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BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-089290
Article Type:	Original research
Date Submitted by the Author:	27-May-2024
Complete List of Authors:	Jiang, Jun; Center for Disease Control and Prevention, Department of Tuberculosis Control Fu, Ying; Center for Disease Control and Prevention, Department of Tuberculosis Control Cui, Caiyan; Center for Disease Control and Prevention, Department of Tuberculosis Control Wang, Feixian; Center for Disease Control and Prevention, Department of Tuberculosis Control Li, Yun; Center for Disease Control and Prevention, Department of Tuberculosis Control Wang, Yu; Center for Disease Control and Prevention, Department of Tuberculosis Control Jiang, Jun; Center for Disease Control and Prevention, Department of Tuberculosis Control Wang, Jianming; Nanjing Medical University, Department of Epidemiology; Nanjing Medical University, Department of Epidemiology Li, Zhongqi; Nanjing Medical University, Department of Epidemiology Tao, Bilin; School of Public Health, Nanjing Medical University, Department of Epidemiology
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Cross-Sectional Studies, EPIDEMIOLOGY

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Outdoor particulate matter and risk of drug resistance for workers and farmers with pulmonary tuberculosis

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Abstract word count and text word count： 193 and 2893

Abstract

Background: The detrimental effects of outdoor air pollutants on human health have been widely corroborated, but the evidence regarding the connection between particulate matter (PM) concentration and the drug resistant risk of tuberculosis is limited and inconclusive.

Methods: We collected the registration information of pulmonary tuberculosis (PTB) in Suzhou, China, from 2017 to 2021, as well as data on air pollutants and meteorological factors. The generalized additive model was utilized to estimate the effects of outdoor PM on the drug resistance risk of workers and farmers with PTB.

Results: Despite no association between PM_{10} and drug resistant risk in the overall analysis, subgroup analysis found a significant positive association in winter at all lag days. Similarly, $PM_{2.5}$ was significantly associated with drug resistance risk among males at a lag of 0-3 days, cases ≤60 years with a lag of 0-7 days, and in winter at a lag of 0-7 days, 0-15 days, 0-90 days, and 0-180 days.

Conclusions: The concentrations of outdoor PM_{10} and $PM_{2.5}$ were positively related to the drug resistance risk of workers and farmers with PTB, indicating that reducing ambient PM concentrations might decrease the burden of tuberculosis.

Key words: Pulmonary tuberculosis; Drug resistance; Particulate matter; Risk

Strengths and limitations

This study acknowledged several limitations warranting discussion. First, estimating the PM exposure level for each patient relied on data acquired from stationary monitoring points, potentially failing to represent individual exposure scenarios accurately. This introduced a potential measurement bias that could affect the validity of our findings. Second, during the study period, the Suzhou Infectious Disease Online Reporting System provided detection results solely for multidrug-resistant, rifampicin-resistant, and isoniazid-resistant tuberculosis, limiting the number of DR-TB patients for analysis. Consequently, conducting a stratified analysis for distinct types of DR-TB was unattainable. Third, although PTB patients from the mobile population were excluded, self-selection bias is likely to influence the results, given that their social and economic status may dictate individuals' choice of residence. Fourth, due to the unavailability of data, other factors related to PTB patients' drug resistance risk were not considered, such as smoking and alcohol consumption.

Introduction

Despite global efforts, the diagnosis and treatment of tuberculosis persist as formidable challenges. Developing countries disproportionately shoulder this burden as drug-resistant tuberculosis (DR-TB) continues to surge (World Health Organization, 2022). Antimicrobial resistance presents a significant public health threat, with DR-TB accounting for roughly 29% of all deaths related to antimicrobial-resistant pathogens [1]. Moreover, tackling DR-TB is a critical measure in curbing the spread of tuberculosis due to its lower treatment success rates and worse prognosis than drug-sensitive tuberculosis [2]. The consequences of DR-TB highlight the need for robust public health measures to control its spread [3]. Initial studies proposed that the genesis of DR-TB is attributed to mutations that decrease the pathogen's adaptive capacities, potentially instigated by suboptimal treatment protocols [4,5]. Subsequent research has strengthened the understanding of specific elements, such as a prior history of anti-tuberculosis therapy and infection with Human Immunodeficiency Virus (HIV), in the risk of elevated drug resistance in individuals diagnosed with tuberculosis [6,7].

The detrimental effects of outdoor air pollutants on human health have been widely corroborated, with particulate matter (PM) emerging as a particularly pernicious and pervasive air pollutant that has attracted significant public concern. The most common PMs are inhalable particles (PM_{10}) and fine particles ($PM_{2.5}$), characterized by aerodynamic diameters of ≤10 micrometers and 2.5 micrometers, respectively. Studies have shown that PM exposure not only exacerbates the prevalence of non-communicable diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and cardiovascular disease, but also intensifies the risk of infectious diseases like coronavirus disease 2019, influenza, and tuberculosis [8-12]. Notably, a study in Jinan identified, for the first time, the association between increased PM concentrations and elevated risk of drug resistance among tuberculosis patients[13]. In contrast, a recent study presented conflicting results[14]. The evidence regarding the connection between PM concentration and drug resistance risk of patients with tuberculosis is limited and inconclusive, warranting further research.

Outdoor workers and farmers are more vulnerable to air pollution and have more significant opportunities to contact patients with tuberculosis, placing them at a greater risk of tuberculosis infection. Although this issue is substantial, there is a scarcity of research exploring the effect of PM on drug-resistance risk among outdoor workers and farmers with pulmonary tuberculosis (PTB). To address this research gap, we performed a time-series analysis in eastern China.

Methods

Study population

We extracted information on PTB cases diagnosed between 2017 and 2021 from the Suzhou Center for Disease Control and Prevention. All patients were registered in the National Tuberculosis Online Registration System. We collected epidemiological data from each case, including gender, age, ethnicity, current address, occupation, comorbidities, pathogen examination, drug resistance, and treatment classification. Drug susceptibility testing, primarily on isoniazid and rifampicin, was conducted at the Fifth People's Hospital of Suzhou, a designated tuberculosis treatment facility in the city.

We excluded patients with other respiratory-related disorders, immunodeficiencies, prior tuberculosis treatment, and those who experienced changes in their current address during the treatment period to minimize exposure misclassification. In this investigation, DR-TB included either mono-resistant to isoniazid, mono-resistant to rifampicin, or multidrug-resistant to at least isoniazid and rifampicin. Individuals employed in manufacturing, construction, mining, and transportation were identified as workers. Meanwhile, those engaged in agriculture, forestry, animal husbandry, and fishery were defined as farmers.

Data on air pollutant concentrations and meteorological factors

From the China Meteorological Data Sharing Center (http://data.cma.cn/), we collected data on meteorological factors in Suzhou City between January 1, 2017, and December 31, 2021, including daily average temperature (°C), average wind speed (m/s), and relative humidity (%). Additionally, daily average concentrations of six environmental pollutants, namely PM_{10}, $PM_{2.5}$, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3), during the same period were retrieved from the National Urban Air Quality Real-Time Reporting Platform (http://106.37.208.233:20035/). The pollutant concentrations were reported in units of μg/m³, except for CO, which was reported in the unit of mg/m³.

Statistical analysis

We used a binomial distributed generalized additive model (GAM) to examine the relationship between PM concentration and drug resistance risk of PTB. GAM, with additive smoothing functions, is a powerful analytical tool capable of analyzing complex environmental health data that may exhibit nonlinear or non-monotonic relationships[15,16]. To control the impacts of potential confounding factors, we adjusted some covariates in the model, including sex, age, season, etiological examination, comorbidity, treatment type, average temperature, average wind speed, and average relative humidity. In addition, we utilized a thin plate spline function with a maximum degree of freedom of two to create smooth terms for three meteorological factors to control their potential nonlinear effects[15].

According to previous research, the influence of PM exposure on health may have delayed effects [16,17]. Thus, we calculated the moving average concentration of PM based on the diagnosis date of PTB patients to estimate their exposure levels. We applied eight different lag days to investigate both short-term and relatively long-term effects of PM exposure on the drug resistance risk of PTB, ranging from 0-3 days to 0-180 days. For example, PM concentration with a lag of 0-3 days represented the mean value of the daily average PM concentration on the day of diagnosis and the previous three days. The strength of the association between PM concentration and drug resistance risk of PTB patients was expressed as percentage changes in drug resistance risk and their corresponding 95% confidence intervals (CIs) for every 10-unit increase in PM concentration. Additionally, we conducted subgroup analyses to evaluate the associations in different populations and seasons.

We performed two sensitivity analyses to assess the robustness of the associations. First, we estimated the associations at different lag days, as mentioned earlier. Second, we fitted double-pollutant models, each incorporating adjustment for one of four gas pollutants while maintaining the same parameter settings as the primary model. This approach allowed us to determine if other gas pollutants influenced the relationship between PM concentration and drug resistance risk of patients.

All statistical analyses were carried out using R software version 4.2.0 (https://www.r-project.org/), and model fitting was achieved using the mgcv package. Statistical tests were two-tailed, with a significance level set at 0.05.

Results

Patient characteristics

The characteristics of study subjects are listed in Table 1. Of the 7868 cases, 241 (3.06%) had DR-TB, with a higher drug resistance rate in males (3.35%) than in females (2.20%) (χ^2 =6.533, P =0.011). No significant difference was observed in the drug resistance rate between age or ethnic groups. Sputum smear-positive cases had a higher drug resistance rate (5.92%) than sputum smear negative cases (0.03%) (χ^2 =229.556, P <0.001). Comorbidities, including HIV/AIDS, diabetes, or pneumoconiosis, did not significantly affect the drug resistance rate. However, newly treated cases had a lower drug resistance rate (2.59%) compared to those with antituberculosis treatment history (11.11%) (χ^2 =101.913, P <0.001).

Outdoor air pollutants and meteorological factors

The median concentrations and interquartile ranges (IQR) of daily outdoor air pollutants and meteorological factors in Suzhou City from 2017 to 2021 are shown in Table 2. The pollutants under observation, including PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3, exhibited median concentrations of 50.00 μg/m³ (IQR: 36.00-74.00), 30.00 μg/m³ (IQR: 20.00-46.00), 6.00 μg/m³ (IQR: 5.00-9.00), 37.00 μg/m³ (IQR: 27.00-51.00), 0.70 mg/m³ (IQR: 0.50-0.80), and 92.00 μg/m³ (IQR: 65.00-132.00), respectively. Within the same timeframe, the median (IQR) temperature, wind speed, and relative humidity were calculated as 18.40 °C (10.20-25.50), 2.40 m/s (1.90-3.20), and 73.00% (64.00-83.00), respectively. The temporal trends of air pollutant concentrations and meteorological factors are visually represented in Figure 1.

PM_{10} and drug resistance risk

No significant association was observed between PM_{10} concentration and drug resistance risk across the whole case (Figure 2). However, the association was significant during the winter season on all lag days. The magnitude of this relationship augmented as the lag interval expanded, culminating in the most salient effects at lag 0-180 days, as a 10-unit increment in PM_{10} concentration was associated with a 231.24% increased risk of drug resistance (95% CI: 35.79, 708.04).

In double-pollutant models, PM_{10} concentration and drug resistance risk remained significant at lag 0-60 days after adjusting for each of the four gaseous pollutants (Tables S1).

$PM_{2.5}$ and drug resistance risk

Similarly, no significant relationship was found between $PM_{2.5}$ concentration and drug resistance risk among the cases (Figure 3). However, the subgroup analyses disclosed that a 10-unit elevation in $PM_{2.5}$ concentration corresponded to a 10.73% (95% CI: 0.49, 22.02) increased drug resistance risk in male cases at lag 0-3 days and a 16.28% (95% CI: 1.20, 33.59) rise in drug resistance risk in cases under 60 years old at lag 0-7 days. A positive correlation emerged between $PM_{2.5}$ concentration and drug resistance risk in winter at lag 0-3 days, lag 0-15 days, lag 0-90 days, and lag 0-180 days, with the most pronounced impact observed at lag 0-180 days. At this time, the risk of drug resistance surged by 335.06% for each 10-unit increase in $PM_{2.5}$ concentration (95% CI: 17.71, 1507.95).

In double-pollutant models, the significant association between $PM_{2.5}$ concentration and drug resistance risk persisted in male cases at a lag of 0-3 days and those under 60 years old at a lag of 0- 7 days after adjusting for SO_2. Moreover, $PM_{2.5}$ concentration continued to exhibit a significant positive association with drug resistance risk in winter at lag 0-15 days, lag 0-30 days, and lag 0-180 days after adjusting for SO_2; at lag 0-180 days after adjusting for CO; at lag 0-7 days, lag 0-15 days, and lag 0-90 days after adjusting for O_3 (Table S2).

Discussion

This study examined the relationship between PM concentration and drug resistance risk of workers and farmers with PTB in Suzhou City, a prominent industrial metropolis in eastern China. A positive correlation between PM_{10} concentration and drug resistance risk was observed throughout all lag days in winter. Moreover, $PM_{2.5}$ concentration was found to be positively correlated with drug resistance risk of male cases at lag 0-3 days, cases under 60 years old at lag 0-7 days, and all cases at some lag days during the winter season. To our knowledge, this is the first study to evaluate the relationship between PM concentration and drug resistance risk of PTB cases in specific demographics in China.

The existing body of literature exploring the association between PM concentration and drug resistance risk of tuberculosis patients is scarce and inconclusive. A case-control study identified a positive association between PM concentration and drug resistance risk of tuberculosis patients [13]. Specifically, PM10 was shown to significantly impact this risk from lag 0-90 days to lag 0-540 days, while PM2.5 had a notable effect up to lag 0-540 days. A green environment could mitigate mortality risk of DR-TB patients [18,19]. In contrast, another study suggested a protective effect of $PM_{2.5}$ and PM_{10} against drug resistance risk [14]. In the current, we selected outdoor workers and farmers as the study subjects and did not uncover a significant association between PM concentration and drug resistance risk in the overall analyses. This disparity might stem from differences in PM concentration and composition characteristics [13,14]. Other factors such as geography, meteorological conditions, economic level, population density, and *Mycobacterium tuberculosis* strains might influence the relationship between PM and drug resistance risk [20].

Our findings indicated that elevated levels of PM_{10} and $PM_{2.5}$ during winter significantly contributed to the drug resistance risk of workers and farmers with PTB. This observation aligned with previous studies highlighting increased health risks from winter PM exposure. For example, a time-series study from 202 counties in the United States revealed the strongest correlation between $PM_{2.5}$ concentration and daily hospitalization rates for cardiovascular and respiratory systems during winter [21]. Another study from Wuhan, China, suggested that PM had a more pronounced impact on overall mortality, cardiovascular, stroke, and respiratory system mortality rates in winter[22]. Animal experiments demonstrated that winter exposure to $PM_{2.5}$ caused more severe cardiac toxicity than summer exposure[23], and wintertime PM exhibited higher endotoxin levels than springtime PM [24]. PM samples collected in Italy during winter produced more acute toxicity in mouse models than summer-collected samples [25]. Seasonality has been recognized as a crucial modifier when evaluating the impact of air pollution on human health. The potential influence of wintertime PM on the drug resistance risk of tuberculosis might be attributed to high concentrations of pollutants, as demonstrated by our time-series graphs. Increased atmospheric boundary layer stability and reduced vertical mixing tendencies result in pollutant retention and regional accumulation, contributing to this phenomenon primarily observed during winters[26,27].

Although Suzhou lacks coal heating systems, low wind speeds and temperatures exacerbate ground-level pollutant accumulation [27]. Nonetheless, the rising demand for heating systems may influence this phenomenon through regional transmission and accumulation from northern parts of China [28]. Furthermore, $PM_{2.5}$ has a more significant impact than PM_{10}, consistent with studies on air pollutants related to the onset risk of PTB[29,30]. This observation can be ascribed to smaller particles penetrating deeper into the alveoli and bronchi, resulting in more severe biological toxicity reactions[31] .

Our study uncovered a relationship between $PM_{2.5}$ and drug resistance risk of male PTB patients at a lag of 0-3 days and a similar association among patients under 60 years old at a lag of 0-7 days. However, no association was observed in these two subgroups at other lag days, necessitating cautious interpretation of the results. Thus, further research is required to determine their biological plausibility. Gender differences may stem from various factors, including lifestyle habits (e.g., smoking), social behaviors (e.g., engaging in group activities), and physiological differences, which collectively might render men more susceptible to DR-TB [32-34]. Previous research has indicated that patients with DR-TB tend to be younger than those with drug-sensitive infections. For example, a systematic review reported that the incidence of drug resistance was 2.53 times higher among PTB cases under 65 years old compared to those aged 65 and above[35]. This finding suggested that older individuals might develop DR-TB due to latent infections acquired before the emergence of drug resistance, while a younger age represents a risk factor for recent transmission[36].

Escalating PM levels could potentially amplify PTB patients' drug resistance risk. The exact machinations driving this phenomenon are yet to be entirely comprehended; however, several contributory factors can be hypothesized. Primarily, the composition of PM extends beyond mere physiochemical elements, encapsulating biological constituents such as microbes and antibiotic-resistant genes. An intriguing study revealed discernible disparities between the microbial consortia and their associated antibiotic-resistant genes present in the air, and those found within terrestrial and marine ecosystems [37]. PM has emerged as a principal vector for disseminating antibiotic-resistant genes within the environment [38,39]. Thus, the air could harbor more resistant strains and antibiotic-resistance genes in locales characterized by elevated PM concentrations. Secondarily, PM can incite oxidative stress and elicit inflammatory responses, which could precipitate structural and functional degradation of alveolar epithelial and endothelial cells [40,41]. Furthermore, PM can infiltrate the systemic circulation, provoking vascular dysregulation and systemic inflammation. Such perturbations may aggravate the clinical status of new tuberculosis patients afflicted with chronic pulmonary diseases. This exacerbation might necessitate a complex and protracted diagnostic and treatment regimen, thereby elevating their propensity to develop drug resistance [42]. Lastly, insights gleaned from a molecular epidemiological investigation underscored that the peril of direct transmission of DR-TB distinctly surpasses resistance acquisition attributable to factors such as the injudicious utilization of antibiotics[43]. This implies that PM, laden with resistant strains and antibiotic-resistant genes, could potentially bolster the aerial propagation of drug-resistant *Mycobacterium tuberculosis*.

