Original Article

Independent and Interactive Effects of Air Pollutants, Meteorological Factors, and Green Space on Tuberculosis Incidence in Shanghai

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Abstract

Objective To assess the independent and combined effects of air pollutants, meteorological factors, and greenspace exposure on new tuberculosis (TB) cases.

Methods TB case data from Shanghai (2013–2018) were obtained from the Shanghai Center for Disease Control and Prevention. Environmental data on air pollutants, meteorological variables, and greenspace exposure were obtained from the National Tibetan Plateau Data Center. We employed a distributed-lag nonlinear model to assess the effects of these environmental factors on TB cases.

Results Increased TB risk was linked to $PM_{2.5}$, PM_{10}, and rainfall, whereas NO_2, SO_2, and air pressure were associated with a reduced risk. Specifically, the strongest cumulative effects occurred at various lags: $PM_{2.5}$ (*RR* = 1.166, 95% *CI*: 1.026–1.325) at 0–19 weeks; PM_{10} (*RR* = 1.167, 95% *CI*: 1.028–1.324) at 0–18 weeks; NO_2 (*RR* = 0.968, 95% *CI*: 0.938–0.999) at 0–1 weeks; SO_2 (*RR* = 0.945, 95% *CI*: 0.894–0.999) at 0–2 weeks; air pressure (*RR* = 0.604, 95% *CI*: 0.447–0.816) at 0–8 weeks; and rainfall (*RR* = 1.404, 95% *CI*: 1.076–1.833) at 0–22 weeks. Green space exposure did not significantly impact TB cases. Additionally, low temperatures amplified the effect of $PM_{2.5}$ on TB.

Conclusion Exposure to $PM_{2.5}$, PM_{10}, and rainfall increased the risk of TB, highlighting the need to address air pollutants for the prevention of TB in Shanghai.

Key words: Tuberculosis; Air pollutant; Meteorological factor; Green space; Interaction; $PM_{2.5}$

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INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), is a chronic respiratory infection that remains the second leading cause of infectious disease-related mortality worldwide[1]. Despite significant advances in global TB control efforts, TB continues to present a substantial public health challenge[2,3]. Approximately one-quarter of the global population is estimated to be infected with MTB[1]. In 2022, there were 10.6 million new TB cases worldwide, with an incidence rate of 133 per 100,000 people, and 1.3 million TB-related deaths[1]. Given the

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ongoing burden of TB, identifying the factors that influence its occurrence and progression is essential for effectively advancing the World Health Organization's "End TB Strategy"[4].

Increasing evidence suggests that environmental factors—including air pollution, meteorological conditions, and green space—play significant roles in the development and progression of TB[5–10]. Air pollution can exacerbate TB by impairing immune function and increasing oxidative stress and inflammation in the patient[11–13]. Meteorological factors may affect TB through mechanisms that influence the survival of MTB, or by altering human behavior and susceptibility[5]. Additionally, green space may mitigate TB transmission by enhancing air quality, encouraging physical activity, and improving the immune response[14,15].

Numerous studies have investigated the association between long-term (monthly and annual) and short-term (daily and weekly) exposure to meteorological factors and air pollution in patients with TB. However, findings remain inconsistent[5,6,8–10,16]. A meta-analysis demonstrated a significant positive correlation between rainfall and TB risk, whereas it showed no significant associations with temperature, humidity, air pressure, and sunshine duration[5]. Conversely, a study in Northwest China reported that temperature, rainfall, wind speed, and relative humidity significantly increased TB incidence[7]. A recent meta-analysis suggests that long-term exposure (> 7 weeks) to particulate matter ≤ 10 μm (PM_{10}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) is associated with a higher incidence of TB[9]. Another meta-analysis confirmed a positive association between TB incidence and exposure to particulate matter ≤ 2.5 μm ($PM_{2.5}$), PM_{10}, and SO_2[16]. Thus, the association between air pollutants, meteorological factors, and TB incidence remains unclear.

Research on the relationship between green space and TB incidence is limited. One study found that increased exposure to green space reduced mortality among patients with MDR-TB in Zhejiang Province, China[17]. Additionally, an exosome-wide association study combined with machine learning revealed that higher proportions of forests, shrublands, and grasslands were associated with lower TB prevalence[7]. Considering the potential lagged effects of greenspace exposure on TB incidence, a time-series analysis may be an appropriate method to study this impact. However, to date, no such studies have been conducted.

Notably, there may be interactions among environmental factors[18-20]. The inconsistent conclusions regarding the association between environmental factors and TB incidence may be partly due to a failure to consider these interactions. Previous studies have explored the combined effects of environmental factors on mortality, cardiovascular diseases, hand-foot-and-mouth disease, and other illnesses[21-24]. However, the combined effects of air pollutants, meteorological factors, and greenspace interactions on TB incidence are not well established. Meteorological factors are crucial determinants of air pollutant concentrations[25]; for example, the wind speed can alter pollutant levels[25]. These factors may also exacerbate the impact of pollutants on TB incidence by affecting the patient; for example, temperature fluctuations may induce physiological stress, thereby modifying the body's responses to toxins[26]. Additionally, growing evidence suggests that green space can reduce air pollution and regulate temperature[27-29]. This implies that potential interactions among air pollutants, meteorological factors, and green space exposure influence TB incidence. Further research is required to comprehensively understand the combined effects of environmental exposure and TB incidence.

This study, therefore, aimed to apply a time-series analysis to quantify and evaluate the independent and interactive effects of air pollutants, meteorological factors, and greenspace exposure on TB cases in Shanghai. We employed a method involving the multiplication of a cross-basis matrix with stratified terms to analyze the interactions across multiple classification levels, thereby capturing critical information regarding nonlinear and lagged effects. These results could provide robust scientific evidence to guide strategies for air pollution control, greenspace development, and TB prevention.

MATERIALS AND METHODS

Study Region

Shanghai, located between the latitudes of 30.40°–31.53° N and longitudes of 120.52°–122.12° E, covers an area of 6340.5 km². By the end of 2022, the city—which can be divided into 16 districts—had a permanent resident population of 24.76 million, with a density of 3,905 people per km² and a gross domestic product of 4.47 trillion Yuan[30]. Shanghai is situated in the Yangtze River Delta alluvial plain and has an average elevation of 4 m. The region experiences a subtropical monsoon climate with short springs and autumns, long winters and summers, abundant sunshine, and significant rainfall. In 2022, the air quality excellence rate was 87.1%[30]. This percentage represents the proportion of days classified as having “excellent” or “good” air quality, according to the Technical Regulation on Ambient Air Quality Index (on trial) (HJ 633-2012)[31].

TB Patient Data

In 2005, the Shanghai Center for Disease Control and Prevention established a TB surveillance system. We extracted data on patients with TB from this system between 2013 and 2018, including sociodemographic details (age, sex, race, occupation, household register, and current address), epidemiological information (patient source, severe case, and TB history), and laboratory results (sputum smear, sputum culture, and molecular test results). Active TB can develop shortly after initial exposure, or following a period of latent infection[32]. Our study included all newly diagnosed patients with TB in Shanghai, encompassing both primary and reactivated cases, and excluding patients whose current residence addresses were outside Shanghai. The diagnoses adhered to the national diagnostic criteria for TB[33], with cases defined as bacteriologically confirmed (positive sputum smear, sputum culture, or molecular test) or clinically diagnosed (initiated TB treatment without bacteriological confirmation). The clinical visit time, defined as the first visit following symptom onset, was used in this study instead of the symptom onset date because the latter is often based on patient recall and may be inaccurate. Accordingly, many studies examining the impact of environmental factors on TB risk have relied on the clinical visit time[34,35].

Residential addresses were geocoded using the Gaode Map Application Programming Interface (Gaode, AutoNavi Software Co., Ltd., Beijing, China), and addresses unsuitable for batch geocoding were manually corrected and geocoded. Geocoded TB case data were subsequently mapped onto a vector map of Shanghai, using ArcMap 10.7 (Esri, Redlands, California, United States). The spatial density distributions of the reported TB cases from 2013 to 2018 were analyzed using kernel density estimation (KDE). Additionally, we performed a classical multiplicative decomposition of the time series for weekly TB cases, from 2013 to 2018, to assess periodic and seasonal variations[36].

