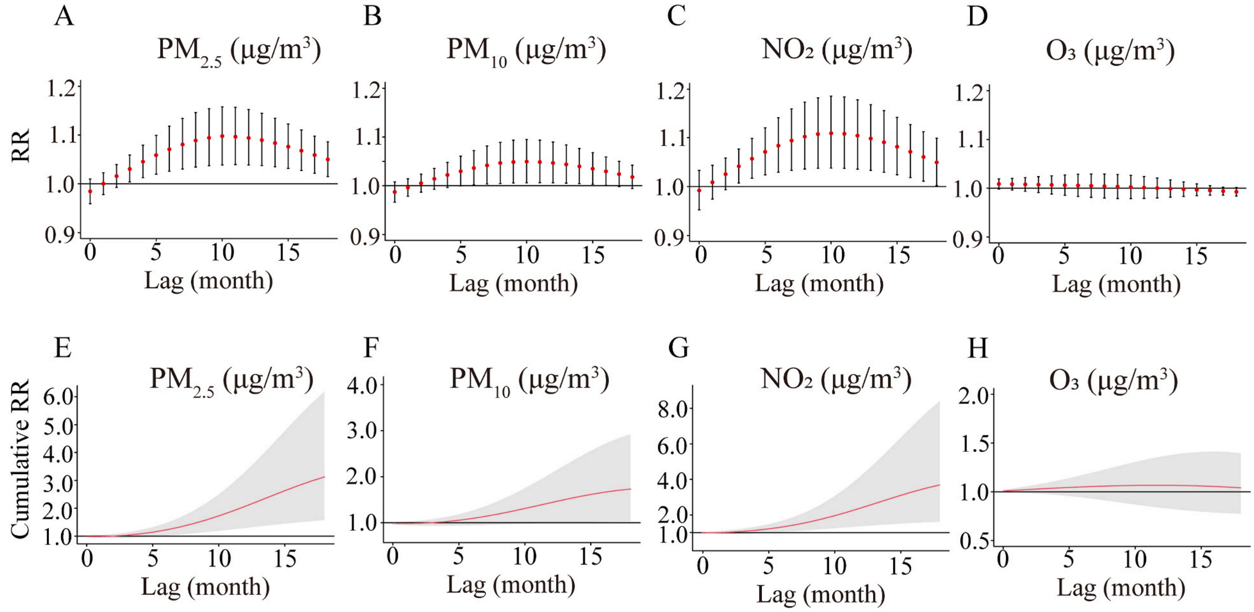

Fig. 5. The lag-specific relative risks and cumulative relative risks of per 10 μg/m^3 increase in four air pollutants on TB cases at different lag months, according to the single-pollutant model. RR: relative risk; $PM_{2.5}$: particulate matter with aerodynamic diameter less than 2.5 μm; PM_{10}: particulate matter with aerodynamic diameter less than 10 μm; NO_2: nitrogen dioxide; O_3: ozone.

Table 3
Cumulative RR (95%CI) for the association between a 10 μg/m^3 increase in air pollutants and TB cases stratified by sex and age, and *p*-value for testing difference.

Pollutants	Classification	Category	Cumulative RR (95%CI)	*p*-value
$PM_{2.5}$	Sex	Male	3.16 (1.59, 6.26)	0.764
		Female	3.03 (1.29, 7.10)	
	Age group	<65 years old	2.44 (1.23, 4.84)	0.472
		≥65 years old	5.16 (2.16, 12.33)	
PM_{10}	Sex	Male	1.92 (1.14, 3.24)	0.140
		Female	1.35 (0.71, 2.60)	
	Age group	<65 years old	1.42 (0.85, 2.39)	0.387
		≥65 years old	2.64 (1.35 5.15)	
NO_2	Sex	Male	3.66 (1.60, 8.35)	0.938
		Female	3.74 (1.34, 10.45)	
	Age group	<65 years old	2.81 (1.24, 6.40)	0.551
		≥65 years old	6.37 (2.22, 18.30)	
O_3	Sex	Male	0.96 (0.72, 1.29)	0.267
		Female	1.25 (0.87, 1.78)	
	Age group	<65 years old	1.08 (0.81, 1.44)	0.128
		≥65 years old	0.98 (0.67, 1.41)	

RR: relative risk; CI: confidence interval; TB: tuberculosis; $PM_{2.5}$: particulate matter with aerodynamic diameter less than 2.5 μm; PM_{10}: particulate matter with aerodynamic diameter less than 10 μm; NO_2: nitrogen dioxide; O_3: ozone.

Table 4
Cumulative RR (95%CI) of TB risks associated with per 10 μg/m^3 increase in air pollutant concentration in Nantong.

Pollutants		Cumulative RR (95%CI)
$PM_{2.5}$		3.12 (1.58, 6.18)
	+ NO_2	3.31 (1.68, 6.54)
	+ O_3	2.79 (1.41, 5.51)
	+ NO_2 + O_3	2.77 (1.40, 5.45)
PM_{10}		1.73 (1.03, 2.92)
	+ NO_2	1.87 (1.11, 3.17)
	+ O3	1.54 (0.89, 2.67)
	+ NO_2 + O_3	1.61 (0.93, 2.80)
NO_2		3.69 (1.62, 8.40)
	+ $PM_{2.5}$	3.99 (1.75, 9.08)
	+ PM_{10}	4.28 (1.87, 9.80)
	+ O_3	3.48 (1.48, 8.17)
	+ $PM_{2.5}$ + O_3	3.48 (1.46, 8.30)
	+ PM_{10} + O_3	3.76 (1.60, 8.83)
O_3		1.04 (0.78, 1.40)
	+ $PM_{2.5}$	1.03 (0.76, 1.38)
	+ PM_{10}	1.01 (0.75, 1.35)
	+ NO_2	1.02 (0.76, 1.37)
	+ $PM_{2.5}$ + NO_2	1.01 (0.75, 1.36)
	+ PM_{10} + NO_2	1.00 (0.74, 1.34)