In conclusion, our results demonstrated that PM concentration might positively correlate with the drug resistance risk of workers and farmers with PTB. Reducing outdoor PM concentration was likely to decrease the burden of tuberculosis.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (81973103), Medical Research Project of Jiangsu Health Commission (ZDB2020013), Nanjing Major Science and Technology Specific Project (2021-11005), and Suzhou Health Youth Backbone Talent "National Tutor System" Training Project (Gngg2022031). The funders had no role in the study design, data collection and

analysis, decision to publish, or preparation of the manuscript.

Competing interests

None declared.

Patient consent for publication

Not required.

Data availability statement

All data generated or analyzed during this study are included in this published article plus its Supplementary Information.

Author contributions

Xiaolong Zhang: Conceptualization, Methodology, Data Curation, Software, Formal analysis, Writing - Original Draft, Visualization. Zhongqi Li: Conceptualization, Formal analysis, Writing-Review & Editing. Bilin Tao: Formal analysis, Software, Visualization. Ying Fu: Data Curation, Methodology. Caiyan Cui, Feixian Wang and Yun Li: Data Curation. Jun Jiang: Conceptualization, Project administration. Jianming Wang: Conceptualization, Resources, Visualization, Writing-Review & Editing, Project administration, Supervision, Funding acquisition.

Ethical approval

The present study was approved by the Ethics Committee of Nanjing Medical University, which recognized it as a secondary analysis of retrospective, non-identifiable data employing anonymized, pre-existing public health records, without any direct interaction or intervention with the participants. Given the low-risk nature of this research and the inability to trace the data back to individual subjects, the Ethics Committee granted a waiver for the requirement of informed consent.

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Table 1. Characteristics of workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

Variables	Drug sensitivity n (%)	Drug resistance n (%)	χ^2	*P*
Sex				
Male	5715 (96.65)	198 (3.35)	6.533	0.011
Female	1912 (97.80)	43 (2.20)		
Age (years)				
<60	5532 (96.93)	175 (3.07)	0.001	0.978
≥60	2095 (96.95)	66 (3.05)		
Ethnic groups				
Han	7531 (96.96)	236 (3.04)	0.668	0.414
Others	96 (95.05)	5 (4.95)		
Sputum smear test				
Positive	3817 (94.08)	240 (5.92)	229.556	<0.001
Negative	3810 (99.97)	1 (0.03)		
Comorbidity*				
Yes	182 (95.79)	8 (4.21)	0.863	0.353
No	7445 (96.97)	233 (3.03)		
Treatment history				
No	7235 (97.41)	192 (2.59)	101.913	<0.001
Yes	392 (88.89)	49 (11.11)		

*: HIV/AIDS, diabetes, or pneumoconiosis.

1 Table 2. Characteristics of daily average outdoor air pollutant concentrations and meteorological factors in Suzhou City between 2017 and 2021.

Variables	Minimum	Q25	Median	Mean	Q75	Maximum
Outdoor air pollutants						
PM_{10} (μg/m^3)	7.00	36.00	50.00	58.8[illegible]	74.00	283.00
$PM_{2.5}$ (μg/m^3)	3.00	20.00	30.00	37.1[illegible]	46.00	222.00
SO_2 (μg/m^3)	2.00	5.00	6.00	7.[illegible]4	9.00	33.00
NO_2 (μg/m^3)	3.00	27.00	37.00	40.[illegible]	51.00	132.00
CO (mg/m^3)	0.20	0.50	0.70	0.70	0.80	2.20
O_3 (μg/m^3)	6.00	65.00	92.00	100.55	132.00	257.00
Meteorological factors						
Average temperature (°C)	-4.50	10.20	18.40	17.94	25.50	35.70
Average wind speed (m/s)	0.20	1.90	2.40	2.[illegible]1	3.20	8.20
Average relative humidity (%)	31.00	64.00	73.00	72.91	83.00	99.80

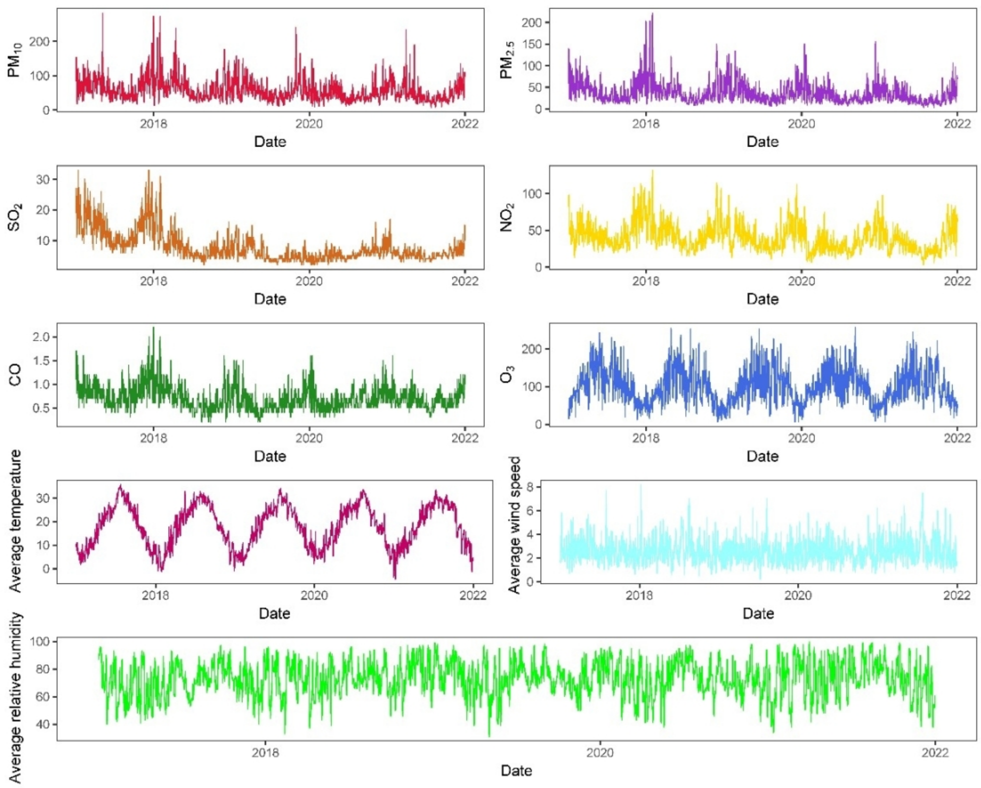
2

Figure legends

Figure 1. The time-series plots of outdoor air pollutant concentrations and meteorological factors in Suzhou City between 2017 and 2021.

Figure 2. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in PM_{10} concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

Figure 3. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in $PM_{2.5}$ concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.



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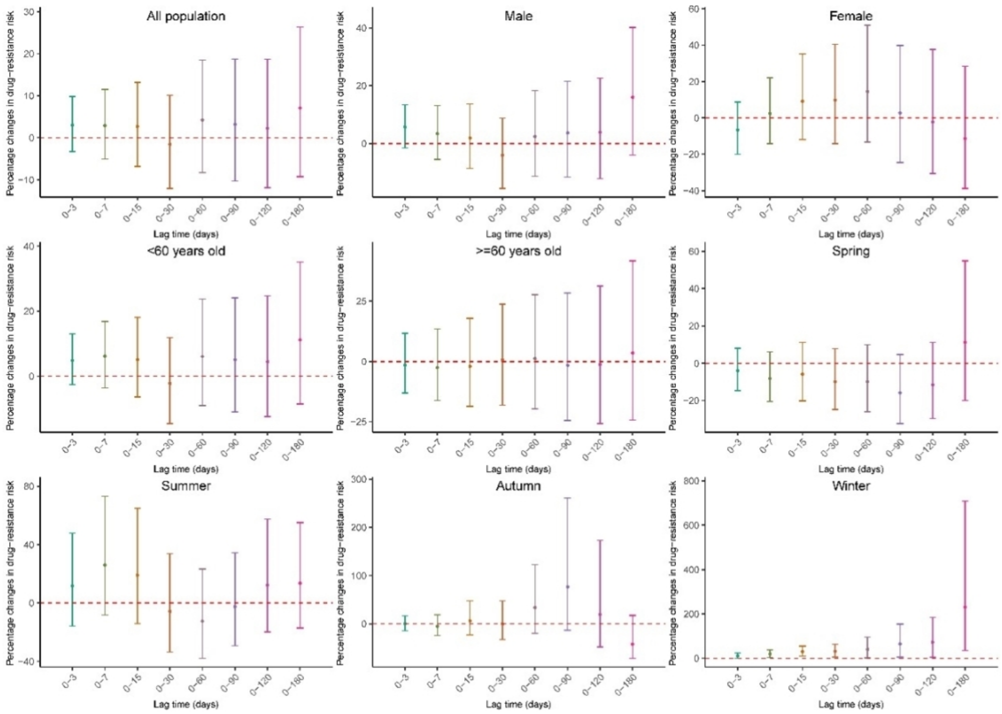

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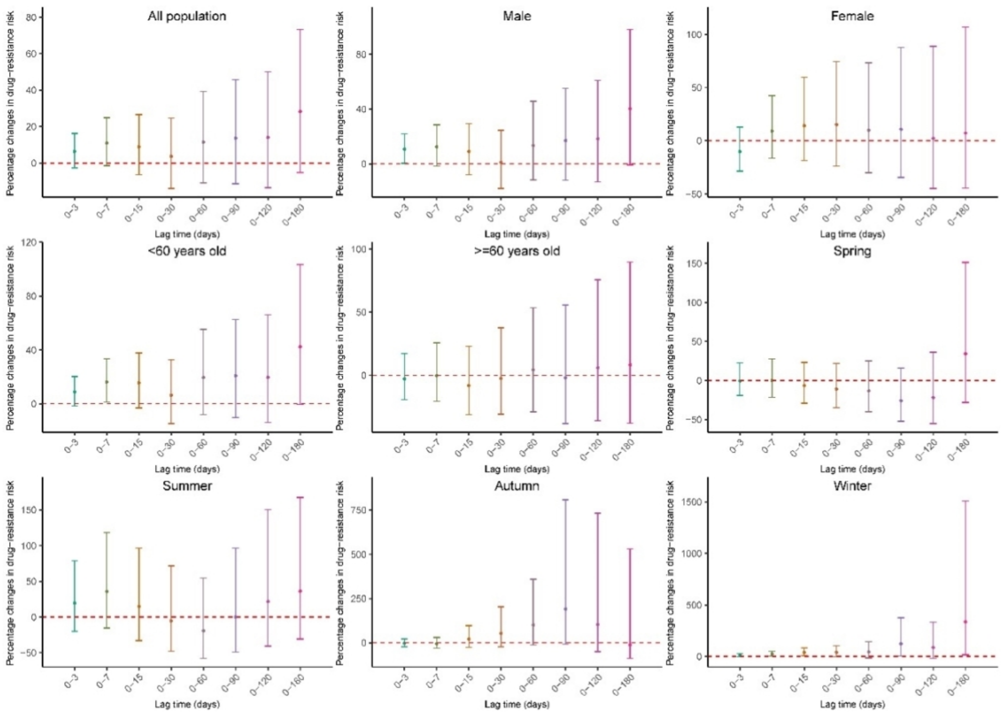

146x103mm (220 x 220 DPI)