Environmental Exposure Data

Daily air pollutant data were obtained from the China High Air Pollutants dataset[37–48] for the study period in Shanghai, provided by the National Tibetan Plateau Data Center (http://data.tpdc.ac.cn). Weekly averages for $PM_{2.5}$, PM_{10}, NO_2, SO_2, ozone (O_3), and carbon monoxide (CO) were calculated. Spatial resolutions were as follows: $PM_{2.5}$, PM_{10}, and O_3 at 1 km; NO_2, SO_2, and CO at 10 km. These pollutants were predicted with high accuracy based on a moderate-resolution imaging spectroradiometer multi-angle aerosol optical depth product, meteorological data, land-use information, and emission sources[37–48].

Daily meteorological data with a spatial resolution of 10 km were sourced from the China Meteorological Forcing Dataset[49–51], also provided by the National Tibetan Plateau Data Center (http://data.tpdc.ac.cn). Weekly averages were calculated for the temperature, air pressure, relative humidity, solar radiation, rainfall, and wind speed. The heat index, which integrates temperature and humidity to reflect the perceived human comfort[52], was calculated using the following Formula 1:

$$heat\ index = \begin{cases} 1.8T_{max} - 0.55\,(1.8T_{max} - 26) \times (1 - 0.6) + 32\,(relative\ humidity \leqslant 60\%) \\ 1.8T_{max} - 0.55\,(1.8T_{max} - 26) \times (1 - relative\ humidity) + 32\,(relative\ humidity > 60\%) \end{cases} \quad (1)$$

T_{max} is the maximum daily temperature in degrees Celsius.

To assess greenspace exposure, daily normalized difference vegetation index (NDVI) data with a spatial resolution of 0.05° (approximately 5.5 km) were obtained from the public platform Figshare (https://figshare.com/)[53]. NDVI, a crucial indicator of vegetation density, is based on the principle that chlorophyll absorbs visible light for photosynthesis and reflects near-infrared light. The NDVI was calculated as the ratio of the difference between near-infrared and red visible light reflectance to their sum, ranging from −1 to 1, with higher values indicating denser vegetation[54].

To estimate the environmental exposure of each participant residing in Shanghai, weekly averages of environmental data (air pollutants, meteorological factors, and NDVI) for all grids within the administrative boundaries of Shanghai were calculated.

Statistical Analysis

The research framework is illustrated in Supplementary Figure S1. Initially, the distributions of TB cases, air pollutants, meteorological factors, and NDVI were characterized using frequency distributions, means, percentiles, and time-series plots. Subsequently, we investigated the associations between air pollutants, meteorological factors, NDVI, and the number of new weekly TB cases using quasi-Poisson regression, combined with a distributed-lag nonlinear model (DLNM). Third, subgroup analyses by age, sex, and household register were conducted to explore differential effects. Subsequently, the interaction terms among the environmental variables were included in the model to evaluate their combined influence on TB cases. Finally, a sensitivity analysis was performed to assess the robustness of the results.

Distributed-Lag Nonlinear Model

Recognizing the latency and nonlinear exposure–response relationships of ambient air pollutants and meteorological factors on TB cases, as demonstrated in numerous epidemiological studies[55-58], we utilized a quasi-Poisson regression combined with DLNM to evaluate these associations and their lag effects. To mitigate multicollinearity, Spearman's correlation coefficient was used to examine relationships among environmental factors, excluding factors with a correlation coefficient $|r| \geq 0.7$ from the model[59]. Single-factor regression models were then developed for each environmental factor. The model is specified as follows Formula 2:

$$log\left[E\left(Y_t\right)\right]=b+\sum_{p=0}^{n}\beta_p X_{t-p}+\sum ns\left(Z_i,df_1\right)+ns\left(time,df_2\right)+\beta Holiday \quad (2)$$

where, $E(Y_t)$ represents the expected number of new TB cases in week t, b is the intercept term, and X is the weekly average of a specific environmental factor. β_p represents the effect estimate of the cross-basis matrix for environmental factors, with a natural cubic spline(ns) as the basis function in both the exposure–response and exposure-lag dimensions, each with 3 degrees of freedom (*df*)[60,61]. The maximum lag time, *n,* was determined based on the Quasi-Akaike Information Criterion (QAIC)[35]. The natural cubic spline function *ns. ()* was used to adjust for the confounding effects of other environmental factors Z_i. Long-term trends and seasonality were controlled for using *ns (time, df_2)* with 6 degrees of freedom[57,62,63]. The *holiday* refers to the number of public holidays in a week, with the regression coefficient β representing its effect. To identify vulnerable subpopulations, stratified analyses were performed according to sex (male and female), age (15–65 years and > 65 years), and household register (migrant or resident). Owing to the low proportion of individuals in the 0–14 year age group (0.41%), this group was excluded from the subgroup analysis. TB risk was expressed as the lag-specific and cumulative-lag TB relative risk (*RR*) with 95% confidence intervals (*CI*) for an interquartile range (*IQR*) increase in environmental variables, referenced to their median levels.

Interaction Analysis

To examine the interactive effects of air pollutants, meteorological factors, and greenspace exposure on TB cases, we performed interaction analyses. Meteorological variables and NDVI were categorized into three quartiles: low (< 25%), median (25%–75%), and high (> 75%). This model incorporated interaction terms between the cross-basis matrix of air pollutant variables and the strata of meteorological variables or NDVI, to evaluate the effects of air pollutant variables at different levels of meteorological variables or NDVI[21]. Similarly, air pollutant variables and NDVI were divided into quartiles to assess the effects of meteorological variables on different levels of air pollutants or NDVI. For instance, to evaluate how varying levels of temperature influence the relationship between $PM_{2.5}$ and TB cases, the model is specified as follows Formula 3:

$$log\left[E\left(Y_t\right)\right]=b+cb\left(PM2.5_t\right)+cb\left(PM2.5_t\right)\times temperature_t+\sum ns\left(Z_i,df_1\right)+ns\left(time,df_2\right)+\beta Holiday \quad (3)$$

Sensitivity Analysis

These analyses aimed to assess the robustness of the model. They involved adjusting the maximum lag time, varying the degrees of freedom for confounding environmental variables between 2 and 4, and incorporating additional air pollutants or meteorological factors to construct multi-pollutant and multi-meteorological models.

The threshold of significance was set at $P < 0.05$. All statistical analyses were primarily conducted using the "dlnm", "spline", and "mgcv" packages in

R, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of TB Cases and Environmental Factors

Overall, 39,579 TB cases were reported in Shanghai between 2013 and 2018 (Table 1). The spatial KDE of TB cases (Figure 1) revealed that the highest estimated density values were concentrated in the central districts of Shanghai, including Huangpu, Xuhui, and Jing'an. Among the reported cases, 68.60% were male, 82.48% were aged 15–65 years, and the bacteriological positivity rate was 47.26%. As shown in Table 2, the average weekly number of new active TB cases was 126.60. Supplementary Figure S2 illustrates a declining trend in weekly TB cases, accompanied by clear seasonal and cyclical patterns. During the study period, the weekly air pollutant levels, meteorological factors, and NDVI in Shanghai showed cyclical changes (Supplementary Figure S3). Table 2 also reveals that the mean concentrations of $PM_{2.5}$ and PM_{10} exceeded the national air quality class II standards (GB3095–2012), with values above 35 μg/m^3 and 70 μg/m^3, respectively.

The results of the Spearman's correlation analysis between the environmental factors are provided in Supplementary Table S1. The weekly mean temperature, heat index, and NDVI were significantly and positively correlated, whereas air pressure was negatively correlated with the temperature, heat index, and NDVI. In addition, the weekly average CO concentration was positively correlated with NO_2, SO_2, $PM_{2.5}$, and PM_{10}. To mitigate the risk of multicollinearity in the analysis, variables with a correlation coefficient $|r| \geq 0.7$ were excluded from the models.