RR: relative risk; CI: confidence interval; TB: tuberculosis; $PM_{2.5}$: particulate matter with aerodynamic diameter less than 2.5 μm; PM_{10}: particulate matter with aerodynamic diameter less than 10 μm; NO_2: nitrogen dioxide; O_3: ozone.

pollutants $PM_{2.5}$ and NO_2 on TB risk remained statistically significant across subgroups in the stratified analysis. PM_{10} exposure was positively associated with TB risk in the male and older adult subgroup. However, there was no modifying effect of sex and age on the association between air pollutants and the TB risk. Sensitivity analysis confirmed the reliability and robustness of the results.

In the study, we set the maximum lag time at 18 months. An epidemiological study in the Netherlands found a median latency of 1.26 years for TB cases [16]. However, there is often a delay between the onset of symptoms and diagnosis, including delays in patients seeking diagnosis and health care providers. One study reported a total delay of 62 days ((Interquartile range (IQR):38–102) in getting a diagnosis after the onset of symptoms of TB [17]. The effect of air pollutant exposure on TB risk was also observed in the Jinan, China study from up to 18 months [15].

Particulate matter (PM) is a mixture of tiny solid particles and liquid droplets suspended in the air and can be classified as $PM_{2.5}$ and PM_{10} according to their diameter. This study confirmed that $PM_{2.5}$ and PM_{10} exposure increased the risk of TB, which had been supported by various ecological studies [18,19]. The $PM_{2.5}$ and PM_{10} share similar mechanisms of action. They enable aerosolized nuclear energy-carrying *M. tb* to colonize deep into lung tissues [20]. The PMs also disrupts the iron balance in respiratory epithelial cells, promoting the accumulation of iron in the cells, creating an environment conducive to the growth of *M. tb* [21]. The PM exposure could lead to the senescence of alveolar type II epithelial cells, downregulate the expression of antimicrobial peptides human β-defensin 2 (HBD-2) and HBD-3, and increase the growth of intracellular *M. tb* [22]. Furthermore, PM exposure can damage the antibacterial T-cell immune function of the body [23].

The NO_2 exposure was associated with an increased risk of TB, which is consistent with the results of two studies conducted in the United States and Taiwan [24,25]. Atmospheric NO_2 exposure could damage the airway mucosa and mucosal ciliary clearance, making it easier for pathogens to enter the respiratory tract and reach the lungs [26]. Prolonged exposure to NO_2 can reduce the host resistance to *M. tb* by reducing the mRNA expression levels of the pro-inflammatory cytokines interleukin-1β (IL-1β), IL-6, IL-8, and tumor necrosis factor-α in alveolar macrophages due to the lipid peroxidation effect of the irritant gas NO_2 [27].

No association was identified between O_3 exposure and TB risk in the single-pollutant model or the multi-pollutant model, which is consistent with several previous studies [5,18,28]. The O_3 was unstable and could react chemically with various air pollutants in different environments, resulting in the formation of new compounds [25]. The biological mechanism of O_3 in relation to TB infection remains unclear, and further research is needed to better understand the impact of O_3 exposure on TB risk.

Subgroup analysis showed that exposure to air pollutants ($PM_{2.5}$, PM_{10}, and NO_2) had a significant impact on both male and older adult subgroups. This may be due to the higher frequency of smoking and alcohol consumption in men compared to women, both of which are risk factors for TB [29]. Testosterone is often thought to have an immunosuppressive effect and men may be more susceptible to inflammation caused by infection than women [30]. In addition, due to differences in social roles, men spend more time outdoors and participate in more social activities [31]. Aging is one of the risk factors for TB, as older adults have diminished immune defense abilities, especially as older adults often have co-morbid underlying conditions such as diabetes, making them more susceptible to complications associated with air pollution [32–34].

The study has several strengths. First, we collected data on TB cases in Nantong since 2005, which, to our knowledge, is a comprehensive survey of the epidemiological characteristics of TB in Nantong, which helps us to understand the changing patterns of the TB epidemic in Nantong. Second, important confounders associated with TB incidence were controlled for in the study model to quantitatively assess the impact of air pollutant exposure on TB risk. Last, the results of the sensitivity analyses confirm the reliability of the results.

Admittedly, this study has a few limitations. First, a causal relationship between air pollutants and TB incidence was not demonstrated. Second, although the study controlled for long-term trends, the Spring-Festival vacation, meteorological factors, and socioeconomic covariates, some relevant individual characteristics such as diabetes, alcohol abuse, and smoking were not obtained, and thus could not be adjusted for confounding effects. Finally, the actual levels of air pollutants to which each person was exposed were not consistent, and the monthly air pollutant concentration levels collected from satellite data may not accurately reflect individual pollutant exposure levels.

5. Conclusion

This study demonstrated that long-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 pose a substantial threat to the TB risk, while no association was observed for O_3. Reducing air pollution might have a positive effect on TB prevention and control in Nantong.

Author contribution statement

Xun Zhuang, Bin Zhang and Gang Qin: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Jia-Wang Lu, Jun-Jie Mao, Rong-Rong Zhang: Performed the experiments; Analyzed and interpreted the data.

Chun-Hu Li, Yu Sun, Wan-Qing Xu: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17347.

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