Supplementary Tables

Table S1. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in PM_{10} concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
All population	0-3 days	3.02 (-3.34, 9.79)	3.89 (-3.35, 11.67)	1.95 (-7.20, 11.99)	1.87 (-6.26, 10.70)	3.16 (-3.23, 9.96)
	0-7 days	2.89 (-5.07, 11.51)	3.35 (-5.57, 13.12)	-2.47 (-14.10, 10.73)	1.02 (-8.61, 11.66)	2.83 (-5.14, 11.47)
	0-15 days	2.66 (-6.87, 13.17)	4.14 (-6.79, 16.36)	0.77 (-14.50, 18.76)	3.41 (-8.03, 16.26)	2.80 (-6.77, 13.35)
	0-30 days	-1.60 (-12.07, 10.11)	-1.02 (-13.33, 13.03)	-1.74 (-19.52, 19.97)	-0.56 (-13.25, 13.99)	-1.52 (-12.03, 10.24)
	0-60 days	4.24 (-8.32, 18.52)	9.58 (-6.39, 28.28)	21.29 (-7.26, 58.63)	12.41 (-4.37, 32.13)	5.98 (-6.97, 20.73)
	0-90 days	3.19 (-10.33, 18.74)	7.69 (-10.73, 29.91)	12.29 (-22.71, 63.15)	9.78 (-7.96, 30.94)	3.40 (-10.21, 19.08)
	0-120 days	2.25 (-11.91, 18.70)	4.36 (-15.27, 28.53)	10.70 (-28.56, 71.52)	9.57 (-9.07, 32.03)	2.09 (-12.14, 18.63)
	0-180 days	7.08 (-9.27, 26.37)	8.38 (-14.35, 37.14)	14.39 (-34.45, 99.60)	17.45 (-4.06, 43.78)	8.62 (-8.12, 28.40)
Male	0-3 days	5.66 (-1.58, 13.42)	6.58 (-1.69, 15.54)	5.32 (-4.96, 16.73)	3.89 (-5.28, 13.95)	5.88 (-1.38, 13.68)
	0-7 days	3.38 (-5.54, 13.15)	3.21 (-6.77, 14.26)	-4.02 (-16.75, 10.64)	1.32 (-9.40, 13.31)	3.36 (-5.61, 13.19)
	0-15 days	1.93 (-8.65, 13.73)	3.23 (-8.81, 16.85)	-3.74 (-20.00, 15.82)	2.17 (-10.33, 16.41)	2.13 (-8.50, 14.00)
	0-30 days	-4.13 (-15.51, 8.79)	-4.20 (-17.45, 11.17)	-12.42 (-30.50, 10.38)	-3.52 (-17.20, 12.42)	-3.86 (-15.32, 9.15)
	0-60 days	2.44 (-11.29, 18.31)	8.68 (-8.77, 29.46)	7.44 (-20.73, 45.61)	10.45 (-7.76, 32.24)	4.57 (-9.71, 21.10)
	0-90 days	3.65 (-11.57, 21.48)	10.10 (-10.47, 35.41)	-1.99 (-35.81, 49.66)	10.48 (-9.24, 34.50)	4.03 (-11.37, 22.10)
	0-120 days	3.82 (-12.06, 22.56)	9.11 (-12.88, 36.64)	3.50 (-36.50, 68.70)	11.88 (-8.98, 37.52)	4.21 (-11.84, 23.18)
	0-180 days	15.99 (-3.98, 40.13)	22.55 (-5.30, 58.60)	13.98 (-38.57, 111.50)	30.12 (3.33, 63.85)	17.26 (-3.19, 42.03)
Female	0-3 days	-6.73 (-19.99, 8.73)	-6.50 (-21.31, 11.09)	-7.00 (-26.58, 17.79)	-6.38 (-23.38, 14.38)	-6.90 (-20.21, 8.61)
	0-7 days	2.31 (-14.19, 21.99)	4.30 (-14.15, 26.72)	8.68 (-17.93, 43.92)	0.40 (-19.82, 25.73)	2.46 (-14.07, 22.17)
	0-15 days	9.10 (-11.93, 35.16)	11.24 (-13.46, 42.98)	28.57 (-11.81, 87.45)	12.88 (-13.90, 48.00)	9.26 (-11.79, 35.34)
	0-30 days	9.76 (-14.18, 40.38)	14.03 (-15.17, 53.29)	48.37 (-3.13, 127.25)	17.18 (-14.47, 60.55)	8.58 (-15.18, 39.00)
	0-60 days	14.44 (-13.26, 50.99)	17.80 (-17.83, 68.88)	90.05 (4.94, 244.18)	23.68 (-13.95, 77.77)	11.85 (-14.95, 47.10)
	0-90 days	2.72 (-24.52, 39.80)	-4.82 (-38.91, 48.29)	85.70 (-19.72, 329.53)	7.78 (-28.17, 61.71)	3.42 (-23.86, 40.46)
	0-120 days	-2.23 (-30.51, 37.57)	-17.93 (-51.04, 37.57)	43.55 (-47.44, 292.02)	0.63 (-34.87, 55.47)	-3.06 (-31.35, 36.90)
	0-180 days	-11.32 (-38.74, 28.37)	-31.17 (-62.16, 25.20)	17.40 (-68.64, 339.42)	-10.00 (-42.80, 41.60)	-10.22 (-38.25, 30.53)
<60 years old	0-3 days	4.91 (-2.58, 12.98)	7.81 (-0.79, 17.16)	4.43 (-6.56, 16.72)	5.10 (-4.65, 15.84)	4.85 (-2.67, 12.94)
	0-7 days	6.13 (-3.62, 16.88)	9.90 (-1.16, 22.21)	2.73 (-11.81, 19.67)	6.90 (-5.06, 20.36)	6.11 (-3.65, 16.87)
	0-15 days	5.14 (-6.39, 18.09)	10.05 (-3.35, 25.30)	5.03 (-13.88, 28.09)	7.22 (-6.53, 22.99)	5.14 (-6.39, 18.10)
	0-30 days	-2.25 (-14.59, 11.88)	2.03 (-12.87, 19.49)	-6.11 (-26.38, 19.73)	1.57 (-13.67, 19.51)	-2.15 (-14.56, 12.07)
	0-60 days	6.09 (-9.06, 23.75)	15.67 (-3.94, 39.28)	24.82 (-9.01, 71.21)	17.39 (-3.03, 42.12)	7.35 (-8.19, 25.53)
	0-90 days	5.06 (-11.07, 24.12)	16.12 (-6.81, 44.70)	16.94 (-24.76, 81.73)	16.09 (-5.62, 42.79)	5.01 (-11.11, 24.05)
	0-120 days	4.49 (-12.44, 24.70)	14.78 (-10.20, 46.71)	35.23 (-19.25, 126.46)	15.71 (-7.03, 44.02)	5.28 (-11.88, 25.77)
	0-180 days	11.15 (-8.57, 35.11)	21.46 (-7.93, 60.24)	32.82 (-30.65, 154.35)	25.49 (-0.90, 58.92)	13.90 (-6.44, 38.66)
≥60 years old	0-3 days	-1.44 (-13.04, 11.71)	-5.28 (-18.14, 9.60)	-3.24 (-19.27, 15.97)	-4.61 (-18.96, 12.28)	-0.93 (-12.60, 12.31)
	0-7 days	-2.49 (-16.21, 13.47)	-9.58 (-24.29, 7.98)	-13.44 (-31.87, 9.98)	-9.51 (-25.62, 10.10)	-2.10 (-16.07, 14.18)
	0-15 days	-2.06 (-18.61, 17.87)	-9.57 (-27.02, 12.04)	-6.76 (-31.15, 26.28)	-3.36 (-23.25, 21.67)	-1.91 (-18.63, 18.26)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
	0-30 days	0.67 (-18.13, 23.80)	-5.76 (-26.34, 20.56)	6.60 (-25.70, 52.93)	-3.19 (-24.98, 24.91)	0.65 (-18.16, 23.79)
	0-60 days	1.26 (-19.71, 27.71)	-5.30 (-29.16, 26.60)	23.35 (-24.80, 102.33)	1.76 (-24.86, 37.79)	2.78 (-18.75, 30.02)
	0-90 days	-1.53 (-24.49, 28.41)	-11.63 (-38.27, 26.50)	-1.69 (-52.18, 102.13)	-3.[illegible]6 (-31.67, 35.26)	-1.63 (-24.63, 28.39)
	0-120 days	-1.29 (-25.74, 31.21)	-11.16 (-41.01, 33.80)	-34.12 (-71.99, 54.95)	-0.[illegible]4 (-31.05, 44.06)	-2.43 (-26.45, 29.42)
	0-180 days	3.56 (-24.35, 41.76)	-11.44 (-44.69, 41.79)	-18.98 (-73.51, 147.78)	[illegible].56 (-29.14, 57.25)	1.86 (-25.93, 40.08)
Spring	0-3 days	-3.97 (-14.66, 8.06)	0.74 (-11.52, 14.71)	-0.69 (-14.90, 15.90)	-2.[illegible]4 (-15.25, 12.54)	-3.14 (-14.19, 9.33)
	0-7 days	-8.12 (-20.49, 6.18)	-2.51 (-17.59, 15.33)	-10.79 (-28.41, 11.18)	-7.[illegible]3 (-23.46, 10.99)	-6.78 (-19.40, 7.82)
	0-15 days	-5.81 (-20.22, 11.20)	6.59 (-12.57, 29.96)	3.28 (-23.79, 39.96)	-2.33 (-21.82, 22.02)	-5.50 (-20.17, 11.87)
	0-30 days	-9.91 (-24.80, 7.93)	1.11 (-21.31, 29.90)	14.91 (-22.28, 69.90)	-8.[illegible]0 (-31.65, 22.77)	-15.66 (-31.25, 3.46)
	0-60 days	-9.83 (-26.02, 9.89)	4.75 (-27.62, 51.58)	52.69 (-18.20, 185.01)	1[illegible].[illegible]9 (-32.82, 105.50)	-11.01 (-27.41, 9.09)
	0-90 days	-15.80 (-32.33, 4.79)	-16.91 (-46.23, 28.40)	35.67 (-46.56, 244.43)	-34.70 (-62.68, 14.27)	-18.73 (-35.18, 1.91)
	0-120 days	-11.58 (-29.71, 11.24)	-5.71 (-43.60, 57.62)	19.42 (-57.99, 239.53)	-3[illegible].54 (-62.45, 3.88)	-10.86 (-28.98, 11.87)
	0-180 days	11.25 (-20.09, 54.86)	82.40 (-4.98, 250.14)	155.97 (-6.63, 601.71)	[illegible]3.[illegible]9 (-1.13, 206.19)	11.02 (-20.10, 54.25)
Summer	0-3 days	11.69 (-15.67, 47.94)	18.64 (-13.87, 63.43)	3.14 (-29.78, 51.49)	14.[illegible]3 (-17.47, 59.76)	18.64 (-11.31, 58.69)
	0-7 days	26.12 (-8.15, 73.19)	35.16 (-4.65, 91.58)	22.26 (-23.89, 96.40)	32.84 (-7.17, 90.08)	31.57 (-4.27, 80.82)
	0-15 days	19.11 (-13.98, 64.93)	29.02 (-9.98, 84.89)	26.02 (-25.66, 113.61)	[illegible]7.[illegible]0 (-10.76, 83.03)	19.45 (-13.05, 64.09)
	0-30 days	-5.73 (-33.66, 33.96)	-5.11 (-37.09, 43.11)	-10.09 (-50.02, 61.73)	[illegible]1.[illegible]3 (-33.24, 53.19)	-3.87 (-32.57, 37.04)
	0-60 days	-12.47 (-37.86, 23.30)	15.23 (-28.29, 85.16)	-29.53 (-66.08, 46.38)	10.[illegible]2 (-33.51, 83.04)	2.39 (-29.95, 49.67)
	0-90 days	-2.45 (-29.24, 34.50)	-6.26 (-36.80, 39.04)	-30.37 (-71.47, 69.89)	13.[illegible]5 (-29.18, 80.46)	-1.66 (-29.58, 37.32)
	0-120 days	12.37 (-19.90, 57.63)	57.82 (-11.10, 180.17)	32.33 (-49.50, 246.78)	70.[illegible]7 (-2.46, 198.28)	34.50 (-8.45, 97.61)
	0-180 days	13.50 (-17.02, 55.24)	-26.98 (-54.20, 16.40)	7.98 (-72.67, 326.67)	-12.[illegible]7 (-52.47, 62.27)	14.25 (-17.88, 58.96)
Autumn	0-3 days	0.01 (-14.36, 16.80)	-1.13 (-16.46, 17.01)	-6.14 (-26.56, 19.96)	-0.[illegible]1 (-17.51, 19.51)	-0.03 (-14.56, 16.98)
	0-7 days	-5.03 (-23.93, 18.56)	-5.19 (-25.19, 20.17)	-12.51 (-38.90, 25.27)	-7.[illegible]8 (-28.52, 18.97)	-4.97 (-23.90, 18.68)
	0-15 days	6.50 (-23.01, 47.33)	11.56 (-21.45, 58.44)	11.54 (-36.57, 96.13)	4.[illegible]8 (-26.44, 49.24)	9.74 (-21.08, 52.59)
	0-30 days	-0.43 (-32.79, 47.52)	-0.43 (-34.18, 50.61)	-22.97 (-63.25, 61.43)	-1.[illegible]9 (-34.49, 47.85)	8.76 (-30.41, 69.97)
	0-60 days	33.66 (-19.76, 122.63)	27.87 (-26.30, 121.88)	17.30 (-55.07, 206.20)	34.[illegible]5 (-20.37, 125.98)	12.96 (-40.50, 114.47)
	0-90 days	76.72 (-13.39, 260.59)	164.24 (-3.60, 624.33)	141.00 (-61.60, 1412.34)	94.48 (-12.77, 333.62)	124.11 (-20.43, 531.22)
	0-120 days	19.11 (-48.07, 173.18)	21.29 (-51.53, 203.53)	-62.48 (-93.36, 112.00)	40.[illegible]4 (-41.93, 241.55)	19.71 (-49.18, 181.97)
	0-180 days	-42.20 (-71.52, 17.33)	-42.66 (-71.91, 17.06)	-89.62 (-97.88, -49.29)	-24.[illegible]1 (-68.50, 82.86)	-56.28 (-83.71, 17.28)
Winter	0-3 days	11.21 (0.02, 23.65)	10.78 (-3.15, 26.70)	13.19 (-3.58, 32.87)	1.[illegible]8 (-15.38, 22.18)	11.73 (0.65, 24.04)
	0-7 days	19.69 (3.58, 38.29)	21.57 (0.50, 47.07)	19.68 (-6.04, 52.43)	8.[illegible]6 (-12.44, 35.34)	20.83 (4.58, 39.60)
	0-15 days	30.51 (9.89, 55.00)	49.97 (15.68, 94.43)	32.70 (-4.53, 84.45)	24.80 (-4.68, 63.41)	31.84 (10.65, 57.10)
	0-30 days	31.42 (5.98, 62.97)	60.58 (14.73, 124.74)	42.45 (-11.87, 130.25)	41.[illegible]2 (0.58, 100.26)	36.11 (7.37, 72.55)
	0-60 days	40.48 (1.23, 94.94)	134.42 (28.84, 326.52)	248.89 (38.62, 778.15)	86.[illegible]0 (12.89, 208.77)	40.11 (0.12, 96.09)
	0-90 days	64.36 (6.21, 154.36)	102.85 (-13.92, 378.03)	3388.62 (211.56, 38962.49)	97.[illegible]9 (-0.58, 294.26)	120.81 (34.55, 262.35)
	0-120 days	72.65 (4.55, 185.12)	84.47 (-23.90, 347.18)	275.06 (-60.78, 3486.92)	84.[illegible]8 (-6.79, 266.32)	44.14 (-12.93, 138.61)
	0-180 days	231.24 (35.79, 708.04)	529.41 (63.91, 2316.96)	3810.34 (10.50, 138283.73)	303.[illegible]3 (43.69, 1030.45)	171.49 (-15.60, 773.32)

Model 1: Adjusted for sex, age, season, etiological examination, comorbidity, treatment type, and average temperature, average wind speed, and average relative

humidity at the same lag time.
Model 2: Based on model 1, additionally adjusted for SO_2 at the same lag time.
Model 3: Based on model 1, additionally adjusted for NO_2 at the same lag time.
Model 4: Based on model 1, additionally adjusted for CO at the same lag time.
Model 5: Based on model 1, additionally adjusted for O_3 at the same lag time.