Association between Air Pollutants and NDVI with the Number of TB Cases

Figure 2 illustrates the lag effects of air pollutants and NDVI on the risk of TB with an increase in *IQR,* with reference to the median in the single-factor models. $PM_{2.5}$ and PM_{10} were positively correlated with TB risk, whereas NO_2 and SO_2 were negatively correlated. The cumulative risk of TB was associated with $PM_{2.5}$ exposure from lag 0–17 weeks (*RR* = 1.122, 95% *CI*: 1.004–1.253) to lag 0–19 weeks (*RR* = 1.166, 95% *CI*: 1.026–1.325). PM_{10} exposure increased the cumulative risk of TB from lag 0–16

Table 1. Characteristics of new TB cases in Shanghai, 2013–2018 (*N* = 39,579)

Characteristics	*N* (%)
Age, median years (IQR)	42 (27, 60)
Age group (years)	
0–14	161 (0.41)
15–65	32,643 (82.48)
> 65	6,775 (17.12)
Sex	
Male	27,150 (68.60)
Female	12,429 (31.40)
Race	
Han nationality	39,320 (99.35)
Ethnic minority	256 (0.65)
Unclear	3 (0.01)
Occupation	
Labor worker	5,757 (14.55)
Farmer	1,622 (4.10)
Commercial service	1,799 (4.55)
Medical staff	230 (0.58)
Teacher and student	1,943 (4.91)
Office worker	1,613 (4.08)
Retired	9,399 (23.75)
Unemployed	5,304 (13.40)
Unclear	3,524 (8.90)
Other	8,388 (21.19)
Household register	
Migrant patients	17,022 (43.01)
Resident patients	22,301 (56.35)
Unclear	256 (0.65)
Severe case	
No	32,248 (81.48)
Yes	7,331 (18.52)
TB history	
New case	36,073 (91.14)
Retreated case	3,506 (8.86)
Patient source	
Active screening	1,210 (3.06)
Passive screening	38,369 (96.94)
Pathogen result	
Positive	18,704 (47.26)
Negative	19,468 (49.19)
Unknown	1,407 (3.55)

Note. IQR, interquartile range; TB, tuberculosis; *N*, number.

weeks (*RR* = 1.123, 95% *CI*: 1.001–1.259) to lag 0–18 weeks (*RR* = 1.167, 95% *CI*: 1.028–1.324). For NO_2, the negative association was statistically significant from lag 0 week (*RR* = 0.983, 95% *CI*: 0.966–0.999) to lag 0–1 week (*RR* = 0.968, 95% *CI*: 0.938–0.999). SO_2 exposure from lag 0 week (*RR* = 0.979, 95% *CI*: 0.959–0.999) to lag 0–2 weeks (*RR* = 0.945, 95% *CI*: 0.894–0.999) was associated with decreased cumulative risk of TB. Additionally, the cumulative-lag risks of CO, O_3, and NDVI on TB cases were not statistically significant (Supplementary Tables S2–S4).

Association between Meteorological Factors and the Number of TB Cases

Figure 3 shows the lag effects of meteorological factors on the risk of TB cases with an increase in *IQR,* with reference to the median in the single-factor models. Rainfall was positively associated with TB risk, whereas air pressure was negatively associated with it. The cumulative risk of TB was linked to rainfall exposure from lag 0 week (*RR* = 1.023, 95% *CI*: 1.002–1.044) to lag 0–22 weeks (*RR* = 1.404, 95% *CI*: 1.076–1.833). For air pressure, a significant negative association was observed between lag 0 week (*RR* = 0.887, 95% *CI*: 0.824–0.955) and 0–13 weeks (*RR* = 0.645, 95% *CI*: 0.429–0.969). There were no significant associations between temperature, relative humidity, wind speed, heat index, solar radiation, and TB cases in cumulative lag times (Supplementary Tables S5–S6).

Subgroup Analysis of the Effects of Environmental Factors

Figure 4 shows the lag effects of $PM_{2.5}$, PM_{10}, NO_2, SO_2, air pressure, and rainfall on the risk of TB at specific and cumulative lag times in different sex subgroups. In the single-factor model, TB associations with $PM_{2.5}$, PM_{10}, and air pressure exposure were significant only in the male group. The highest cumulative *RR*s of TB appeared at a lag of 0–19 weeks (*RR* = 1.193, 95% *CI*: 1.037–1.373) for $PM_{2.5}$ and at a lag of 0–18 weeks (*RR* = 1.199, 95% *CI*: 1.044–1.376) for PM_{10}. The lowest cumulative *RR* for air pressure was observed at a lag of 0–7 weeks (*RR* = 0.576, 95% *CI*: 0.422–0.788). Conversely, we only observed statistically significant relationships between NO_2, SO_2, rainfall exposure and TB in women. In women, the cumulative *RR*s peaked at a lag of 0–8 weeks (*RR* = 0.864, 95% *CI*: 0.747–0.998) for NO_2; 0–11 weeks (*RR* = 0.787, 95% *CI*: 0.641–0.966) for SO_2; and 0–22 weeks (*RR* = 2.050,

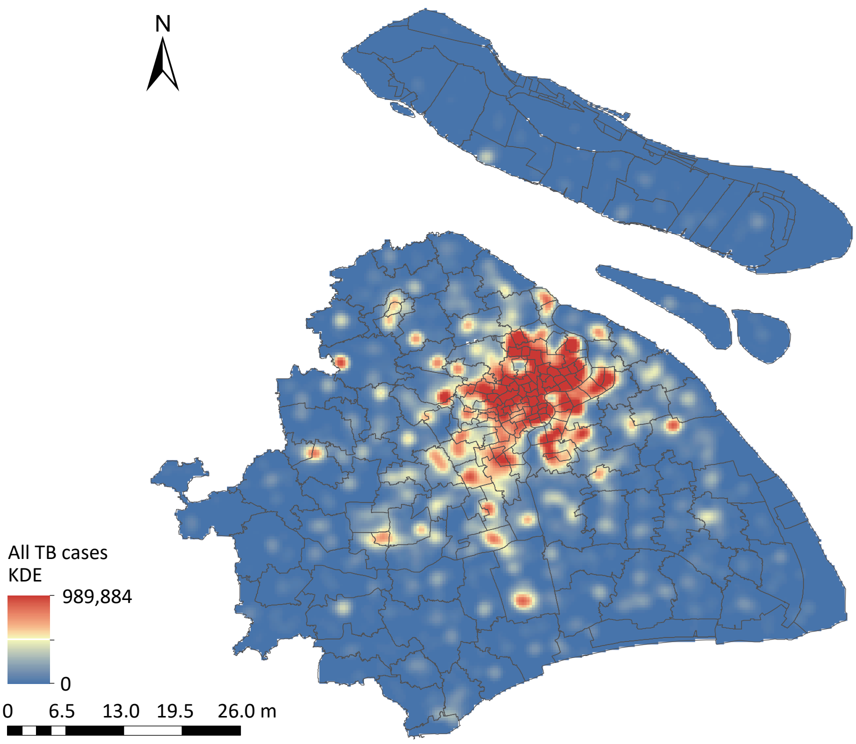

Figure 1. Spatial KDE of Tuberculosis Cases in Shanghai, 2013–2018. TB, tuberculosis; KDE, kernel density estimation. Map Approval No. GS(2024)0650.

95% *CI*: 1.390–3.024) for rainfall (Supplementary Tables S2–S6).

A stratified analysis according to age is shown in Figure 5. When stratified by age, the relationships between $PM_{2.5}$, PM_{10}, NO_2, and air pressure exposure and the risk of TB remained statistically significant only in the 15–65 years age group. In this group, the cumulative *RR*s peaked at a lag of 0–19 weeks (*RR* = 1.199, 95% *CI*: 1.046–1.373) for $PM_{2.5}$, a lag of 0–18 weeks (*RR* = 1.228, 95% *CI*: 1.074–1.405) for PM_{10}, a lag of 0–1 weeks (*RR* = 0.966, 95% *CI*: 0.934–0.998) for NO_2, and a lag of 0–7 weeks (*RR* = 0.580, 95% *CI*: 0.428–0.786) for air pressure. In contrast, in the aged > 65 years group, a significant increase in cumulative TB risk was observed only with higher rainfall exposure, reaching a peak at a lag of 0–20 weeks (*RR* = 1.699, 95% *CI*: 1.071–2.697). No statistically significant association with SO_2 exposure was observed in either age group (Supplementary Tables S2–S6).

Figure 6 shows the lag effects of environmental factors on TB risk, stratified by household registration status. Air pressure and rainfall were significantly associated with TB risk only among the migrant population, with a peak effect occurring at a lag of 0–8 weeks (*RR* = 0.459; 95% *CI*: 0.312–0.676) for air pressure and 0–22 weeks (*RR* = 1.931, 95% *CI*: 1.374–2.713) for rainfall. $PM_{2.5}$ exposure, however, was only significantly associated with TB risk in resident patients, with the highest *RR* observed at 0–19 weeks (*RR* = 1.184, 95% *CI*: 1.014–1.382). No significant associations were observed between PM_{10}, NO_2, or SO_2 in either group. (Supplementary Tables S2–6).

The Interaction Effects of Environmental Factors

Figure 7 and Supplementary Table S7 illustrate the interactive effects of air pollutants, meteorological variables, and NDVI on the TB risk. Significant increases in cumulative TB risk for $PM_{2.5}$ exposure were observed at low temperatures (*RR* = 1.728, 95% *CI*: 1.138–3.125) and high air pressure levels (*RR* = 1.807, 95% *CI*: 1.175–2.779). Notably, both $PM_{2.5}$ (*RR* = 1.605,

Table 2. Distribution characteristics of weekly TB cases, air pollutants, meteorological factors, and NDVI in Shanghai during 2013–2018

Characteristic	Mean ± SD	Min	P_{25}	Median	P_{75}	Max
TB cases	126.60 ± 24.00	21.00	116.00	129.00	143.00	176.00
Air pollutant						
PM_{10} (μg/m^3)	74.48 ± 29.10	28.12	53.61	69.57	87.27	249.04
$PM_{2.5}$ (μg/m^3)	46.88 ± 21.35	11.68	33.08	43.44	56.40	188.60
SO_2 (μg/m^3)	18.88 ± 8.69	6.98	12.94	16.67	21.92	57.20
NO_2 (μg/m^3)	39.89 ± 12.97	13.91	30.98	38.05	46.94	86.58
CO (mg/m^3)	0.85 ± 0.32	0.44	0.70	0.81	0.94	5.22
O_3 (μg/m^3)	102.13 ± 31.39	44.61	77.14	101.11	123.60	210.89
Meteorological factor						
Temperature (°C)	17.40 ± 8.64	−0.84	9.93	18.17	24.33	34.74
Air pressure (kPa)	101.63 ± 0.84	100.12	100.85	101.64	102.33	103.40
Wind speed (m/s)	2.94 ± 0.60	1.74	2.51	2.85	3.29	5.10
Relative humidity (%)	75.15 ± 9.00	48.29	68.99	76.14	81.50	93.84
Heat index	67.90 ± 13.48	38.39	56.60	69.89	78.38	92.93
Solar radiation (MJ/m^2)	87.85 ± 34.79	13.43	61.53	84.35	114.16	177.70
Rainfall (mm)	26.69 ± 30.27	0.00	4.72	17.27	38.00	212.12
NDVI	0.40 ± 0.09	0.20	0.32	0.39	0.48	0.56

Note. NDVI, normalized difference vegetation index; CO, carbon monoxide; O_3, ozone; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter < 10 μm in aerodynamic diameter; TB, tuberculosis; SD, standard deviation; P_{25}, 25th percentile; P_{75}, 75th percentile

95% *CI*: 1.069–2.411) and PM_{10} (*RR* = 1.329, 95% *CI*: 1.019–1.735) exposure posed significant TB risks at low NDVI levels, whereas no significant associations were observed at medium or high NDVI levels. Additionally, the association between PM_{10} exposure and TB cases was significant within the median centiles of wind speed strata (*RR* = 1.260, 95% *CI*: 1.124–1.338).

Sensitivity Analyses

The sensitivity analysis confirmed the robustness of the findings. The results remained consistent when employing different maximum lag times and degrees of freedom for confounding environmental variables, as well as when making additional adjustments to construct multi-pollutant and multi-meteorological factor models (Supplementary Figures S4–S9).

DISCUSSION

In this study, we evaluated the independent effects of meteorological factors, air pollutants, and green space exposure on TB incidence, especially $PM_{2.5}$ and PM_{10}. We also characterized the interaction effects by analyzing varied exposure-

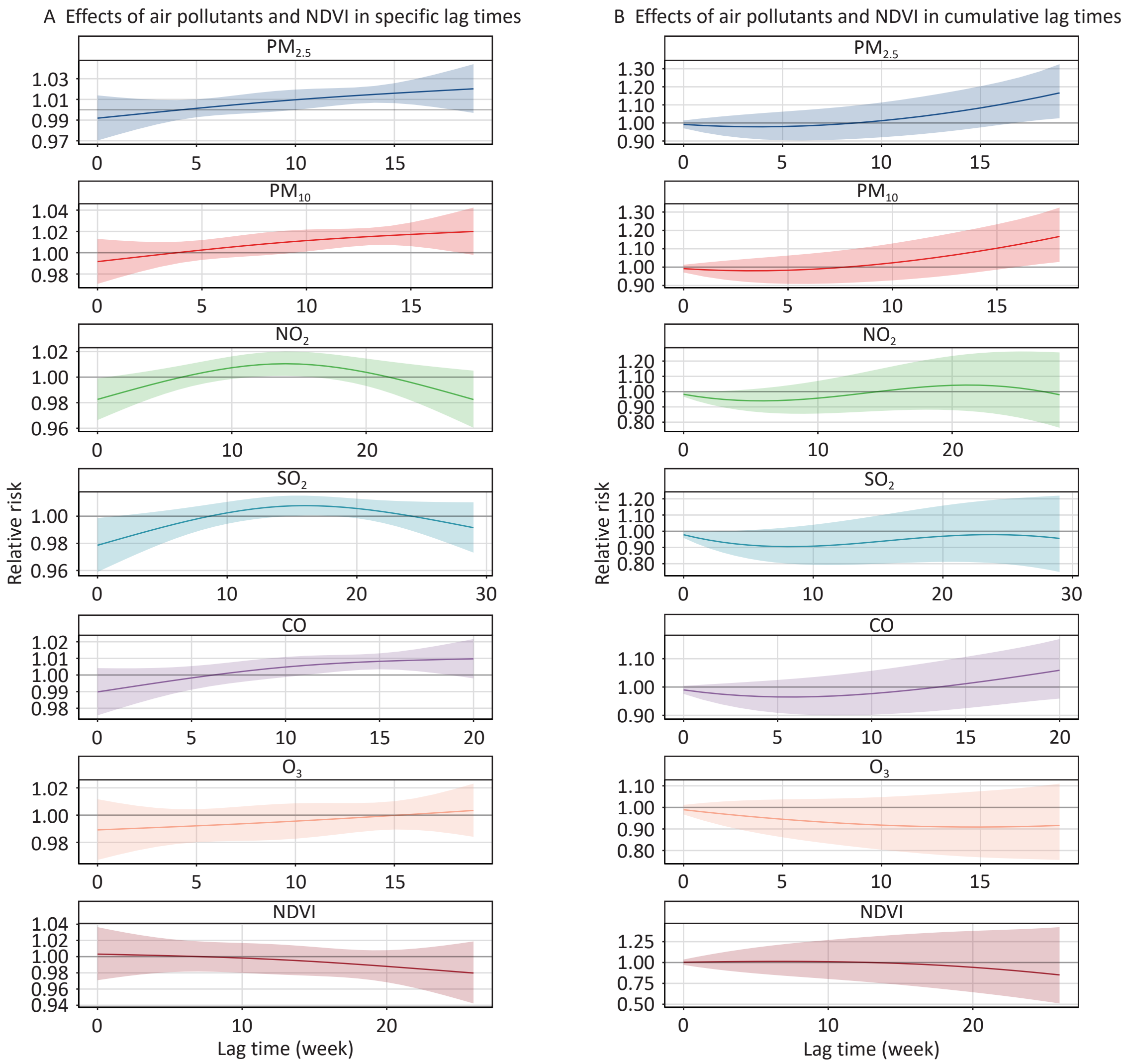

Figure 2. Effects of air pollutants and NDVI on risk of TB in specific and cumulative lag times in single-factor models. The solid line represents the central estimates and the envelopes represent 95% confidence intervals. CO, carbon monoxide; O_3, ozone; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; NDVI, normalized difference vegetation index; TB, tuberculosis.