Table S2. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in $PM_{2.5}$ concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
All population	0-3 days	6.41 (-2.62, 16.29)	8.45 (-1.97, 19.97)	6.48 (-5.25, 19.66)	6.28 (-5.72, 19.80)	7.41 (-1.93, 17.64)
	0-7 days	10.95 (-1.41, 24.86)	13.25 (-0.63, 29.06)	10.21 (-6.10, 29.35)	11.61 (-3.68, 29.31)	12.13 (-0.46, 26.30)
	0-15 days	8.93 (-6.29, 26.62)	12.69 (-4.88, 33.51)	10.17 (-9.81, 34.58)	12.08 (-6.15, 33.85)	9.95 (-5.59, 28.03)
	0-30 days	3.66 (-13.83, 24.70)	7.14 (-13.67, 32.98)	8.86 (-14.48, 38.57)	7.30 (-13.21, 32.65)	4.10 (-13.71, 25.58)
	0-60 days	11.53 (-10.70, 39.30)	22.29 (-6.87, 60.58)	33.74 (-1.35, 81.30)	19.98 (-7.05, 54.89)	16.00 (-6.63, 44.12)
	0-90 days	13.66 (-11.31, 45.65)	29.09 (-7.84, 80.81)	40.19 (-7.91, 113.42)	24.13 (-6.65, 65.07)	12.86 (-11.97, 44.68)
	0-120 days	13.97 (-13.42, 50.02)	27.69 (-12.89, 87.19)	63.22 (-4.85, 179.99)	25.47 (-8.03, 71.16)	13.60 (-13.82, 49.75)
	0-180 days	28.23 (-5.16, 73.38)	41.24 (-6.65, 113.69)	101.31 (2.93, 293.73)	45.53 (3.93, 103.80)	28.09 (-5.36, 73.37)
Male	0-3 days	10.73 (0.49, 22.02)	12.92 (1.08, 26.13)	11.39 (-1.78, 26.33)	10.28 (-3.31, 25.79)	11.78 (1.28, 23.37)
	0-7 days	12.51 (-1.48, 28.48)	14.03 (-1.59, 32.13)	9.88 (-8.08, 31.35)	13.13 (-4.04, 33.37)	14.34 (-0.01, 30.75)
	0-15 days	9.18 (-7.84, 29.33)	13.01 (-6.48, 36.56)	8.47 (-13.36, 35.80)	11.82 (-8.17, 36.16)	11.23 (-6.36, 32.14)
	0-30 days	1.18 (-17.79, 24.55)	4.36 (-17.88, 32.64)	2.45 (-22.43, 35.30)	1.76 (-17.49, 31.99)	2.92 (-16.56, 26.96)
	0-60 days	13.50 (-11.61, 45.73)	28.25 (-5.45, 73.95)	34.65 (-4.32, 89.49)	23.32 (-7.28, 64.00)	18.60 (-7.23, 51.63)
	0-90 days	17.06 (-11.76, 55.29)	38.13 (-5.21, 101.29)	36.06 (-15.64, 119.43)	28.00 (-7.05, 76.27)	15.59 (-12.93, 53.44)
	0-120 days	18.35 (-12.97, 60.96)	40.97 (-7.51, 114.88)	54.74 (-15.78, 184.33)	31.65 (-6.91, 86.19)	18.84 (-12.79, 61.96)
	0-180 days	40.26 (-0.76, 98.24)	63.09 (2.07, 160.58)	65.88 (-21.56, 250.78)	59.06 (8.46, 133.26)	40.27 (-0.87, 98.47)
Female	0-3 days	-10.26 (-28.62, 12.82)	-10.11 (-30.60, 16.43)	-10.25 (-34.90, 23.72)	-10.16 (-33.67, 21.70)	-10.89 (-29.26, 12.26)
	0-7 days	9.12 (-16.42, 42.46)	13.30 (-15.35, 51.66)	24.50 (-15.75, 83.97)	9.40 (-22.09, 53.60)	8.41 (-17.02, 41.62)
	0-15 days	14.01 (-18.57, 59.61)	16.44 (-20.77, 71.14)	32.33 (-19.59, 117.77)	19.05 (-21.69, 80.99)	11.97 (-19.96, 56.64)
	0-30 days	15.23 (-23.87, 74.41)	22.08 (-26.94, 103.99)	39.30 (-19.43, 140.86)	23.48 (-25.78, 105.45)	9.90 (-27.96, 67.66)
	0-60 days	10.04 (-30.08, 73.18)	4.78 (-42.78, 91.85)	27.75 (-34.32, 148.47)	13.38 (-35.67, 99.82)	5.79 (-32.96, 66.92)
	0-90 days	10.83 (-34.53, 87.63)	2.91 (-52.42, 122.56)	65.29 (-31.44, 298.51)	20.62 (-36.53, 128.84)	11.07 (-34.59, 88.61)
	0-120 days	2.13 (-44.74, 88.76)	-18.44 (-67.67, 105.76)	72.41 (-48.12, 472.97)	8.18 (-46.92, 120.46)	0.58 (-45.65, 86.13)
	0-180 days	7.20 (-44.41, 106.73)	4.07 (-60.08, 171.28)	436.86 (2.43, 2713.84)	18.88 (-43.55, 150.36)	8.98 (-43.72, 111.01)
<60 years old	0-3 days	8.84 (-1.58, 20.37)	13.34 (1.26, 26.87)	9.17 (-4.48, 24.78)	10.89 (-3.19, 27.01)	8.80 (-1.77, 20.52)
	0-7 days	16.28 (1.20, 33.59)	23.14 (5.85, 43.25)	17.40 (-2.72, 41.69)	21.08 (2.08, 43.63)	16.98 (1.67, 34.59)
	0-15 days	15.56 (-3.22, 37.98)	24.94 (2.76, 51.92)	20.30 (-5.07, 52.47)	21.13 (-1.27, 48.61)	15.89 (-3.08, 38.57)
	0-30 days	6.43 (-14.66, 32.73)	17.03 (-9.20, 50.84)	13.45 (-15.15, 51.69)	13.87 (-11.33, 46.23)	7.36 (-14.22, 34.39)
	0-60 days	19.52 (-8.00, 55.26)	40.59 (2.23, 93.34)	39.89 (-2.94, 101.62)	33.60 (-0.90, 80.11)	21.40 (-6.72, 57.99)
	0-90 days	20.82 (-10.23, 62.62)	54.81 (3.47, 131.62)	59.26 (-3.13, 161.81)	37.99 (-1.58, 93.48)	21.22 (-9.99, 63.25)
	0-120 days	19.57 (-13.98, 66.20)	52.89 (-3.19, 141.46)	99.29 (3.65, 283.19)	35.66 (-6.12, 96.02)	22.06 (-12.42, 70.13)
	0-180 days	42.34 (-0.39, 103.40)	79.60 (10.12, 192.92)	171.59 (22.57, 501.79)	63.71 (10.33, 142.90)	43.23 (-0.06, 105.28)
≥60 years old	0-3 days	-2.74 (-19.31, 17.23)	-8.63 (-26.85, 14.11)	-5.01 (-25.31, 20.80)	-8.78 (-28.62, 18.10)	-0.62 (-17.74, 20.08)
	0-7 days	-0.19 (-20.72, 25.65)	-9.64 (-31.22, 18.70)	-8.85 (-33.21, 24.39)	-9.71 (-32.88, 23.07)	4.11 (-17.77, 31.81)
	0-15 days	-8.15 (-31.36, 22.92)	-21.29 (-44.61, 11.84)	-14.10 (-41.41, 25.93)	-12.26 (-38.53, 25.24)	-6.02 (-30.10, 26.35)
	0-30 days	-2.51 (-30.91, 37.56)	-15.71 (-45.01, 29.21)	-1.26 (-36.24, 52.91)	-9.23 (-39.69, 36.61)	-2.70 (-31.30, 37.81)
	0-60 days	4.36 (-29.02, 53.44)	-7.06 (-44.34, 55.20)	23.09 (-28.78, 112.74)	5.40 (-34.51, 69.63)	7.40 (-26.67, 57.29)
	0-90 days	-2.01 (-38.27, 55.57)	-22.04 (-59.23, 49.06)	0.43 (-56.00, 129.21)	-3.74 (-44.06, 65.99)	0.16 (-36.01, 56.78)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
	0-120 days	5.96 (-36.09, 75.68)	-5.62 (-55.37, 99.59)	1.16 (-62.68, 174.17)	10.74 (-38.88, 100.65)	6.70 (-35.08, 75.37)
	0-180 days	8.34 (-38.13, 89.72)	-16.17 (-63.31, 91.54)	-3.12 (-73.43, 253.31)	[illegible] (-41.98, 112.78)	8.41 (-37.92, 89.32)
Spring	0-3 days	-0.43 (-19.17, 22.66)	9.52 (-12.95, 37.79)	7.80 (-16.04, 38.40)	[illegible] (-18.12, 34.86)	3.21 (-18.14, 30.13)
	0-7 days	0.15 (-21.49, 27.75)	15.32 (-13.03, 52.90)	6.91 (-21.57, 45.75)	[illegible] (-20.27, 48.26)	9.29 (-16.91, 43.75)
	0-15 days	-6.34 (-28.91, 23.40)	18.34 (-14.71, 64.20)	13.86 (-24.67, 72.10)	[illegible] (-28.77, 47.13)	-5.34 (-29.34, 26.81)
	0-30 days	-10.73 (-34.78, 22.18)	14.32 (-25.88, 76.33)	26.89 (-21.86, 106.04)	[illegible] (-35.46, 50.50)	-25.93 (-48.95, 7.47)
	0-60 days	-13.29 (-39.94, 25.18)	34.81 (-36.16, 184.65)	43.61 (-28.91, 190.10)	[illegible] (-39.33, 105.04)	-19.07 (-47.14, 23.92)
	0-90 days	-25.64 (-52.41, 16.20)	-18.11 (-83.47, 305.76)	14.43 (-52.85, 177.70)	-29.58 (-68.23, 56.08)	-45.63 (-67.52, -9.01)
	0-120 days	-21.67 (-55.02, 36.38)	95.93 (-74.76, 1421.17)	69.48 (-49.61, 469.94)	[illegible] (-82.14, 46.56)	-23.57 (-56.43, 34.05)
	0-180 days	34.39 (-28.11, 151.23)	141.37 (-8.21, 534.66)	163.90 (-14.57, 715.14)	[illegible] (-2.10, 467.17)	19.03 (-38.83, 131.61)
Summer	0-3 days	19.61 (-20.00, 78.83)	27.39 (-17.91, 97.71)	10.78 (-31.04, 77.98)	[illegible] (-22.05, 106.10)	38.00 (-10.54, 112.87)
	0-7 days	35.97 (-15.33, 118.36)	43.39 (-13.14, 136.70)	23.82 (-31.05, 122.34)	[illegible] (-14.27, 162.71)	54.02 (-5.70, 151.56)
	0-15 days	14.87 (-32.96, 96.82)	19.54 (-32.29, 111.06)	5.43 (-47.99, 113.73)	[illegible] (-29.67, 144.56)	27.58 (-25.97, 119.88)
	0-30 days	-5.28 (-47.79, 71.85)	-3.39 (-48.76, 82.14)	-4.36 (-57.47, 115.04)	[illegible] (-46.20, 116.64)	-1.22 (-46.25, 81.56)
	0-60 days	-19.21 (-57.74, 54.48)	7.48 (-48.04, 122.35)	-24.55 (-72.16, 104.49)	[illegible] (-51.77, 125.88)	-0.97 (-50.52, 98.20)
	0-90 days	0.15 (-49.00, 96.64)	-2.98 (-53.49, 102.38)	-17.26 (-80.07, 243.47)	[illegible] (-46.79, 153.50)	0.98 (-48.77, 99.03)
	0-120 days	21.65 (-40.85, 150.21)	47.32 (-40.95, 267.54)	25.59 (-74.96, 529.99)	41.40 (-37.13, 218.01)	59.56 (-26.32, 245.54)
	0-180 days	36.13 (-30.70, 167.42)	-23.97 (-79.46, 181.45)	64.64 (-78.83, 1180.42)	-1.04 (-66.55, 192.75)	38.33 (-31.72, 180.24)
Autumn	0-3 days	-2.96 (-22.65, 21.76)	-4.56 (-25.17, 21.73)	-13.09 (-37.73, 21.29)	-5.[illegible]4 (-28.09, 24.59)	-3.32 (-23.79, 22.64)
	0-7 days	-4.54 (-29.95, 30.11)	-4.35 (-30.52, 31.69)	-9.72 (-42.76, 42.40)	-7.[illegible]7 (-35.10, 31.65)	-4.18 (-30.14, 31.41)
	0-15 days	20.70 (-26.12, 97.21)	25.42 (-24.08, 107.19)	34.63 (-32.59, 168.89)	19.44 (-29.82, 103.26)	18.87 (-27.36, 94.52)
	0-30 days	53.45 (-22.46, 203.68)	57.14 (-22.00, 216.59)	95.52 (-29.40, 441.48)	51.43 (-24.92, 205.45)	62.34 (-19.95, 229.20)
	0-60 days	100.47 (-12.31, 358.31)	97.05 (-21.63, 395.49)	161.05 (-36.72, 976.90)	113.[illegible]1 (-12.31, 421.85)	72.09 (-34.92, 355.02)
	0-90 days	191.09 (-6.67, 807.96)	715.97 (41.58, 4602.55)	604.03 (-50.03, 9819.71)	295.[illegible]9 (1.26, 1443.03)	326.51 (-11.66, 1959.17)
	0-120 days	103.34 (-50.34, 732.58)	132.47 (-52.28, 1032.58)	20.48 (-88.06, 1115.85)	211.[illegible]8 (-34.81, 1393.11)	101.34 (-51.02, 727.62)
	0-180 days	-11.86 (-87.69, 531.11)	-15.79 (-87.99, 490.57)	-73.47 (-98.60, 401.41)	-9.60 (-90.11, 726.57)	-23.90 (-91.96, 620.34)
Winter	0-3 days	13.03 (-0.83, 28.82)	11.89 (-5.11, 31.95)	12.24 (-5.61, 33.47)	-2.50 (-24.08, 25.21)	12.30 (-1.43, 27.94)
	0-7 days	25.29 (3.69, 51.39)	26.69 (-1.46, 62.90)	20.17 (-7.58, 56.24)	6.78 (-22.14, 46.43)	25.00 (3.59, 50.83)
	0-15 days	40.39 (7.36, 83.57)	59.14 (8.51, 133.39)	22.28 (-17.08, 80.32)	18.[illegible]6 (-23.64, 84.09)	40.44 (7.36, 83.71)
	0-30 days	41.89 (-1.21, 103.79)	90.32 (3.90, 248.61)	16.65 (-32.60, 101.90)	41.[illegible]1 (-25.37, 168.71)	41.60 (-1.73, 104.04)
	0-60 days	44.33 (-14.72, 144.26)	81.16 (-20.73, 314.01)	20.99 (-61.70, 282.17)	78.97 (-20.38, 302.26)	41.84 (-16.57, 141.13)
	0-90 days	122.73 (4.15, 376.34)	105.16 (-40.77, 610.68)	319.34 (-57.56, 4043.11)	145.[illegible]9 (-15.94, 615.14)	307.07 (54.14, 975.03)
	0-120 days	88.39 (-17.81, 331.78)	14.55 (-70.70, 347.80)	-78.30 (-96.99, 56.42)	67.[illegible]9 (-44.00, 399.20)	39.86 (-38.48, 217.93)
	0-180 days	335.06 (17.71, 1507.95)	537.94 (16.80, 3384.40)	-84.34 (-99.93, 3336.70)	389.[illegible]7 (17.64, 1935.72)	138.49 (-59.37, 1299.84)

Model 1: Adjusted for sex, age, season, etiological examination, comorbidity, treatment type, and average temperature, average wind speed, and average relative humidity at the same lag time.
Model 2: Based on model 1, additionally adjusted for SO_2 at the same lag time.
Model 3: Based on model 1, additionally adjusted for NO_2 at the same lag time.
Model 4: Based on model 1, additionally adjusted for CO at the same lag time.

Model 5: Based on model 1, additionally adjusted for O_3 at the same lag time.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-089290.R1
Article Type:	Original research
Date Submitted by the Author:	03-Mar-2025
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Epidemiology, Infectious diseases

Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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Outdoor particulate matter and risk of drug resistance for workers and farmers with pulmonary tuberculosis: a population-based time series study

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Abstract word count and text word count：282 and 2923

Abstract

Objectives: The detrimental effects of particulate matter (PM) on human health have been widely corroborated. We sought to examine the association of outdoor PM with drug-resistance risk among workers and farmers with pulmonary tuberculosis (PTB).

Design: We performed a population-based time series study using routinely collected meteorological and TB surveillance data.

Setting: We selected Suzhou City, China, as the study area. Data on PTB patients and meteorological factors were extracted from the National Tuberculosis Online Registration System and the China Meteorological Data Sharing Center.

Participants: This study included 7868 PTB patients diagnosed from January 2017 to December 2021 in Suzhou.

Methods: The generalized additive model was utilized to estimate the effects of outdoor PM on the drug resistance risk of TB among workers and farmers who usually work outside. Additionally, we conducted subgroup analyses to evaluate the associations in different populations and seasons.

Results: Despite no significant association between PM with an aerodynamic diameter ≤10 μm (PM_{10}) and drug-resistant risk in the overall analysis, subgroup analysis observed a significant positive association in the winter season. Similarly, PM with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) was significantly associated with drug resistance risk among males at a lag of 0-3 days, people ≤60 years with a lag of 0-7 days, and in the winter season at a lag of 0-7 days, 0-15 days, 0-90 days, or 0-180 days.

Conclusions: Outdoor PM_{10} and $PM_{2.5}$ were positively related to the drug resistance risk of workers and farmers with PTB. Reducing ambient PM pollution may decrease the burden of TB. Further investigations are needed to verify the association via vitro experiments and extensive cohort studies.

Key wrods: tuberculosis; particulate matter; ambient pollutin; drug resistance

STRENGTHS AND LIMITATIONS OF THIS STUDY

STRENGTHS

- This is the first study to evaluate the relationship between PM concentration and drug resistance of TB among the outside working population in eastern China with a large sample size and reliable data.

LIMITATIONS

- PM exposure levels estimated based on the fixed monitoring sites may not accurately represent individual exposure.
- This is an observational study, and the specific substances that produce biological effects in air pollutants are unclear.

Introduction

Despite global efforts, the diagnosis and treatment of tuberculosis persist as formidable challenges.[1] Developing countries disproportionately shoulder this burden as drug-resistant tuberculosis (DR-TB) continues to surge.[2] Antimicrobial resistance presents a significant public health threat, with DR-TB accounting for roughly 29% of all deaths related to antimicrobial-resistant pathogens.[3] Moreover, tackling DR-TB is a critical measure in curbing the spread of tuberculosis due to its lower treatment success rates and worse prognosis than drug-sensitive tuberculosis.[4] The consequences of DR-TB highlight the need for robust public health measures to control its spread.[5] Initial studies proposed that the genesis of DR-TB is attributed to mutations that decrease the pathogen's adaptive capacities, potentially instigated by suboptimal treatment protocols.[6,7] Subsequent research has strengthened the understanding of specific elements, such as a prior history of antituberculosis therapy and infection with human immunodeficiency virus (HIV), in the risk of elevated drug resistance in individuals diagnosed with tuberculosis.[8,9]

The detrimental effects of outdoor air pollutants on human health have been widely corroborated, with particulate matter (PM) emerging as a particularly pernicious and pervasive air pollutant that has attracted significant public concern.[10] The most common particles are inhalable PMs with an aerodynamic diameter ≤10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$), respectively. Studies have shown that PM exposure not only exacerbates the prevalence of non-communicable diseases, such as chronic obstructive pulmonary disease (COPD),[11] but also intensifies the risk of infectious diseases like COVID-19 and tuberculosis.[12,13] A study in Jinan identified an association between increased PM concentrations and the elevated risk of drug resistance among tuberculosis patients[13]. In contrast, a recent study presented conflicting results.[14] The evidence regarding the connection between PM concentration and drug resistance risk of patients with tuberculosis is limited and inconclusive, warranting further research.

Outdoor workers and farmers are more vulnerable to air pollution and have more significant opportunities to contact patients with tuberculosis, placing them at a greater risk of tuberculosis infection. Although this issue is substantial, there is a scarcity of research exploring the effect of PM on drug-resistance risk among outdoor workers with pulmonary tuberculosis (PTB). To address this research gap, we hypothesize that prolonged exposure to elevated concentrations of $PM_{2.5}$ and PM_{10} is positively correlated with an increased risk of developing DR-TB. To test this hypothesis, we conducted a time-series analysis in eastern China by selecting an outdoor working population in eastern China to compare the correlation between air pollutant levels and DR-TB.

Methods

Study population

We selected Suzhou City, China, as the study area. Data on PTB patients and meteorological factors between 2017 and 2021 were extracted from the National

Tuberculosis Online Registration System and the China Meteorological Data Sharing Center, respectively. We collected epidemiological data from each case, including gender, age, ethnicity, current address, occupation, comorbidities, pathogen examination, drug resistance, and treatment classification. Drug susceptibility testing, primarily on isoniazid and rifampicin, was conducted at the Fifth People's Hospital of Suzhou, a designated tuberculosis treatment facility in the city.

PTB diagnosis refers to the national standard of the People's Republic of China (WS-288). We only recruited PTB cases who were workers or farmers working outside and excluded patients with other respiratory-related disorders, and those who experienced changes in their current address during the treatment period to minimize exposure misclassification. We defined DR-TB as mono-resistant to isoniazid, mono-resistant to rifampicin, or multidrug-resistant to at least isoniazid and rifampicin. Individuals employed in manufacturing, construction, mining, and transportation were identified as workers. Meanwhile, those engaged in agriculture, forestry, animal husbandry, and fishery were defined as farmers.

Data on air pollutant concentrations and meteorological factors

From the China Meteorological Data Sharing Center (http://data.cma.cn/), we collected data on meteorological factors in Suzhou City between January 1, 2017, and December 31, 2021, including daily average temperature (°C), average wind speed (m/s), and relative humidity (%). Additionally, daily average concentrations of six environmental pollutants, namely PM_{10}, $PM_{2.5}$, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3), during the same period were retrieved from the National Urban Air Quality Real-Time Reporting Platform (http://106.37.208.233:20035/). The pollutant concentrations were reported in units of μg/m³, except for CO, which was reported in the unit of mg/m³.

Statistical analysis

We used a binomial distributed generalized additive model (GAM) to examine the relationship between PM and drug resistance risk of PTB. GAM, with additive smoothing functions, is a powerful analytical tool capable of analyzing complex environmental health data that may exhibit nonlinear or non-monotonic relationships[15 16]. To control the impacts of potential confounding factors, we adjusted covariates, including sex, age, season, etiological examination, comorbidity, treatment type, average temperature, average wind speed, and average relative humidity. In addition, we utilized a thin plate spline function with a maximum degree of freedom of two to create smooth terms for three meteorological factors to control their potential nonlinear effects.[15]

According to previous research, the influence of PM exposure on health may have delayed effects.[16 17] Thus, we calculated the moving average concentration of PM based on the diagnosis date of PTB patients to estimate their exposure levels. We applied eight different lag days to investigate both short-term and relatively long-term effects of PM exposure on the drug resistance risk of PTB, ranging from 0-3 days to 0-180 days. For example, PM concentration with a lag of 0-3 days represented the mean value of the daily average PM concentration on the day of diagnosis and the previous three days. The strength of the association between PM concentration and drug resistance risk of PTB patients was expressed as percentage changes in drug resistance risk and their corresponding 95% confidence intervals (CIs) for every 10-unit increase in PM concentration. Additionally, we conducted subgroup analyses to evaluate the associations in different populations and seasons.

We performed two sensitivity analyses to assess the robustness of the association. First, we estimated the association at different lag days, as mentioned above. Second, we fitted double-pollutant models, each incorporating adjustment for one of four gas pollutants while maintaining the same parameter settings as the primary model. This approach allowed us to determine if other gas pollutants influenced the relationship between PM concentration and drug resistance risk of patients.

All statistical analyses were carried out using R software version 4.2.0 (https://www.r-project.org/), and model fitting was achieved using the mgcv package. Statistical tests were two-tailed, with a significance level set at 0.05.

Results

Patient characteristics

The characteristics of study subjects are shown in Table 1. Of the 7868 PTB cases, 241 (3.06%) had DR-TB, with a higher drug resistance rate in males (3.35%) than in females (2.20%) (χ^2 =6.533, P =0.011). No significant difference was observed in the drug resistance rate between age or ethnic groups. Sputum smear-positive cases had a higher drug resistance rate (5.92%) than sputum smear-negative cases (0.03%) (χ^2 =229.556, P <0.001). Comorbidities, including HIV or Acquired Immune Deficiency Syndrome (AIDS), diabetes, or pneumoconiosis, did not significantly affect the drug resistance rate. However, those with previous antituberculosis treatment history had an increased risk of drug resistance (11.11% vs. 2.59%, χ^2 =101.913, P <0.001).