response relationships across different categories, enriching our understanding of the co-exposure effects on TB cases. Our results indicated that $PM_{2.5}$, PM_{10}, and rainfall were positively associated with TB cases, whereas NO_2, SO_2, and air pressure were negatively associated. No significant association was found between green space and TB. Furthermore, low temperatures enhanced the association between $PM_{2.5}$ and TB cases. These findings highlight the need for coordinated strategies to mitigate the impact of environmental factors on TB cases.

This study found positive correlations between $PM_{2.5}$ and PM_{10} exposure and TB incidence. Similar associations have been reported in ecological studies from the Carolinas in the USA[64], as well as time-series studies in the Chinese cities of Lianyungang[10] and Fuyang[65], which all indicated that elevated concentrations of $PM_{2.5}$ and PM_{10} are linked to higher TB incidence rates. However, other studies, including cohort studies from Taiwan[66] and Seoul[67], found no significant association between short- or long-term exposure to $PM_{2.5}$, PM_{10} and active TB

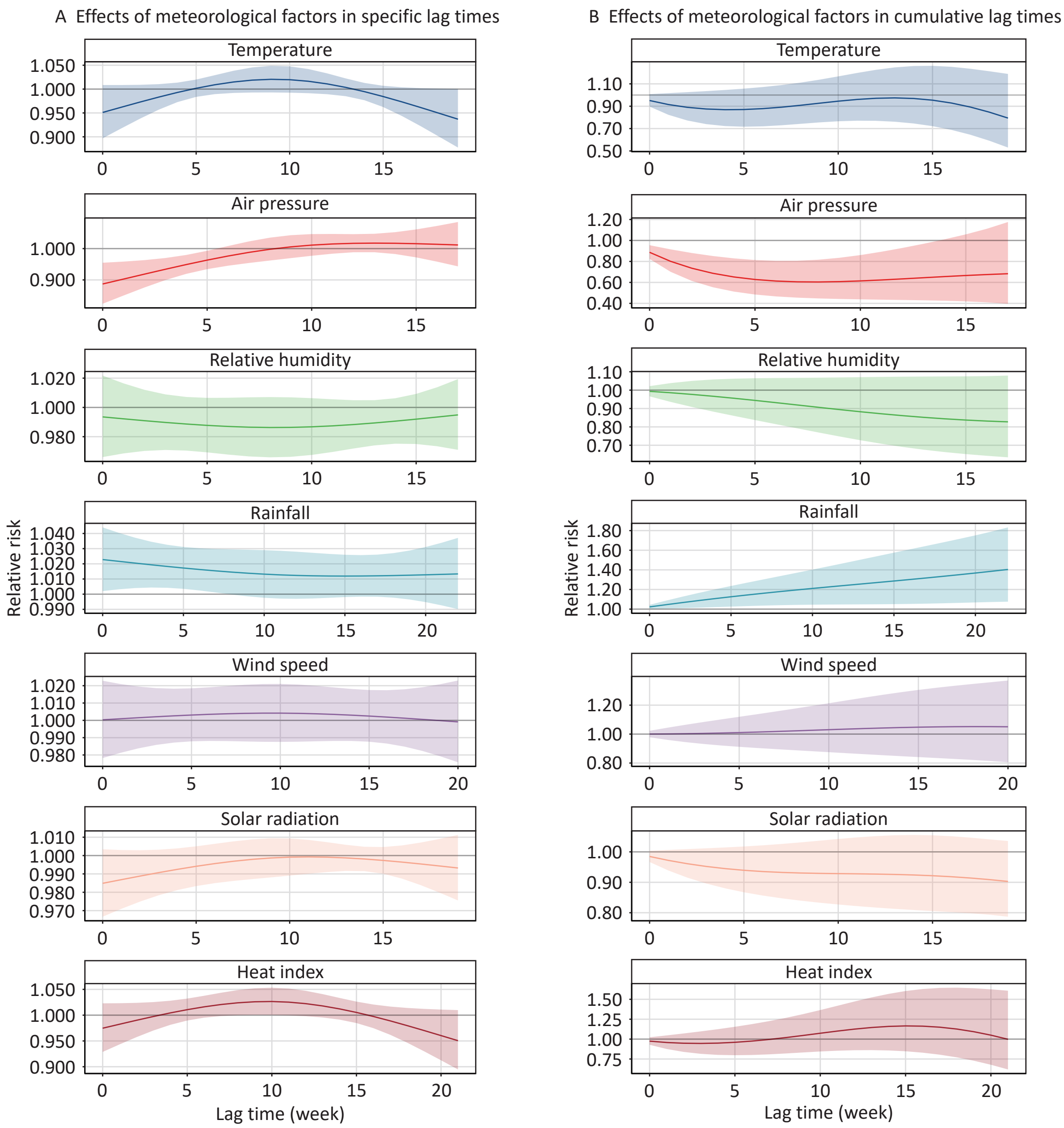

Figure 3. Effects of meteorological factors on the risk of TB in specific and cumulative lag times in single-factor models. The solid line represents the central estimates and the envelopes represent 95% confidence intervals. TB, tuberculosis.

risk. These discrepancies may be partially due to variations in pollution levels. For example, in studies reporting no association, the median PM_{10} concentrations were 47.34 μg/m^3 in Taiwan[66] and 62.80 μg/m^3 in Seoul[67], both lower than the 85.43 μg/m^3 in Lianyungang[10]. Similarly, Taiwan's median $PM_{2.5}$ concentration was 27.79 μg/m^3[66], compared to 48.56 μg/m^3 in Lianyungang[10]. In addition to pollution levels, other factors, such as meteorological conditions, industrialization, and the presence of toxic substances adsorbed onto $PM_{2.5}$ or PM_{10} might contribute to differences in exposure-response effects[35]. Subgroup analyses further revealed that the association between $PM_{2.5}$ and PM_{10} exposure and the risk of pulmonary TB was significant only among males; this could be attributed to higher rates of smoking and alcohol consumption, which suppress cell-mediated immunity and tumor necrosis factor-α (TNF-α) production, thus increasing vulnerability to TB[68,69].