Outdoor air pollutants and meteorological factors

The median concentrations and interquartile ranges (IQR) of daily outdoor air pollutants and meteorological factors in Suzhou City from 2017 to 2021 are shown in Table 2. The pollutants under observation, including PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3, exhibited median concentrations of 50.00 μg/m³ (IQR: 36.00-74.00), 30.00 μg/m³ (IQR: 20.00-46.00), 6.00 μg/m³ (IQR: 5.00-9.00), 37.00 μg/m³ (IQR: 27.00-51.00), 0.70 mg/m³ (IQR: 0.50-0.80), and 92.00 μg/m³ (IQR: 65.00-132.00), respectively. Within the same timeframe, the median (IQR) temperature, wind speed, and relative humidity were calculated as 18.40 °C (10.20-25.50), 2.40 m/s (1.90-3.20), and 73.00% (64.00-83.00), respectively. The temporal trends of air pollutant concentrations and meteorological factors are visually represented in Figure 1.

PM_{10} and drug resistance risk

No significant association was observed between PM_{10} concentration and drug resistance risk across the whole case (Figure 2). However, the association was significant during the winter season on all lag days. The magnitude of this relationship augmented as the lag interval expanded, culminating in the most salient effects at lag 0-180 days, as a 10-unit increment in PM_{10} concentration was associated with a 231.24% increased risk of drug resistance (95% CI: 35.79, 708.04).

In double-pollutant models, PM_{10} concentration and drug resistance risk remained significant at a lag of 0-60 days after adjusting for each of the four gaseous pollutants (Table S1).

$PM_{2.5}$ and drug resistance risk

Similarly, the overall analysis found no significant relationship between $PM_{2.5}$ and drug resistance risk (Figure 3). However, the subgroup analyses disclosed that a 10-unit elevation in $PM_{2.5}$ concentration corresponded to a 10.73% (95% CI: 0.49, 22.02) increased drug resistance risk in male cases at lag 0-3 days and a 16.28% (95% CI: 1.20, 33.59) rise in drug resistance risk in cases under 60 years old at lag 0-7 days. A positive correlation emerged between $PM_{2.5}$ concentration and drug resistance risk in winter at lag 0-3 days, lag 0-15 days, lag 0-90 days, and lag 0-180 days, with the most pronounced impact observed at lag 0-180 days. At this time, the risk of drug resistance surged by 335.06% for each 10-unit increase in $PM_{2.5}$ concentration (95% CI: 17.71, 1507.95).

In double-pollutant models, the significant association between $PM_{2.5}$ concentration and drug resistance risk persisted in male cases at a lag of 0-3 days and those under 60 years old at a lag of 0-7 days after adjusting for SO_2. Moreover, $PM_{2.5}$ concentration continued to exhibit a significant positive association with drug resistance risk in winter at lag 0-15 days, lag 0-30 days, and lag 0-180 days after adjusting for SO_2; at lag 0-180 days after adjusting for CO; at lag 0-7 days, lag 0-15 days, and lag 0-90 days after adjusting for O_3 (Table S2).

Discussion

This study examined the relationship between PM concentration and drug resistance risk of workers and farmers with PTB in Suzhou City, a prominent industrial metropolis in eastern China. A positive correlation between PM_{10} concentration and drug resistance risk was observed throughout all lag days in winter. Moreover, $PM_{2.5}$ concentration was found to be positively correlated with drug resistance risk of male cases at lag 0-3 days, cases under 60 years old at lag 0-7 days, and all cases at some lag days during the winter season. To our knowledge, this is the first study to evaluate the relationship between PM concentration and drug resistance of PTB among the outside working populations in China. This study emphasizes the importance of air quality in the prevention and control of infectious diseases. It is necessary to take a comprehensive, cross-sectoral approach to effectively control air pollution and reduce the burden of drug resistance in tuberculosis. We suggest combining air quality control measures with the existing tuberculosis prevention and control programs, such as strengthening screening and protection of high-risk groups in seasons with severe air pollution, to facilitate the early detection and management of drug-resistant tuberculosis.

The existing body of literature exploring the association between PM concentration and drug resistance risk of tuberculosis patients is scarce and inconclusive. A case-control study identified a positive association between PM concentration and drug resistance risk of tuberculosis patients.[13] Specifically, PM_{10} was shown to significantly impact this risk from lag 0-90 days to lag 0-540 days, while $PM_{2.5}$ had a notable effect up to lag 0-540 days. A green environment could mitigate mortality risk of DR-TB patients.[18,19] In contrast, another study suggested a protective effect of $PM_{2.5}$ and PM_{10} against drug resistance risk.[14] In the current study, we selected outdoor workers and farmers as the study subjects and did not uncover a significant association between PM concentration and drug resistance risk in the overall analyses. This disparity might stem from differences in PM concentration and composition characteristics.[13,14] Other factors such as geography, meteorological conditions, economic level, population density, and *Mycobacterium tuberculosis* strains might influence the relationship between PM and drug resistance risk.[20]

Our findings indicated that elevated levels of PM_{10} and $PM_{2.5}$ during winter significantly contributed to the drug resistance risk of workers and farmers with PTB.

This observation aligned with previous studies highlighting increased health risks from winter PM exposure. For example, a time-series study from 202 counties in the United States revealed the strongest correlation between $PM_{2.5}$ concentration and daily hospitalization rates for cardiovascular and respiratory systems during winter.[21] Another study from Wuhan, China, suggested that PM had a more pronounced impact on overall mortality, cardiovascular, stroke, and respiratory system mortality rates in winter[22]. Animal experiments demonstrated that winter exposure to $PM_{2.5}$ caused more severe cardiac toxicity than summer exposure,[23] and wintertime PM exhibited higher endotoxin levels than springtime PM.[24] PM samples collected in Italy during winter produced more acute toxicity in mouse models than summer-collected samples.[25] Seasonality has been recognized as a crucial modifier when evaluating the impact of air pollution on human health. The potential influence of wintertime PM on the drug resistance risk of tuberculosis might be attributed to high concentrations of pollutants, as demonstrated by our time-series graphs. Studies have indicated that increased atmospheric boundary layer stability and reduced vertical mixing tendencies in winter result in pollutant retention and regional accumulation; this may account for the increased risk of resistance observed in winter.[26,27]

Although Suzhou lacks coal heating systems, low wind speeds and temperatures exacerbate ground-level pollutant accumulation.[27] Nonetheless, the rising demand for heating systems may influence this phenomenon through regional transmission and accumulation from northern parts of China.[28] Furthermore, $PM_{2.5}$ has a more significant impact than PM_{10}, consistent with studies on air pollutants related to the onset risk of PTB.[29,30] This observation can be ascribed to smaller particles penetrating deeper into the alveoli and bronchi, resulting in more severe biological toxicity reactions.[31]

Our study uncovered a relationship between $PM_{2.5}$ and drug resistance risk of male PTB patients at a lag of 0-3 days and a similar association among patients under 60 years old at a lag of 0-7 days. However, no association was observed in these two subgroups at other lag days, necessitating cautious interpretation of the results. Thus, further research is required to determine their biological plausibility. The difference in different lag days may be related to individual immunity. For example, individuals with poor immunity may be exposed for a few weeks to increase the risk of developing resistance, while those with better immunity may take longer.[32] Gender differences may stem from various factors, including lifestyle habits (e.g., smoking), social behaviors (e.g., engaging in group activities), and physiological differences, which collectively might render men more susceptible to DR-TB.[33-35] Previous research has indicated that patients with DR-TB tend to be younger than those with drug-sensitive infections. For example, a systematic review reported that the incidence of drug resistance was 2.53 times higher among PTB cases under 65 years old compared to those aged 65 and above.[36] This finding suggested that older individuals might develop DR-TB due to latent infections acquired before the emergence of drug resistance, while a younger age represents a risk factor for recent transmission.[37]

Escalating PM levels could potentially amplify PTB patients' drug resistance risk. The exact machinations driving this phenomenon are yet to be entirely comprehended; however, several contributory factors can be hypothesized. Primarily, the composition of PM extends beyond mere physiochemical elements, encapsulating biological constituents such as microbes and antibiotic-resistant genes. An intriguing study revealed discernible disparities between the microbial consortia and their associated antibiotic-resistant genes present in the air, and those found within terrestrial and marine ecosystems.[38] PM has emerged as a principal vector for disseminating antibiotic-resistant genes within the environment.[39,40] Thus, the air could harbor more resistant strains and antibiotic-resistance genes in locales characterized by elevated PM concentrations. Secondarily, PM can incite oxidative stress and elicit inflammatory responses, which could precipitate structural and functional degradation of alveolar epithelial and endothelial cells.[41,42] Furthermore, PM can infiltrate the systemic circulation, provoking vascular dysregulation and systemic inflammation.[43] Such perturbations may aggravate the clinical status of new tuberculosis patients afflicted with chronic pulmonary diseases.[44] This exacerbation might necessitate a complex and protracted diagnostic and treatment regimen, thereby elevating their propensity to develop drug resistance.[45] Lastly, insights gleaned from a molecular epidemiological investigation underscored that the peril of direct transmission of DR-TB distinctly surpasses resistance acquisition attributable to factors such as the injudicious utilization of antibiotics.[46] This implies that PM, laden with resistant strains and antibiotic-resistant genes, could potentially bolster the aerial propagation of drug-resistant

Mycobacterium tuberculosis.

This study has several limitations. First, we estimated PM exposure relying on stationary monitoring data, which may not accurately reflect individual exposure. Future research should utilize mobile monitoring devices or geographic information systems (GIS) for more precise assessments. Second, we only measured the drug resistance to rifampicin and isoniazid, restricting our analysis of the risk of resistance to other antituberculosis drugs. Expanding the sample size to include a broader range of drug-resistant tuberculosis is essential for elucidating the relationship between PM exposure and resistance mechanisms. Third, besides air pollution, other factors, such as tobacco smoking, alcohol consumption, and socioeconomic status, may also affect the association between PM and drug resistance. Future studies should integrate these variables to provide a comprehensive understanding of the multifactorial influences of PM on drug resistance in PTB patients.

Conclusion

In conclusion, our study demonstrated a positive association between outdoor PM_{10} and $PM_{2.5}$ concentrations and drug-resistant tuberculosis among workers and farmers who usually work outside. Our findings indicate the role of reducing ambient PM levels in alleviating the burden of infectious disease. Further research, including in vitro experiments and extensive cohort studies, is needed to confirm the association and explore the long-term effects of air pollution intervention measures.

Data availability statement

Data are available upon reasonable request. Data are available upon reasonable requests by contacting the corresponding author through the following email address: gsdx_zxl@163.com.

Ethics statements

Patient consent for publication

Not required.

Ethical approval

The present study was approved by the Ethics Committee of Nanjing Medical University. It is a secondary analysis of retrospective, non-identifiable data employing anonymized, pre-existing public health records without direct interaction or intervention with the participants. Given the low-risk nature of this research and the inability to trace the data back to individual subjects, the Ethics Committee granted a waiver for the requirement of informed consent (SZJKJFS2023-001).

Contributors

Xiaolong Zhang: Conceptualization, Methodology, Data Curation, Software, Formal analysis, Writing - Original Draft, Visualization. Zhongqi Li: Conceptualization, Formal analysis, Writing-Review & Editing. Bilin Tao: Formal analysis, Software, Visualization. Ying Fu: Data Curation, Methodology. Caiyan Cui, Feixian Wang ,Yun Li and Yu Wang: Data Curation. Jun Jiang: Conceptualization, Project administration. Jianming Wang: Conceptualization, Resources, Visualization, Writing-Review &

Editing, Project administration, Supervision, Funding acquisition. Xiaolong Zhang is responsible for the overall content as guarantor.

Funding

This study was funded by the National Natural Science Foundation of China (82473693, 81973103), Medical Research Project of Jiangsu Health Commission (ZDB2020013), Nanjing Major Science and Technology Specific Project (2021-11005), and Suzhou Health Youth Backbone Talent "National Tutor System" Training Project (Gngg2022031). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research

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Figure legends

Figure 1. Time-series plots of outdoor air pollutants and meteorological factors in Suzhou City between 2017 and 2021.

Figure 2. Percentage changes in the risk of drug-resistant tuberculosis and their 95% CIs for each 10-unit increase in PM_{10} concentration in Suzhou City between 2017 and 2021.

Figure 3. Percentage changes in the risk of drug-resistant tuberculosis and their 95% CIs for each 10-unit increase in $PM_{2.5}$ concentration in Suzhou City between 2017 and 2021.

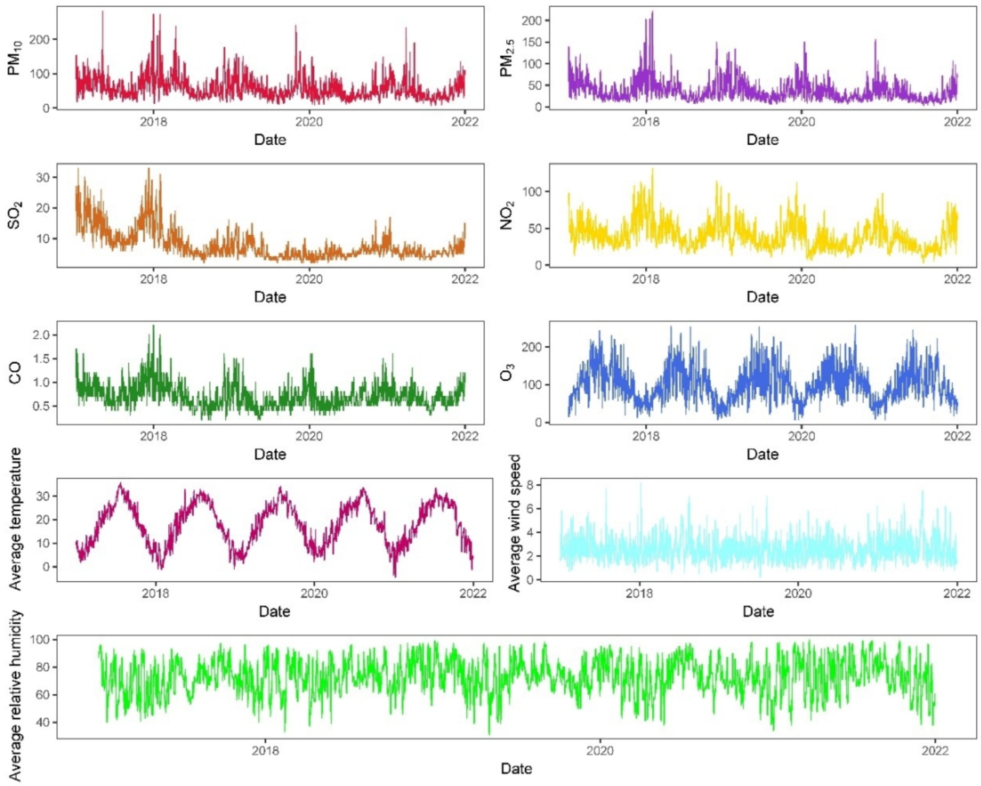
Table 1. Characteristics of study subjects.

Variables	Drug resistance		χ^2	*P*
	Sensitive n (%)	Resistant n (%)		
Sex				
Male	5715 (96.65)	198 (3.35)	6.533	0.011
Female	1912 (97.80)	43 (2.20)		
Age (years)				
<60	5532 (96.93)	175 (3.07)	0.001	0.978
≥60	2095 (96.95)	66 (3.05)		
Ethnic groups				
Han	7531 (96.96)	236 (3.04)	0.668	0.414
Others	96 (95.05)	5 (4.95)		
Sputum smear test				
Positive	3817 (94.08)	240 (5.92)	229.556	<0.001
Negative	3810 (99.97)	1 (0.03)		
Comorbidity*				
Yes	182 (95.79)	8 (4.21)	0.863	0.353
No	7445 (96.97)	233 (3.03)		
Treatment history				
No	7235 (97.41)	192 (2.59)	101.913	<0.001
Yes	392 (88.89)	49 (11.11)		

*: HIV/AIDS, diabetes, or pneumoconiosis.

Table 2. Characteristics of daily average outdoor air pollutant concentrations and meteorological factors in Suzhou City between 2017 and 2021.

Variables	Minimum	Q25	Median	Mean	Q75	Maximum
Outdoor air pollutants						
PM_{10} (μg/m^3)	7.00	36.00	50.00	58.89	74.00	283.00
$PM_{2.5}$ (μg/m^3)	3.00	20.00	30.00	37.15	46.00	222.00
SO_2 (μg/m^3)	2.00	5.00	6.00	7.84	9.00	33.00
NO_2 (μg/m^3)	3.00	27.00	37.00	40.63	51.00	132.00
CO (mg/m^3)	0.20	0.50	0.70	0.70	0.80	2.20
O_3 (μg/m^3)	6.00	65.00	92.00	100.55	132.00	257.00
Meteorological factors						
Average temperature (°C)	-4.50	10.20	18.40	17.94	25.50	35.70
Average wind speed (m/s)	0.20	1.90	2.40	2.61	3.20	8.20
Average relative humidity (%)	31.00	64.00	73.00	72.91	83.00	99.80



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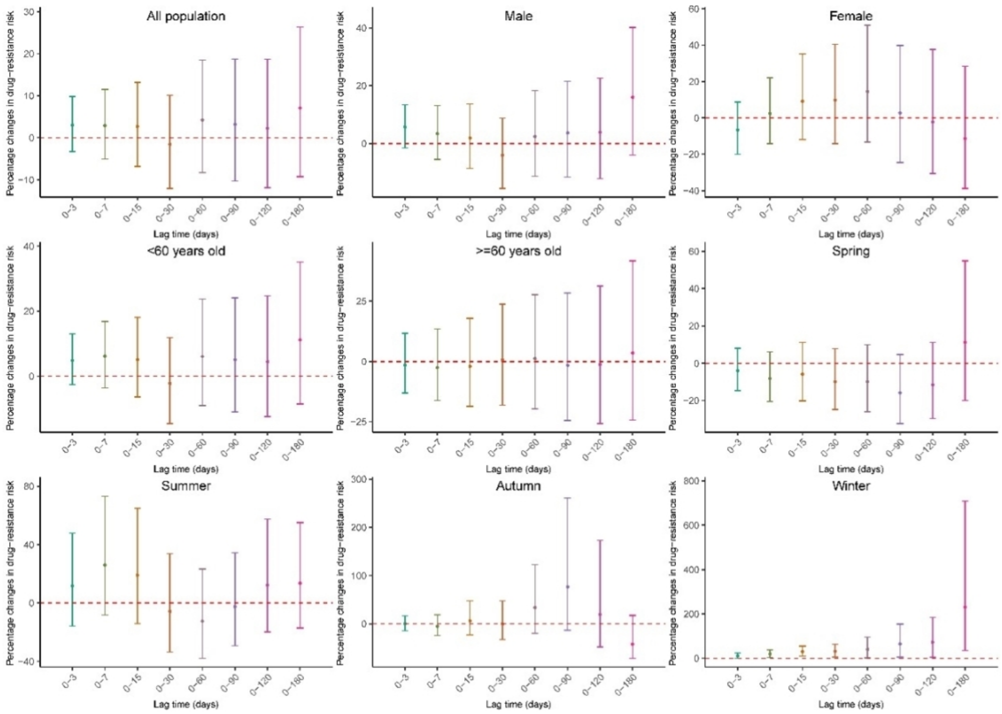

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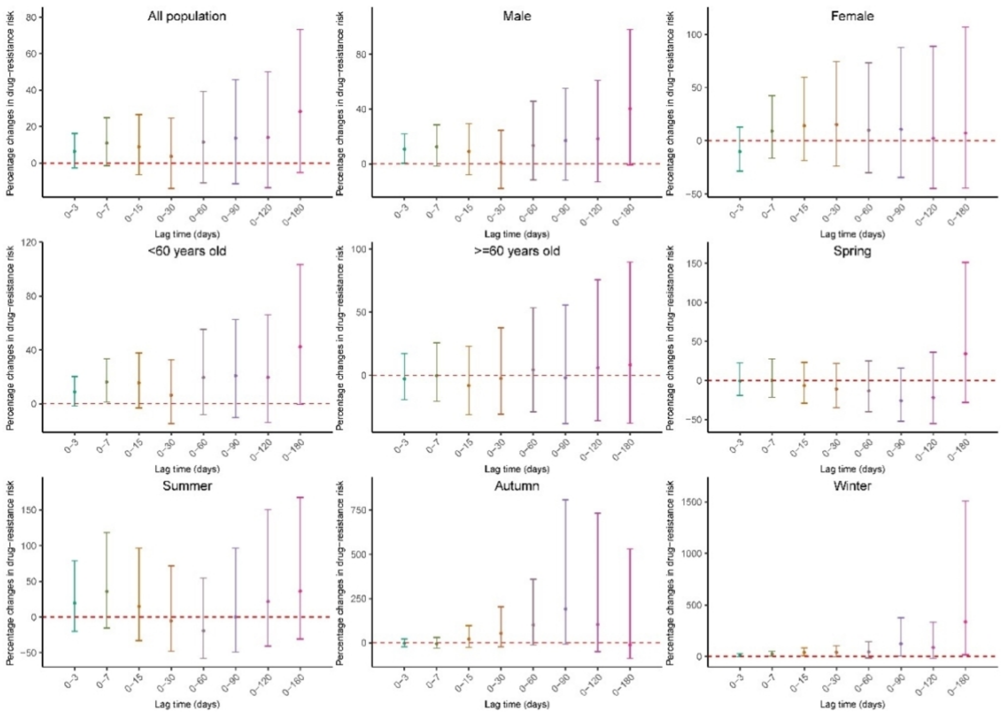

146x103mm (220 x 220 DPI)

Supplementary Tables

Table S1. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in PM_{10} concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
All population	0-3 days	3.02 (-3.34, 9.79)	3.89 (-3.35, 11.67)	1.95 (-7.20, 11.99)	1.87 (-6.26, 10.70)	3.16 (-3.23, 9.96)
	0-7 days	2.89 (-5.07, 11.51)	3.35 (-5.57, 13.12)	-2.47 (-14.10, 10.73)	1.52 (-8.61, 11.66)	2.83 (-5.14, 11.47)
	0-15 days	2.66 (-6.87, 13.17)	4.14 (-6.79, 16.36)	0.77 (-14.50, 18.76)	3.41 (-8.03, 16.26)	2.80 (-6.77, 13.35)
	0-30 days	-1.60 (-12.07, 10.11)	-1.02 (-13.33, 13.03)	-1.74 (-19.52, 19.97)	0.36 (-13.25, 13.99)	-1.52 (-12.03, 10.24)
	0-60 days	4.24 (-8.32, 18.52)	9.58 (-6.39, 28.28)	21.29 (-7.26, 58.63)	12.41 (-4.37, 32.13)	5.98 (-6.97, 20.73)
	0-90 days	3.19 (-10.33, 18.74)	7.69 (-10.73, 29.91)	12.29 (-22.71, 63.15)	9.58 (-7.96, 30.94)	3.40 (-10.21, 19.08)
	0-120 days	2.25 (-11.91, 18.70)	4.36 (-15.27, 28.53)	10.70 (-28.56, 71.52)	9.57 (-9.07, 32.03)	2.09 (-12.14, 18.63)
	0-180 days	7.08 (-9.27, 26.37)	8.38 (-14.35, 37.14)	14.39 (-34.45, 99.60)	17.45 (-4.06, 43.78)	8.62 (-8.12, 28.40)
Male	0-3 days	5.66 (-1.58, 13.42)	6.58 (-1.69, 15.54)	5.32 (-4.96, 16.73)	3.59 (-5.28, 13.95)	5.88 (-1.38, 13.68)
	0-7 days	3.38 (-5.54, 13.15)	3.21 (-6.77, 14.26)	-4.02 (-16.75, 10.64)	1.52 (-9.40, 13.31)	3.36 (-5.61, 13.19)
	0-15 days	1.93 (-8.65, 13.73)	3.23 (-8.81, 16.85)	-3.74 (-20.00, 15.82)	2.57 (-10.33, 16.41)	2.13 (-8.50, 14.00)
	0-30 days	-4.13 (-15.51, 8.79)	-4.20 (-17.45, 11.17)	-12.42 (-30.50, 10.38)	-3.52 (-17.20, 12.42)	-3.86 (-15.32, 9.15)
	0-60 days	2.44 (-11.29, 18.31)	8.68 (-8.77, 29.46)	7.44 (-20.73, 45.61)	10.45 (-7.76, 32.24)	4.57 (-9.71, 21.10)
	0-90 days	3.65 (-11.57, 21.48)	10.10 (-10.47, 35.41)	-1.99 (-35.81, 49.66)	10.48 (-9.24, 34.50)	4.03 (-11.37, 22.10)
	0-120 days	3.82 (-12.06, 22.56)	9.11 (-12.88, 36.64)	3.50 (-36.50, 68.70)	11.88 (-8.98, 37.52)	4.21 (-11.84, 23.18)
	0-180 days	15.99 (-3.98, 40.13)	22.55 (-5.30, 58.60)	13.98 (-38.57, 111.50)	30.12 (3.33, 63.85)	17.26 (-3.19, 42.03)
Female	0-3 days	-6.73 (-19.99, 8.73)	-6.50 (-21.31, 11.09)	-7.00 (-26.58, 17.79)	-6.38 (-23.38, 14.38)	-6.90 (-20.21, 8.61)
	0-7 days	2.31 (-14.19, 21.99)	4.30 (-14.15, 26.72)	8.68 (-17.93, 43.92)	0.40 (-19.82, 25.73)	2.46 (-14.07, 22.17)
	0-15 days	9.10 (-11.93, 35.16)	11.24 (-13.46, 42.98)	28.57 (-11.81, 87.45)	12.88 (-13.90, 48.00)	9.26 (-11.79, 35.34)
	0-30 days	9.76 (-14.18, 40.38)	14.03 (-15.17, 53.29)	48.37 (-3.13, 127.25)	17.18 (-14.47, 60.55)	8.58 (-15.18, 39.00)
	0-60 days	14.44 (-13.26, 50.99)	17.80 (-17.83, 68.88)	90.05 (4.94, 244.18)	23.68 (-13.95, 77.77)	11.85 (-14.95, 47.10)
	0-90 days	2.72 (-24.52, 39.80)	-4.82 (-38.91, 48.29)	85.70 (-19.72, 329.53)	7.78 (-28.17, 61.71)	3.42 (-23.86, 40.46)
	0-120 days	-2.23 (-30.51, 37.57)	-17.93 (-51.04, 37.57)	43.55 (-47.44, 292.02)	0.83 (-34.87, 55.47)	-3.06 (-31.35, 36.90)
	0-180 days	-11.32 (-38.74, 28.37)	-31.17 (-62.16, 25.20)	17.40 (-68.64, 339.42)	-10.00 (-42.80, 41.60)	-10.22 (-38.25, 30.53)
<60 years old	0-3 days	4.91 (-2.58, 12.98)	7.81 (-0.79, 17.16)	4.43 (-6.56, 16.72)	5.10 (-4.65, 15.84)	4.85 (-2.67, 12.94)
	0-7 days	6.13 (-3.62, 16.88)	9.90 (-1.16, 22.21)	2.73 (-11.81, 19.67)	6.90 (-5.06, 20.36)	6.11 (-3.65, 16.87)
	0-15 days	5.14 (-6.39, 18.09)	10.05 (-3.35, 25.30)	5.03 (-13.88, 28.09)	7.92 (-6.53, 22.99)	5.14 (-6.39, 18.10)
	0-30 days	-2.25 (-14.59, 11.88)	2.03 (-12.87, 19.49)	-6.11 (-26.38, 19.73)	1.97 (-13.67, 19.51)	-2.15 (-14.56, 12.07)
	0-60 days	6.09 (-9.06, 23.75)	15.67 (-3.94, 39.28)	24.82 (-9.01, 71.21)	17.39 (-3.03, 42.12)	7.35 (-8.19, 25.53)
	0-90 days	5.06 (-11.07, 24.12)	16.12 (-6.81, 44.70)	16.94 (-24.76, 81.73)	16.09 (-5.62, 42.79)	5.01 (-11.11, 24.05)
	0-120 days	4.49 (-12.44, 24.70)	14.78 (-10.20, 46.71)	35.23 (-19.25, 126.46)	15.71 (-7.03, 44.02)	5.28 (-11.88, 25.77)
	0-180 days	11.15 (-8.57, 35.11)	21.46 (-7.93, 60.24)	32.82 (-30.65, 154.35)	25.49 (-0.90, 58.92)	13.90 (-6.44, 38.66)
≥60 years old	0-3 days	-1.44 (-13.04, 11.71)	-5.28 (-18.14, 9.60)	-3.24 (-19.27, 15.97)	-4.61 (-18.96, 12.28)	-0.93 (-12.60, 12.31)
	0-7 days	-2.49 (-16.21, 13.47)	-9.58 (-24.29, 7.98)	-13.44 (-31.87, 9.98)	-9.51 (-25.62, 10.10)	-2.10 (-16.07, 14.18)
	0-15 days	-2.06 (-18.61, 17.87)	-9.57 (-27.02, 12.04)	-6.76 (-31.15, 26.28)	-3.76 (-23.25, 21.67)	-1.91 (-18.63, 18.26)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
	0-30 days	0.67 (-18.13, 23.80)	-5.76 (-26.34, 20.56)	6.60 (-25.70, 52.93)	-3.19 (-24.98, 24.91)	0.65 (-18.16, 23.79)
	0-60 days	1.26 (-19.71, 27.71)	-5.30 (-29.16, 26.60)	23.35 (-24.80, 102.33)	1.76 (-24.86, 37.79)	2.78 (-18.75, 30.02)
	0-90 days	-1.53 (-24.49, 28.41)	-11.63 (-38.27, 26.50)	-1.69 (-52.18, 102.13)	-3.86 (-31.67, 35.26)	-1.63 (-24.63, 28.39)
	0-120 days	-1.29 (-25.74, 31.21)	-11.16 (-41.01, 33.80)	-34.12 (-71.99, 54.95)	-0.34 (-31.05, 44.06)	-2.43 (-26.45, 29.42)
	0-180 days	3.56 (-24.35, 41.76)	-11.44 (-44.69, 41.79)	-18.98 (-73.51, 147.78)	5.56 (-29.14, 57.25)	1.86 (-25.93, 40.08)
Spring	0-3 days	-3.97 (-14.66, 8.06)	0.74 (-11.52, 14.71)	-0.69 (-14.90, 15.90)	-2.34 (-15.25, 12.54)	-3.14 (-14.19, 9.33)
	0-7 days	-8.12 (-20.49, 6.18)	-2.51 (-17.59, 15.33)	-10.79 (-28.41, 11.18)	-7.83 (-23.46, 10.99)	-6.78 (-19.40, 7.82)
	0-15 days	-5.81 (-20.22, 11.20)	6.59 (-12.57, 29.96)	3.28 (-23.79, 39.96)	-2.33 (-21.82, 22.02)	-5.50 (-20.17, 11.87)
	0-30 days	-9.91 (-24.80, 7.93)	1.11 (-21.31, 29.90)	14.91 (-22.28, 69.90)	-8.40 (-31.65, 22.77)	-15.66 (-31.25, 3.46)
	0-60 days	-9.83 (-26.02, 9.89)	4.75 (-27.62, 51.58)	52.69 (-18.20, 185.01)	17.49 (-32.82, 105.50)	-11.01 (-27.41, 9.09)
	0-90 days	-15.80 (-32.33, 4.79)	-16.91 (-46.23, 28.40)	35.67 (-46.56, 244.43)	-34.70 (-62.68, 14.27)	-18.73 (-35.18, 1.91)
	0-120 days	-11.58 (-29.71, 11.24)	-5.71 (-43.60, 57.62)	19.42 (-57.99, 239.53)	-37.54 (-62.45, 3.88)	-10.86 (-28.98, 11.87)
	0-180 days	11.25 (-20.09, 54.86)	82.40 (-4.98, 250.14)	155.97 (-6.63, 601.71)	73.99 (-1.13, 206.19)	11.02 (-20.10, 54.25)
Summer	0-3 days	11.69 (-15.67, 47.94)	18.64 (-13.87, 63.43)	3.14 (-29.78, 51.49)	14.83 (-17.47, 59.76)	18.64 (-11.31, 58.69)
	0-7 days	26.12 (-8.15, 73.19)	35.16 (-4.65, 91.58)	22.26 (-23.89, 96.40)	32.84 (-7.17, 90.08)	31.57 (-4.27, 80.82)
	0-15 days	19.11 (-13.98, 64.93)	29.02 (-9.98, 84.89)	26.02 (-25.66, 113.61)	27.80 (-10.76, 83.03)	19.45 (-13.05, 64.09)
	0-30 days	-5.73 (-33.66, 33.96)	-5.11 (-37.09, 43.11)	-10.09 (-50.02, 61.73)	1.13 (-33.24, 53.19)	-3.87 (-32.57, 37.04)
	0-60 days	-12.47 (-37.86, 23.30)	15.23 (-28.29, 85.16)	-29.53 (-66.08, 46.38)	10.32 (-33.51, 83.04)	2.39 (-29.95, 49.67)
	0-90 days	-2.45 (-29.24, 34.50)	-6.26 (-36.80, 39.04)	-30.37 (-71.47, 69.89)	13.05 (-29.18, 80.46)	-1.66 (-29.58, 37.32)
	0-120 days	12.37 (-19.90, 57.63)	57.82 (-11.10, 180.17)	32.33 (-49.50, 246.78)	70.57 (-2.46, 198.28)	34.50 (-8.45, 97.61)
	0-180 days	13.50 (-17.02, 55.24)	-26.98 (-54.20, 16.40)	7.98 (-72.67, 326.67)	-12.17 (-52.47, 62.27)	14.25 (-17.88, 58.96)
Autumn	0-3 days	0.01 (-14.36, 16.80)	-1.13 (-16.46, 17.01)	-6.14 (-26.56, 19.96)	-0.71 (-17.51, 19.51)	-0.03 (-14.56, 16.98)
	0-7 days	-5.03 (-23.93, 18.56)	-5.19 (-25.19, 20.17)	-12.51 (-38.90, 25.27)	-7.78 (-28.52, 18.97)	-4.97 (-23.90, 18.68)
	0-15 days	6.50 (-23.01, 47.33)	11.56 (-21.45, 58.44)	11.54 (-36.57, 96.13)	4.78 (-26.44, 49.24)	9.74 (-21.08, 52.59)
	0-30 days	-0.43 (-32.79, 47.52)	-0.43 (-34.18, 50.61)	-22.97 (-63.25, 61.43)	-1.59 (-34.49, 47.85)	8.76 (-30.41, 69.97)
	0-60 days	33.66 (-19.76, 122.63)	27.87 (-26.30, 121.88)	17.30 (-55.07, 206.20)	34.15 (-20.37, 125.98)	12.96 (-40.50, 114.47)
	0-90 days	76.72 (-13.39, 260.59)	164.24 (-3.60, 624.33)	141.00 (-61.60, 1412.34)	94.48 (-12.77, 333.62)	124.11 (-20.43, 531.22)
	0-120 days	19.11 (-48.07, 173.18)	21.29 (-51.53, 203.53)	-62.48 (-93.36, 112.00)	40.84 (-41.93, 241.55)	19.71 (-49.18, 181.97)
	0-180 days	-42.20 (-71.52, 17.33)	-42.66 (-71.91, 17.06)	-89.62 (-97.88, -49.29)	-24.11 (-68.50, 82.86)	-56.28 (-83.71, 17.28)
Winter	0-3 days	11.21 (0.02, 23.65)	10.78 (-3.15, 26.70)	13.19 (-3.58, 32.87)	1.68 (-15.38, 22.18)	11.73 (0.65, 24.04)
	0-7 days	19.69 (3.58, 38.29)	21.57 (0.50, 47.07)	19.68 (-6.04, 52.43)	8.86 (-12.44, 35.34)	20.83 (4.58, 39.60)
	0-15 days	30.51 (9.89, 55.00)	49.97 (15.68, 94.43)	32.70 (-4.53, 84.45)	24.80 (-4.68, 63.41)	31.84 (10.65, 57.10)
	0-30 days	31.42 (5.98, 62.97)	60.58 (14.73, 124.74)	42.45 (-11.87, 130.25)	41.92 (0.58, 100.26)	36.11 (7.37, 72.55)
	0-60 days	40.48 (1.23, 94.94)	134.42 (28.84, 326.52)	248.89 (38.62, 778.15)	86.70 (12.89, 208.77)	40.11 (0.12, 96.09)
	0-90 days	64.36 (6.21, 154.36)	102.85 (-13.92, 378.03)	3388.62 (211.56, 38962.49)	97.99 (-0.58, 294.26)	120.81 (34.55, 262.35)
	0-120 days	72.65 (4.55, 185.12)	84.47 (-23.90, 347.18)	275.06 (-60.78, 3486.92)	84.78 (-6.79, 266.32)	44.14 (-12.93, 138.61)
	0-180 days	231.24 (35.79, 708.04)	529.41 (63.91, 2316.96)	3810.34 (10.50, 138283.73)	303.03 (43.69, 1030.45)	171.49 (-15.60, 773.32)

Model 1: Adjusted for sex, age, season, etiological examination, comorbidity, treatment type, and average temperature, average wind speed, and average relative

humidity at the same lag time.
Model 2: Based on model 1, additionally adjusted for SO_2 at the same lag time.
Model 3: Based on model 1, additionally adjusted for NO_2 at the same lag time.
Model 4: Based on model 1, additionally adjusted for CO at the same lag time.
Model 5: Based on model 1, additionally adjusted for O_3 at the same lag time.