Several biological mechanisms have been proposed to explain the association between TB cases and particulate matter exposure. Air pollutants can independently exacerbate airway epithelial

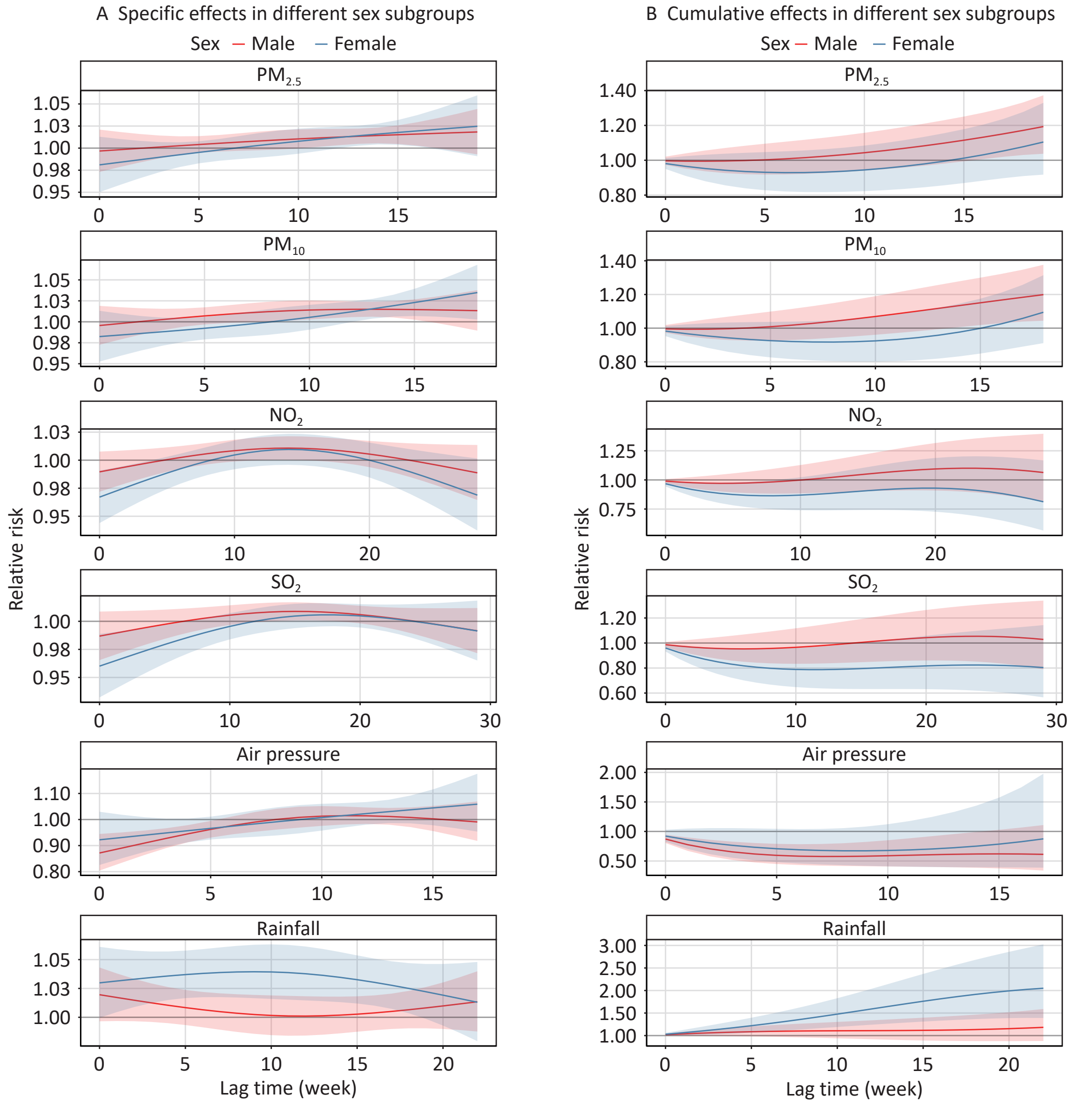

Figure 4. Effects of air pollutants and meteorological factors on risk of TB in different sex subgroups in single-factor models. The solid line represents the central estimates and the envelopes represent 95% confidence intervals. SO_2, sulfur dioxide; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; NDVI, normalized difference vegetation index; TB, tuberculosis.

damage, leading to oxidative stress or other toxic effects[70,71]. These harmful effects are particularly pronounced for smaller particles, such as $PM_{2.5}$, which can penetrate deep into the alveolar region and impair alveolar macrophage activity[72]. Elevated $PM_{2.5}$ levels increase iron availability, which facilitates MTB proliferation[73–75]. Furthermore, exposure to $PM_{2.5}$ has been shown to enhance MTB colony-forming units in alveolar cells and disrupt immune responses, including the production of key inflammatory cytokines such as interferon-γ and TNF-α[76-78]. These factors create a favorable environment for MTB invasion.

Our study found no significant association between O_3 exposure and TB cases, consistent with findings from Seoul, South Korea[67]. In contrast, a USA case-control study[79] reported a negative association, whereas a time-series analysis in Urumqi, China[80], found a positive correlation. These studies relied on O_3 exposure estimates from fixed monitoring stations, which may not accurately reflect individual exposure levels, due to the chemical interactions between O_3 and NO in the environment[81]. Therefore, the findings should be

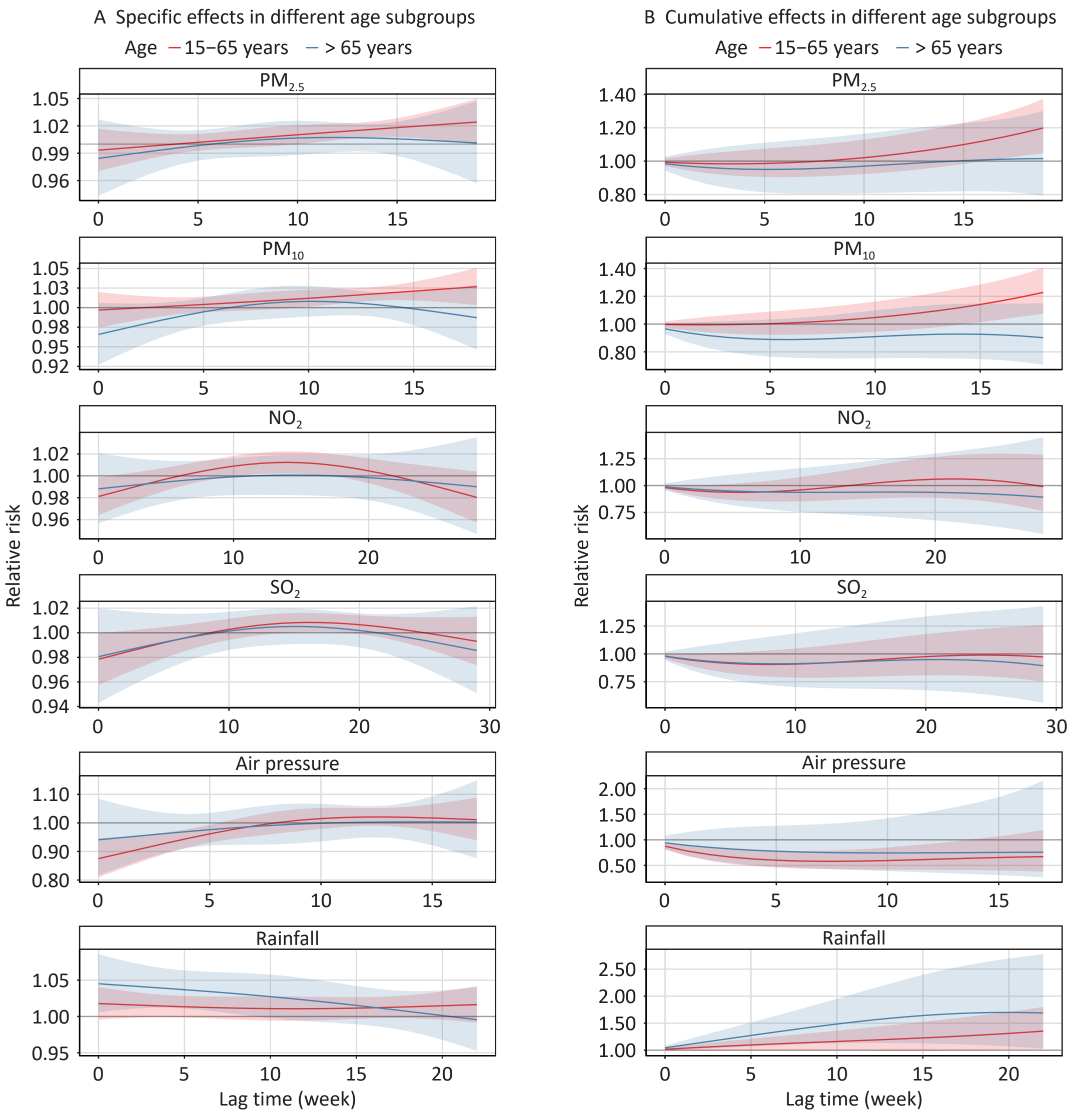

Figure 5. Effects of air pollutants and meteorological factors on risk of TB in different age subgroups in single-factor models. The solid line represents the central estimates and the envelopes represent 95% confidence intervals. SO_2, sulfur dioxide; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; NDVI, normalized difference vegetation index; TB, tuberculosis.

interpreted with caution.