Table S2. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in $PM_{2.5}$ concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
All population	0-3 days	6.41 (-2.62, 16.29)	8.45 (-1.97, 19.97)	6.48 (-5.25, 19.66)	6.[illegible]8 (-5.72, 19.80)	7.41 (-1.93, 17.64)
	0-7 days	10.95 (-1.41, 24.86)	13.25 (-0.63, 29.06)	10.21 (-6.10, 29.35)	11.61 (-3.68, 29.31)	12.13 (-0.46, 26.30)
	0-15 days	8.93 (-6.29, 26.62)	12.69 (-4.88, 33.51)	10.17 (-9.81, 34.58)	12.[illegible]8 (-6.15, 33.85)	9.95 (-5.59, 28.03)
	0-30 days	3.66 (-13.83, 24.70)	7.14 (-13.67, 32.98)	8.86 (-14.48, 38.57)	7.[illegible]0 (-13.21, 32.65)	4.10 (-13.71, 25.58)
	0-60 days	11.53 (-10.70, 39.30)	22.29 (-6.87, 60.58)	33.74 (-1.35, 81.30)	19.98 (-7.05, 54.89)	16.00 (-6.63, 44.12)
	0-90 days	13.66 (-11.31, 45.65)	29.09 (-7.84, 80.81)	40.19 (-7.91, 113.42)	24.13 (-6.65, 65.07)	12.86 (-11.97, 44.68)
	0-120 days	13.97 (-13.42, 50.02)	27.69 (-12.89, 87.19)	63.22 (-4.85, 179.99)	25.47 (-8.03, 71.16)	13.60 (-13.82, 49.75)
	0-180 days	28.23 (-5.16, 73.38)	41.24 (-6.65, 113.69)	101.31 (2.93, 293.73)	45.53 (3.93, 103.80)	28.09 (-5.36, 73.37)
Male	0-3 days	10.73 (0.49, 22.02)	12.92 (1.08, 26.13)	11.39 (-1.78, 26.33)	10.28 (-3.31, 25.79)	11.78 (1.28, 23.37)
	0-7 days	12.51 (-1.48, 28.48)	14.03 (-1.59, 32.13)	9.88 (-8.08, 31.35)	13.13 (-4.04, 33.37)	14.34 (-0.01, 30.75)
	0-15 days	9.18 (-7.84, 29.33)	13.01 (-6.48, 36.56)	8.47 (-13.36, 35.80)	11.82 (-8.17, 36.16)	11.23 (-6.36, 32.14)
	0-30 days	1.18 (-17.79, 24.55)	4.36 (-17.88, 32.64)	2.45 (-22.43, 35.30)	4.[illegible]6 (-17.49, 31.99)	2.92 (-16.56, 26.96)
	0-60 days	13.50 (-11.61, 45.73)	28.25 (-5.45, 73.95)	34.65 (-4.32, 89.49)	23.32 (-7.28, 64.00)	18.60 (-7.23, 51.63)
	0-90 days	17.06 (-11.76, 55.29)	38.13 (-5.21, 101.29)	36.06 (-15.64, 119.43)	28.00 (-7.05, 76.27)	15.59 (-12.93, 53.44)
	0-120 days	18.35 (-12.97, 60.96)	40.97 (-7.51, 114.88)	54.74 (-15.78, 184.33)	31.65 (-6.91, 86.19)	18.84 (-12.79, 61.96)
	0-180 days	40.26 (-0.76, 98.24)	63.09 (2.07, 160.58)	65.88 (-21.56, 250.78)	59.06 (8.46, 133.26)	40.27 (-0.87, 98.47)
Female	0-3 days	-10.26 (-28.62, 12.82)	-10.11 (-30.60, 16.43)	-10.25 (-34.90, 23.72)	-10.16 (-33.67, 21.70)	-10.89 (-29.26, 12.26)
	0-7 days	9.12 (-16.42, 42.46)	13.30 (-15.35, 51.66)	24.50 (-15.75, 83.97)	9.40 (-22.09, 53.60)	8.41 (-17.02, 41.62)
	0-15 days	14.01 (-18.57, 59.61)	16.44 (-20.77, 71.14)	32.33 (-19.59, 117.77)	19.05 (-21.69, 80.99)	11.97 (-19.96, 56.64)
	0-30 days	15.23 (-23.87, 74.41)	22.08 (-26.94, 103.99)	39.30 (-19.43, 140.86)	23.48 (-25.78, 105.45)	9.90 (-27.96, 67.66)
	0-60 days	10.04 (-30.08, 73.18)	4.78 (-42.78, 91.85)	27.75 (-34.32, 148.47)	13.38 (-35.67, 99.82)	5.79 (-32.96, 66.92)
	0-90 days	10.83 (-34.53, 87.63)	2.91 (-52.42, 122.56)	65.29 (-31.44, 298.51)	20.[illegible]2 (-36.53, 128.84)	11.07 (-34.59, 88.61)
	0-120 days	2.13 (-44.74, 88.76)	-18.44 (-67.67, 105.76)	72.41 (-48.12, 472.97)	8.1[illegible] (-46.92, 120.46)	0.58 (-45.65, 86.13)
	0-180 days	7.20 (-44.41, 106.73)	4.07 (-60.08, 171.28)	436.86 (2.43, 2713.84)	18.[illegible]8 (-43.55, 150.36)	8.98 (-43.72, 111.01)
<60 years old	0-3 days	8.84 (-1.58, 20.37)	13.34 (1.26, 26.87)	9.17 (-4.48, 24.78)	10.89 (-3.19, 27.01)	8.80 (-1.77, 20.52)
	0-7 days	16.28 (1.20, 33.59)	23.14 (5.85, 43.25)	17.40 (-2.72, 41.69)	21.08 (2.08, 43.63)	16.98 (1.67, 34.59)
	0-15 days	15.56 (-3.22, 37.98)	24.94 (2.76, 51.92)	20.30 (-5.07, 52.47)	21.13 (-1.27, 48.61)	15.89 (-3.08, 38.57)
	0-30 days	6.43 (-14.66, 32.73)	17.03 (-9.20, 50.84)	13.45 (-15.15, 51.69)	13.[illegible]7 (-11.33, 46.23)	7.36 (-14.22, 34.39)
	0-60 days	19.52 (-8.00, 55.26)	40.59 (2.23, 93.34)	39.89 (-2.94, 101.62)	33.60 (-0.90, 80.11)	21.40 (-6.72, 57.99)
	0-90 days	20.82 (-10.23, 62.62)	54.81 (3.47, 131.62)	59.26 (-3.13, 161.81)	37.[illegible]9 (-1.58, 93.48)	21.22 (-9.99, 63.25)
	0-120 days	19.57 (-13.98, 66.20)	52.89 (-3.19, 141.46)	99.29 (3.65, 283.19)	35.[illegible]6 (-6.12, 96.02)	22.06 (-12.42, 70.13)
	0-180 days	42.34 (-0.39, 103.40)	79.60 (10.12, 192.92)	171.59 (22.57, 501.79)	63.[illegible]1 (10.33, 142.90)	43.23 (-0.06, 105.28)
≥60 years old	0-3 days	-2.74 (-19.31, 17.23)	-8.63 (-26.85, 14.11)	-5.01 (-25.31, 20.80)	-8.[illegible]8 (-28.62, 18.10)	-0.62 (-17.74, 20.08)
	0-7 days	-0.19 (-20.72, 25.65)	-9.64 (-31.22, 18.70)	-8.85 (-33.21, 24.39)	-9.[illegible]1 (-32.88, 23.07)	4.11 (-17.77, 31.81)
	0-15 days	-8.15 (-31.36, 22.92)	-21.29 (-44.61, 11.84)	-14.10 (-41.41, 25.93)	-12.26 (-38.53, 25.24)	-6.02 (-30.10, 26.35)
	0-30 days	-2.51 (-30.91, 37.56)	-15.71 (-45.01, 29.21)	-1.26 (-36.24, 52.91)	-9.[illegible]3 (-39.69, 36.61)	-2.70 (-31.30, 37.81)
	0-60 days	4.36 (-29.02, 53.44)	-7.06 (-44.34, 55.20)	23.09 (-28.78, 112.74)	5.[illegible] (-34.51, 69.63)	7.40 (-26.67, 57.29)
	0-90 days	-2.01 (-38.27, 55.57)	-22.04 (-59.23, 49.06)	0.43 (-56.00, 129.21)	-3.[illegible]4 (-44.06, 65.99)	0.16 (-36.01, 56.78)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
	0-120 days	5.96 (-36.09, 75.68)	-5.62 (-55.37, 99.59)	1.16 (-62.68, 174.17)	10.74 (-38.88, 100.65)	6.70 (-35.08, 75.37)
	0-180 days	8.34 (-38.13, 89.72)	-16.17 (-63.31, 91.54)	-3.12 (-73.43, 253.31)	11.[illegible] (-41.98, 112.78)	8.41 (-37.92, 89.32)
Spring	0-3 days	-0.43 (-19.17, 22.66)	9.52 (-12.95, 37.79)	7.80 (-16.04, 38.40)	5.[illegible]8 (-18.12, 34.86)	3.21 (-18.14, 30.13)
	0-7 days	0.15 (-21.49, 27.75)	15.32 (-13.03, 52.90)	6.91 (-21.57, 45.75)	[illegible] (-20.27, 48.26)	9.29 (-16.91, 43.75)
	0-15 days	-6.34 (-28.91, 23.40)	18.34 (-14.71, 64.20)	13.86 (-24.67, 72.10)	[illegible] (-28.77, 47.13)	-5.34 (-29.34, 26.81)
	0-30 days	-10.73 (-34.78, 22.18)	14.32 (-25.88, 76.33)	26.89 (-21.86, 106.04)	[illegible] (-35.46, 50.50)	-25.93 (-48.95, 7.47)
	0-60 days	-13.29 (-39.94, 25.18)	34.81 (-36.16, 184.65)	43.61 (-28.91, 190.10)	[illegible] (-39.33, 105.04)	-19.07 (-47.14, 23.92)
	0-90 days	-25.64 (-52.41, 16.20)	-18.11 (-83.47, 305.76)	14.43 (-52.85, 177.70)	-29.58 (-68.23, 56.08)	-45.63 (-67.52, -9.01)
	0-120 days	-21.67 (-55.02, 36.38)	95.93 (-74.76, 1421.17)	69.48 (-49.61, 469.94)	[illegible]8.84 (-82.14, 46.56)	-23.57 (-56.43, 34.05)
	0-180 days	34.39 (-28.11, 151.23)	141.37 (-8.21, 534.66)	163.90 (-14.57, 715.14)	[illegible] (-2.10, 467.17)	19.03 (-38.83, 131.61)
Summer	0-3 days	19.61 (-20.00, 78.83)	27.39 (-17.91, 97.71)	10.78 (-31.04, 77.98)	[illegible] (-22.05, 106.10)	38.00 (-10.54, 112.87)
	0-7 days	35.97 (-15.33, 118.36)	43.39 (-13.14, 136.70)	23.82 (-31.05, 122.34)	[illegible] (-14.27, 162.71)	54.02 (-5.70, 151.56)
	0-15 days	14.87 (-32.96, 96.82)	19.54 (-32.29, 111.06)	5.43 (-47.99, 113.73)	[illegible] (-29.67, 144.56)	27.58 (-25.97, 119.88)
	0-30 days	-5.28 (-47.79, 71.85)	-3.39 (-48.76, 82.14)	-4.36 (-57.47, 115.04)	[illegible] (-46.20, 116.64)	-1.22 (-46.25, 81.56)
	0-60 days	-19.21 (-57.74, 54.48)	7.48 (-48.04, 122.35)	-24.55 (-72.16, 104.49)	[illegible] (-51.77, 125.88)	-0.97 (-50.52, 98.20)
	0-90 days	0.15 (-49.00, 96.64)	-2.98 (-53.49, 102.38)	-17.26 (-80.07, 243.47)	[illegible] (-46.79, 153.50)	0.98 (-48.77, 99.03)
	0-120 days	21.65 (-40.85, 150.21)	47.32 (-40.95, 267.54)	25.59 (-74.96, 529.99)	41.[illegible] (-37.13, 218.01)	59.56 (-26.32, 245.54)
	0-180 days	36.13 (-30.70, 167.42)	-23.97 (-79.46, 181.45)	64.64 (-78.83, 1180.42)	-1.04 (-66.55, 192.75)	38.33 (-31.72, 180.24)
Autumn	0-3 days	-2.96 (-22.65, 21.76)	-4.56 (-25.17, 21.73)	-13.09 (-37.73, 21.29)	-5.[illegible]4 (-28.09, 24.59)	-3.32 (-23.79, 22.64)
	0-7 days	-4.54 (-29.95, 30.11)	-4.35 (-30.52, 31.69)	-9.72 (-42.76, 42.40)	-7.[illegible]7 (-35.10, 31.65)	-4.18 (-30.14, 31.41)
	0-15 days	20.70 (-26.12, 97.21)	25.42 (-24.08, 107.19)	34.63 (-32.59, 168.89)	19.[illegible]4 (-29.82, 103.26)	18.87 (-27.36, 94.52)
	0-30 days	53.45 (-22.46, 203.68)	57.14 (-22.00, 216.59)	95.52 (-29.40, 441.48)	51.[illegible]3 (-24.92, 205.45)	62.34 (-19.95, 229.20)
	0-60 days	100.47 (-12.31, 358.31)	97.05 (-21.63, 395.49)	161.05 (-36.72, 976.90)	113.[illegible]1 (-12.31, 421.85)	72.09 (-34.92, 355.02)
	0-90 days	191.09 (-6.67, 807.96)	715.97 (41.58, 4602.55)	604.03 (-50.03, 9819.71)	295.29 (1.26, 1443.03)	326.51 (-11.66, 1959.17)
	0-120 days	103.34 (-50.34, 732.58)	132.47 (-52.28, 1032.58)	20.48 (-88.06, 1115.85)	211.[illegible]8 (-34.81, 1393.11)	101.34 (-51.02, 727.62)
	0-180 days	-11.86 (-87.69, 531.11)	-15.79 (-87.99, 490.57)	-73.47 (-98.60, 401.41)	-9.[illegible]0 (-90.11, 726.57)	-23.90 (-91.96, 620.34)
Winter	0-3 days	13.03 (-0.83, 28.82)	11.89 (-5.11, 31.95)	12.24 (-5.61, 33.47)	-2.50 (-24.08, 25.21)	12.30 (-1.43, 27.94)
	0-7 days	25.29 (3.69, 51.39)	26.69 (-1.46, 62.90)	20.17 (-7.58, 56.24)	6.[illegible]8 (-22.14, 46.43)	25.00 (3.59, 50.83)
	0-15 days	40.39 (7.36, 83.57)	59.14 (8.51, 133.39)	22.28 (-17.08, 80.32)	18.[illegible]6 (-23.64, 84.09)	40.44 (7.36, 83.71)
	0-30 days	41.89 (-1.21, 103.79)	90.32 (3.90, 248.61)	16.65 (-32.60, 101.90)	41.[illegible]1 (-25.37, 168.71)	41.60 (-1.73, 104.04)
	0-60 days	44.33 (-14.72, 144.26)	81.16 (-20.73, 314.01)	20.99 (-61.70, 282.17)	78.[illegible]7 (-20.38, 302.26)	41.84 (-16.57, 141.13)
	0-90 days	122.73 (4.15, 376.34)	105.16 (-40.77, 610.68)	319.34 (-57.56, 4043.11)	145.[illegible]9 (-15.94, 615.14)	307.07 (54.14, 975.03)
	0-120 days	88.39 (-17.81, 331.78)	14.55 (-70.70, 347.80)	-78.30 (-96.99, 56.42)	67.[illegible] (-44.00, 399.20)	39.86 (-38.48, 217.93)
	0-180 days	335.06 (17.71, 1507.95)	537.94 (16.80, 3384.40)	-84.34 (-99.93, 3336.70)	389.[illegible]7 (17.64, 1935.72)	138.49 (-59.37, 1299.84)

Model 1: Adjusted for sex, age, season, etiological examination, comorbidity, treatment type, and average temperature, average wind speed, and average relative humidity at the same lag time.