Our study identified a negative correlation between SO_2 exposure and TB cases, consistent with findings from time-series studies in Ningbo[82], Wuhan[83], and Hefei[84]. A case-crossover study in Madrid also reported a significant association between elevated SO_2 concentrations and a reduced likelihood of PTB hospitalization (OR = 0.92, 95% CI: 0.86–0.99, P = 0.029)[77]. The antimicrobial properties of SO_2 might explain this association. SO_2 can penetrate microbial cell membranes and disrupt enzyme and protein activity, thereby effectively inhibiting microbial growth[85]. An experimental study demonstrated that inhalation of 14 mg/m³ of SO_2 increases levels of the pro-inflammatory cytokines TNF-α and interleukin-6 in murine lung tissue[86]. These cytokines play a crucial role in host's defense against MTB by regulating granuloma formation[87].

Additionally, we observed a negative association between NO_2 exposure and TB cases, which aligns with an experimental study demonstrating that NO_2 exhibits antimycobacterial activity[88]. In contrast, a meta-analysis by Xiang et al.[9] indicated that NO_2

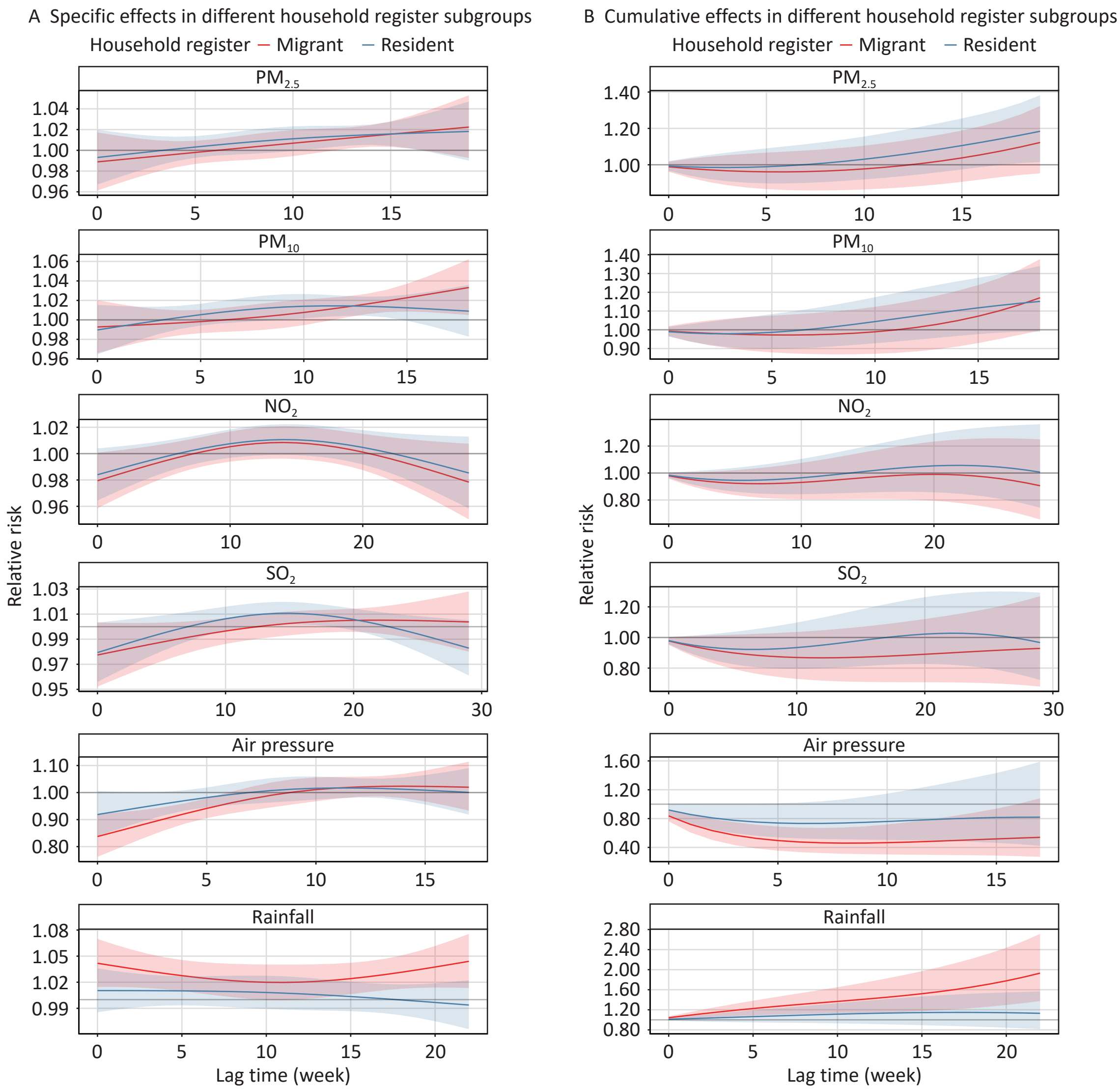

Figure 6. Effects of air pollutants and meteorological factors on risk of TB in different household register subgroups in single-factor models. The solid line represents the central estimates and the envelopes represent 95% confidence intervals. SO_2, sulfur dioxide; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; NDVI, normalized difference vegetation index; TB, tuberculosis.

exposure (per 1 ppb increase; *RR* = 1.010) was associated with an increased risk of TB. These discrepancies may be due to variations in demographic factors, population susceptibility, geographic and climatic differences, methods of exposure quantification, and modeling choices[6]. Further research with larger sample sizes and more sensitive methodologies is essential to accurately assess the relationship between air pollutants and TB.

In our study, rainfall was positively correlated with TB, consistent with the findings of a previous geographically weighted regression analysis[89]. Rainfall reduces outdoor activity and exposure to sunlight, thereby decreasing ultraviolet (UV) radiation, which inhibits inflammation, enhances antimicrobial activity, and regulates vitamin D production[90]. Reduced UV exposure may weaken immune function and increase TB risk[90]. A subgroup analysis revealed that rainfall exposure was significantly associated with TB risk only in migrant populations. Living, working, and social interactions often occur in densely populated environments and may facilitate TB transmission[91]. Additionally, migrants may face greater barriers to accessing healthcare and social security, which further contributes to their heightened vulnerability to TB[92].

Our findings also indicated that higher air pressure was associated with a decreased risk of TB, which is consistent with the results of a generalized linear mixed model by Guo et al.[93] at the national level, in China. However, another study conducted in Lanzhou using a generalized additive model found a positive association between air pressure and TB incidence, with a lag of 4–6 days[94]. This discrepancy may be explained by differences in regional environmental factors such as temperature, humidity, and specific temporal lags. We hypothesized that high air pressure may influence atmospheric stability, potentially reducing the dispersion of air pollutants and pathogens; this, in turn, reduces the chances of human exposure to and infection with MTB. However, the mechanisms underlying this relationship remain unclear, and may involve complex interactions with other environmental factors. Further studies are required to elucidate these mechanisms.

Regrettably, we found no significant correlation for cumulative lagged risk, potentially because longer lag periods are needed to fully capture the cumulative impact of NDVI on TB risk. Furthermore, the absence of data on the quality or type of green spaces, as well as their distribution and accessibility in different parts of Shanghai, limited our ability to assess their potential influence on the results[95,96]. A

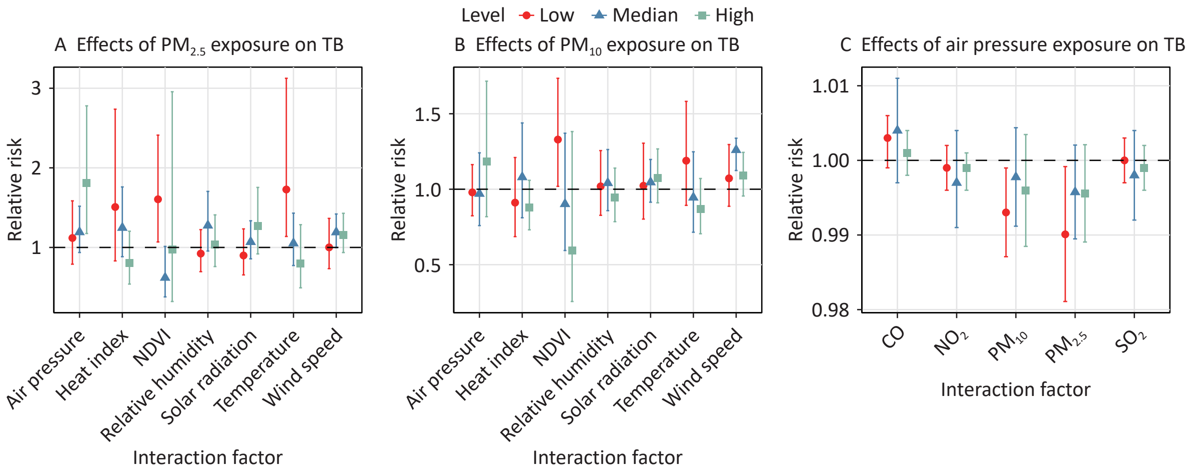

Figure 7. Interaction analysis between air pollutants, meteorological factors, and NDVI on risk of TB. (A) The cumulative-lag *RR* of 10 ug/m^3 increase in $PM_{2.5}$ for TB cases stratified by meteorological factors and NDVI levels. (B) The cumulative-lag *RR* of 10 μg/m^3 increase in PM_{10} for TB cases stratified by meteorological factors and NDVI levels. (C) The cumulative-lag *RR* of 10 Pa increase in air pressure for TB cases stratified by air pollutants. The points indicate central estimates, while the vertical lines indicate 95% *CI*. NDVI, normalized difference vegetation index; CO, carbon monoxide; O_3, ozone; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; TB, tuberculosis; *RR*, relative risk; *CI*, confidence interval.

nationwide modeling study in China reported that NDVI could mitigate the impact of air pollutants on TB incidence[97]. Exposure to green space may reduce ambient respirable particulate matter through the deposition effect of vegetation leaves[98] and alter the diffusion trajectory and speed of these particulates[99], thereby influencing MTB transmission and decreasing TB incidence. Additionally, greenery can change the chemical composition of particles by removing polycyclic aromatic hydrocarbons and heavy metals, thereby altering the relationship between particulate matter and TB incidence[100]. Currently, there is a lack of research on the independent effects of green space on TB incidence of TB. Further studies are required to provide data-driven recommendations for the utilization of green space to enhance TB prevention and control in China.

The interaction analysis revealed interesting interactive effects of environmental factors on TB cases, providing comprehensive insights into the complex interplay between air pollution, weather conditions, green space, and TB cases in Shanghai. Specifically, low temperatures combined with high $PM_{2.5}$ concentrations may jointly promote TB risk. Similarly, Huang et al.[63] reported a downward trend in the $PM_{2.5}$-TB association with increasing temperature levels, while another study found that high $PM_{2.5}$ concentrations reinforce the association between temperature and TB hospitalizations, particularly in cold environments[101]. This interaction may be explained by the cold-induced nasal mucosal responses and epithelial desquamation, which trigger inflammation and accelerate latent TB activation[60,102]. Low temperatures are often associated with reduced UV radiation exposure, leading to vitamin D deficiency. This deficiency impairs immune function and increases vulnerability to the adverse effects of air pollution, further heightening susceptibility to TB in individuals with latent infections[103,104]. Furthermore, experimental studies have demonstrated that at low temperatures, both metabolism and minute ventilation are elevated, which increase particulate matter uptake[105]. These factors, combined with the ability of $PM_{2.5}$ to carry MTB and penetrate deeply into the lungs, may synergistically promote TB reactivation or new infections. Additionally, moderate wind speeds may enhance the spread of both particulate matter and MTB, intensifying the impact of PM_{10} on TB[62].

This study has several key public health implications. First, to reduce TB incidence and improve overall health, stringent air quality standards targeting $PM_{2.5}$ and PM_{10} are crucial, especially in high-pollution areas, along with allocating medical resources to these regions. Second, during periods of elevated $PM_{2.5}$ and PM_{10} concentrations, particularly under haze conditions, enhancing TB screening among symptomatic individuals and high-risk populations (e.g., those with HIV or diabetes) within specific lag periods could help mitigate the impact of air pollution on TB. Additionally, during cold seasons, measures such as wearing masks in crowded areas should be implemented to mitigate the combined effects of low temperatures and high $PM_{2.5}$ levels on TB risk. Finally, public education campaigns can raise awareness of the health impacts of air pollution and weather, encouraging preventive actions such as reducing outdoor activities during high pollution and cold weather.

This study had several limitations. First, ecological studies are inherently constrained in establishing causality, offering only correlational evidence, rather than confirming a direct relationship between environmental factors and TB cases. Additionally, we used NDVI as the sole indicator of greenness, without considering the quality, type (e.g., parks vs. tree-lined streets), or accessibility of green spaces, which may vary across Shanghai and influence health outcomes[95,96]. Future studies should incorporate these factors to better understand the relationship between green space and TB incidence. Furthermore, owing to data limitations, individual-level factors such as socioeconomic status, smoking, and healthcare-seeking behaviors could not be accounted for, restricting our ability to assess their modifying effects. Finally, relying on municipal-level environmental exposure data as a proxy for individual exposure may result in misclassifications that could affect the accuracy of the results. Future research should focus on cohort studies based on individual-level data and incorporate more precise exposure and covariate information to provide more reliable findings and strengthen the conclusions of this study.

CONCLUSION

Our study elucidated the independent and interactive effects of air pollutants, meteorological variables, and greenspace exposure on TB incidence in Shanghai, China. Specifically, $PM_{2.5}$, PM_{10}, and rainfall were positively associated with TB, whereas

NO_2, SO_2, and air pressure were negatively correlated. Additionally, low temperatures enhanced the association between $PM_{2.5}$ and TB cases. No significant association was observed between greenspace exposure and TB cases. Future research utilizing larger-scale TB case studies and advanced epidemiological methods, such as prospective cohort or case-control studies, is essential to elucidate the impact of environmental exposure on TB cases. These findings contribute to a deeper understanding of the TB risk factors and provide valuable evidence for public health policymakers to guide TB prevention, control, and air quality improvement.

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Competing Interests All authors declare that they have no competing interests.

Ethics The study and the use of data were reviewed and approved by the Ethical Review Committee of the School of Public Health (Shenzhen), Sun Yat-sen University (2022014).

Authors' Contributions Conceptualization: Qi Ye, Yating Ji, Xiaoyu Lu, Zhiyuan Li, and Chongguang Yang. Methodology: Qi Ye, Jiale Deng, Zhiyuan Li, Jianbang Xiang, Xu Gao, Xin Shen and Chongguang Yang. Investigation: Qi Ye, Xiaoyu Lu, Jiale Deng, and Nan Li. Formal analysis: Qi Ye and Jiale Deng. Resources: Jing Chen and Xin Shen. Data curation: Nan Li and Wei Wei. Validation: Yating Ji, Wei Wei and Renjie Hou. Writing the original draft: Qi Ye. Writing, review, and editing: Jing Chen, Yating Ji, Xiaoyu Lu, Renjie Hou, Zhiyuan Li, Jianbang Xiang, Xu Gao, Xin Shen, and Chongguang Yang. Supervision: Chongguang Yang.

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