Model 2: Based on model 1, additionally adjusted for SO_2 at the same lag time.

Model 3: Based on model 1, additionally adjusted for NO_2 at the same lag time.

Model 4: Based on model 1, additionally adjusted for CO at the same lag time.

Model 5: Based on model 1, additionally adjusted for O_3 at the same lag time.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-089290.R2
Article Type:	Original research
Date Submitted by the Author:	12-Mar-2025
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Epidemiology, Infectious diseases

Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

Outdoor particulate matter and risk of drug resistance for workers and farmers with pulmonary tuberculosis: a population-based time series study in Suzhou, China

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Abstract word count and text word count：278 and 2947

Abstract

Objectives: The detrimental effects of particulate matter (PM) on human health have been widely corroborated. We aimed to examine the association between outdoor PM and the drug-resistance risk among workers and farmers with pulmonary tuberculosis (PTB).

Design: We performed a population-based time series study using routinely collected meteorological and TB surveillance data.

Setting: We selected Suzhou City, China, as the study area. Data on PTB patients and meteorological factors were extracted from the National Tuberculosis Online Registration System and the China Meteorological Data Sharing Center.

Participants: This study included 7868 PTB patients diagnosed from January 2017 to December 2021 in Suzhou.

Methods: The generalized additive model was utilized to estimate the effects of outdoor PM on the drug resistance risk of TB among workers and farmers who typically work outdoors. Moreover, subgroup analyses were carried out to evaluate the associations in different populations and seasons.

Results: Although there was no significant association between PM with an aerodynamic diameter ≤10 μm (PM_{10}) and drug-resistant risk in the overall analysis, subgroup analysis revealed a significant positive association in the winter season. Similarly, PM with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) was significantly associated with drug resistance risk among males with a lag of 0-3 days, people ≤60 years with a lag of 0-7 days, and in the winter season with a lag of 0-7 days, 0-15 days, 0-90 days, or 0-180 days.

Conclusions: Outdoor PM_{10} and $PM_{2.5}$ were positively related to the drug resistance risk of workers and farmers with PTB. Reducing ambient PM pollution might reduce the burden of TB. Further research is required to verify the association through in vitro experiments and extensive cohort studies.

Key words: tuberculosis; particulate matter; ambient pollutin; drug resistance

STRENGTHS AND LIMITATIONS OF THIS STUDY

STRENGTHS

- This study utilized a generalized additive model to evaluate the relationship between particulate matter concentration and the drug resistance risk of pulmonary tuberculosis among the outdoor working population.
- This approach enabled the analysis of complex environmental health data that might present nonlinear or non-monotonic relationships.

LIMITATIONS

- Particulate matter exposure levels estimated based on the fixed monitoring sites may not precisely reflect individual exposure.
- As an observational study, the specific substances within air pollutants that generate biological effects remain unclear.

Introduction

Despite global efforts, the diagnosis and treatment of tuberculosis persist as formidable challenges.[1] Developing countries disproportionately shoulder this burden as drug-resistant tuberculosis (DR-TB) continues to surge.[2] Antimicrobial resistance presents a significant public health threat, with DR-TB accounting for roughly 29% of all deaths related to antimicrobial-resistant pathogens.[3] Moreover, tackling DR-TB is a critical measure in curbing the spread of tuberculosis due to its lower treatment success rates and worse prognosis than drug-sensitive tuberculosis.[4] The consequences of DR-TB highlight the need for robust public health measures to control its spread.[5] Initial studies proposed that the genesis of DR-TB is attributed to mutations that decrease the pathogen's adaptive capacities, potentially instigated by suboptimal treatment protocols.[6,7] Subsequent research has strengthened the understanding of specific elements, such as a prior history of antituberculosis therapy and infection with human immunodeficiency virus (HIV), in the risk of elevated drug resistance in individuals diagnosed with tuberculosis.[8,9]

The detrimental effects of outdoor air pollutants on human health have been widely corroborated, with particulate matter (PM) emerging as a particularly pernicious and pervasive air pollutant that has attracted significant public concern.[10] The most common particles are inhalable PMs with an aerodynamic diameter ≤10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$), respectively. Studies have shown that PM exposure not only exacerbates the prevalence of non-communicable diseases, such as chronic obstructive pulmonary disease (COPD),[11] but also intensifies the risk of infectious diseases like COVID-19 and tuberculosis.[12,13] A study in Jinan identified an association between increased PM concentrations and the elevated risk of drug resistance among tuberculosis patients[13]. However, a recent study presented conflicting results.[14] The evidence regarding the connection between PM concentration and drug resistance risk of patients with tuberculosis is limited and inconclusive, warranting further research.

Outdoor workers and farmers are more vulnerable to air pollution and have more significant opportunities to contact patients with tuberculosis, placing them at a greater risk of tuberculosis infection. Although this issue is substantial, there is a scarcity of research exploring the effect of PM on drug-resistance risk among outdoor workers with pulmonary tuberculosis (PTB). To address this research gap, we hypothesize that prolonged exposure to elevated concentrations of $PM_{2.5}$ and PM_{10} is positively correlated with an increased risk of developing DR-TB. To test this hypothesis, we conducted a time-series analysis in eastern China by selecting an outdoor working population in eastern China to compare the correlation between air pollutant levels and DR-TB.

Methods

Study population

We selected Suzhou City, China, as the study area. Data on PTB patients and meteorological factors between 2017 and 2021 were extracted from the National

Tuberculosis Online Registration System and the China Meteorological Data Sharing Center, respectively. We collected epidemiological data from each case, including gender, age, ethnicity, current address, occupation, comorbidities, pathogen examination, drug resistance, and treatment classification. Drug susceptibility testing, primarily on isoniazid and rifampicin, was conducted at the Fifth People's Hospital of Suzhou, a designated tuberculosis treatment facility in the city.

PTB diagnosis refers to the national standard of the People's Republic of China (WS-288). We only recruited PTB cases from workers or farmers working outside and excluded patients with other respiratory-related disorders and those who experienced changes in their current address during the treatment period to minimize exposure misclassification. We defined DR-TB as mono-resistant to isoniazid, mono-resistant to rifampicin, or multidrug-resistant to at least isoniazid and rifampicin. Individuals employed in manufacturing, construction, mining, and transportation were identified as workers. Meanwhile, those engaged in agriculture, forestry, animal husbandry, and fishery were defined as farmers.

Data on air pollutant concentrations and meteorological factors

From the China Meteorological Data Sharing Center (http://data.cma.cn/), we collected data on meteorological factors in Suzhou City between January 1, 2017, and December 31, 2021, including daily average temperature (℃), average wind speed (m/s), and relative humidity (%). Additionally, daily average concentrations of six environmental pollutants, namely PM_{10}, $PM_{2.5}$, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3), during the same period were retrieved from the National Urban Air Quality Real-Time Reporting Platform (http://106.37.208.233:20035/). The pollutant concentrations were reported in units of μg/m³, except for CO, which was reported in the unit of mg/m³.

Statistical analysis

We used a binomial distributed generalized additive model (GAM) to examine the relationship between PM and drug resistance risk of PTB. GAM, with additive smoothing functions, is a powerful analytical tool capable of analyzing complex environmental health data that may exhibit nonlinear or non-monotonic relationships[15 16]. To control the impacts of potential confounding factors, we adjusted covariates, including sex, age, season, etiological examination, comorbidity, treatment type, average temperature, average wind speed, and average relative humidity. In addition, we utilized a thin plate spline function with a maximum degree of freedom of two to create smooth terms for three meteorological factors to control their potential nonlinear effects.[15]

According to previous research, the influence of PM exposure on health may have delayed effects.[16 17] Thus, we calculated the moving average concentration of PM based on the diagnosis date of PTB patients to estimate their exposure levels. We applied eight different lag days to investigate both short-term and relatively long-term effects of PM exposure on the drug resistance risk of PTB, ranging from 0-3 days to 0-180 days. For example, PM concentration with a lag of 0-3 days represented the mean value of the daily average PM concentration on the day of diagnosis and the previous three days. The strength of the association between PM concentration and drug resistance risk of PTB patients was expressed as percentage changes in drug resistance risk and their corresponding 95% confidence intervals (CIs) for every 10-unit increase in PM concentration. Additionally, we conducted subgroup analyses to evaluate the associations in different populations and seasons.

We performed two sensitivity analyses to assess the robustness of the association. First, we estimated the association at different lag days, as mentioned above. Second, we fitted double-pollutant models, each incorporating adjustment for one of four gas pollutants while maintaining the same parameter settings as the primary model. This approach allowed us to determine if other gas pollutants influenced the relationship between PM concentration and drug resistance risk of patients.

All statistical analyses were carried out using R software version 4.2.0 (https://www.r-project.org/), and model fitting was achieved using the mgcv package. Statistical tests were two-tailed, with a significance level set at 0.05.

Results

Patient characteristics

The characteristics of study subjects are shown in Table 1. Of the 7868 PTB cases, 241 (3.06%) had DR-TB, with a higher drug resistance rate in males (3.35%) than in females (2.20%) (χ^2 =6.533, P =0.011). No significant difference was observed in the drug resistance rate between age or ethnic groups. Sputum smear-positive cases had a higher drug resistance rate (5.92%) than sputum smear-negative cases (0.03%) (χ^2 =229.556, P <0.001). Comorbidities, including HIV or Acquired Immune Deficiency Syndrome (AIDS), diabetes, or pneumoconiosis, did not significantly affect the drug resistance rate. However, those with previous antituberculosis treatment history had an increased risk of drug resistance (11.11% vs. 2.59%, χ^2 =101.913, P <0.001).

Outdoor air pollutants and meteorological factors

The median concentrations and interquartile ranges (IQR) of daily outdoor air pollutants and meteorological factors in Suzhou City from 2017 to 2021 are shown in Table 2. The pollutants under observation, including PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3, exhibited median concentrations of 50.00 μg/m³ (IQR: 36.00-74.00), 30.00 μg/m³ (IQR: 20.00-46.00), 6.00 μg/m³ (IQR: 5.00-9.00), 37.00 μg/m³ (IQR: 27.00-51.00), 0.70 mg/m³ (IQR: 0.50-0.80), and 92.00 μg/m³ (IQR: 65.00-132.00), respectively. Within the same timeframe, the median (IQR) temperature, wind speed, and relative humidity were calculated as 18.40 ℃ (10.20-25.50), 2.40 m/s (1.90-3.20), and 73.00% (64.00-83.00), respectively. The temporal trends of air pollutant concentrations and meteorological factors are visually represented in Figure 1.

PM_{10} and drug resistance risk

No significant association was observed between PM_{10} concentration and drug resistance risk across the whole case (Figure 2). However, the association was significant during the winter season on all lag days. The magnitude of this relationship augmented as the lag interval expanded, culminating in the most salient effects at lag 0-180 days, as a 10-unit increment in PM_{10} concentration was associated with a 231.24% increased risk of drug resistance (95% CI: 35.79, 708.04).

In double-pollutant models, PM_{10} concentration and drug resistance risk remained significant at a lag of 0-60 days after adjusting for each of the four gaseous pollutants (Table S1).

$PM_{2.5}$ and drug resistance risk

Similarly, the overall analysis found no significant relationship between $PM_{2.5}$ and drug resistance risk (Figure 3). However, the subgroup analyses disclosed that a 10-unit elevation in $PM_{2.5}$ concentration corresponded to a 10.73% (95% CI: 0.49, 22.02) increased drug resistance risk in male cases at lag 0-3 days and a 16.28% (95% CI: 1.20, 33.59) rise in drug resistance risk in cases under 60 years old at lag 0-7 days. A positive correlation emerged between $PM_{2.5}$ concentration and drug resistance risk in winter at lag 0-3 days, lag 0-15 days, lag 0-90 days, and lag 0-180 days, with the most pronounced impact observed at lag 0-180 days. At this time, the risk of drug resistance surged by 335.06% for each 10-unit increase in $PM_{2.5}$ concentration (95% CI: 17.71, 1507.95).

In double-pollutant models, the significant association between $PM_{2.5}$ concentration and drug resistance risk persisted in male cases at a lag of 0-3 days and those under 60 years old at a lag of 0-7 days after adjusting for SO_2. Moreover, $PM_{2.5}$ concentration continued to exhibit a significant positive association with drug resistance risk in winter at lag 0-15 days, lag 0-30 days, and lag 0-180 days after adjusting for SO_2; at lag 0-180 days after adjusting for CO; at lag 0-7 days, lag 0-15 days, and lag 0-90 days after adjusting for O_3 (Table S2).

Discussion

This study examined the relationship between PM concentration and drug resistance risk of workers and farmers with PTB in Suzhou City, a prominent industrial metropolis in eastern China. A positive correlation between PM_{10} concentration and drug resistance risk was observed throughout all lag days in winter. Moreover, $PM_{2.5}$ concentration was found to be positively correlated with drug resistance risk of male cases at lag 0-3 days, cases under 60 years old at lag 0-7 days, and all cases at some lag days during the winter season. To our knowledge, this is the first study to evaluate the relationship between PM concentration and drug resistance of PTB among the outside working populations in China. This study emphasizes the importance of air quality in the prevention and control of infectious diseases. It is necessary to take a comprehensive, cross-sectoral approach to effectively control air pollution and reduce the burden of drug resistance in tuberculosis. We suggest combining air quality control measures with the existing tuberculosis prevention and control programs, such as strengthening screening and protection of high-risk groups in seasons with severe air pollution, to facilitate the early detection and management of drug-resistant tuberculosis.

The existing body of literature exploring the association between PM concentration and drug resistance risk of tuberculosis patients is scarce and inconclusive. A case-control study identified a positive association between PM concentration and drug resistance risk of tuberculosis patients.[13] Specifically, PM_{10} was shown to significantly impact this risk from lag 0-90 days to lag 0-540 days, while $PM_{2.5}$ had a notable effect up to lag 0-540 days. A green environment could mitigate the mortality risk of DR-TB patients.[18,19] In contrast, another study suggested a protective effect of $PM_{2.5}$ and PM_{10} against drug resistance risk.[14] In the current study, we selected outdoor workers and farmers as the study subjects and did not uncover a significant association between PM concentration and drug resistance risk in the overall analyses. This disparity might stem from differences in PM concentration and composition characteristics.[13,14] Other factors such as geography, meteorological conditions, economic level, population density, and *Mycobacterium tuberculosis* strains might influence the relationship between PM and drug resistance risk.[20]

Our findings indicated that elevated levels of PM_{10} and $PM_{2.5}$ during winter significantly contributed to the drug resistance risk of workers and farmers with PTB.

276 This observation aligned with previous studies highlighting increased health risks from winter PM exposure. For example, a time-series study from 202 counties in the United States revealed the strongest correlation between $PM_{2.5}$ concentration and daily hospitalization rates for cardiovascular and respiratory systems during winter.[21] Another study from Wuhan, China, suggested that PM had a more pronounced impact on overall mortality, cardiovascular, stroke, and respiratory system mortality rates in winter[22]. Animal experiments demonstrated that winter exposure to $PM_{2.5}$ caused more severe cardiac toxicity than summer exposure,[23] and wintertime PM exhibited higher endotoxin levels than springtime PM.[24] PM samples collected in Italy during winter produced more acute toxicity in mouse models than summer-collected samples.[25] Seasonality has been recognized as a crucial modifier when evaluating the impact of air pollution on human health. The potential influence of wintertime PM on the drug resistance risk of tuberculosis might be attributed to high concentrations of pollutants, as demonstrated by our time-series graphs. Studies have indicated that increased atmospheric boundary layer stability and reduced vertical mixing tendencies in winter result in pollutant retention and regional accumulation; this may account for the increased risk of resistance observed in winter.[26,27]

Although Suzhou lacks coal heating systems, low wind speeds and temperatures exacerbate ground-level pollutant accumulation.[27] Nonetheless, the rising demand for heating systems may influence this phenomenon through regional transmission and accumulation from northern parts of China.[28] Furthermore, $PM_{2.5}$ has a more significant impact than PM_{10}, consistent with studies on air pollutants related to the onset risk of PTB.[29,30] This observation can be ascribed to smaller particles penetrating deeper into the alveoli and bronchi, resulting in more severe biological toxicity reactions.[31]

Our study uncovered a relationship between $PM_{2.5}$ and drug resistance risk of male PTB patients at a lag of 0-3 days and a similar association among patients under 60 years old at a lag of 0-7 days. However, no association was observed in these two subgroups at other lag days, necessitating cautious interpretation of the results. Thus, further research is required to determine their biological plausibility. The difference in different lag days may be related to individual immunity. For example, individuals with poor immunity may be exposed for a few weeks to increase the risk of developing resistance, while those with better immunity may take longer.[32] Gender differences may stem from various factors, including lifestyle habits (e.g., smoking), social behaviors (e.g., engaging in group activities), and physiological differences, which collectively might render men more susceptible to DR-TB.[33-35] Previous research has indicated that patients with DR-TB tend to be younger than those with drug-sensitive infections. For example, a systematic review reported that the incidence of drug resistance was 2.53 times higher among PTB cases under 65 years old compared to those aged 65 and above.[36] This finding suggested that older individuals might develop DR-TB due to latent infections acquired before the emergence of drug resistance, while a younger age represents a risk factor for recent transmission.[37]

Escalating PM levels could potentially amplify PTB patients' drug resistance risk. The exact machinations driving this phenomenon are yet to be entirely comprehended; however, several contributory factors can be hypothesized. Primarily, the composition of PM extends beyond mere physiochemical elements, encapsulating biological constituents such as microbes and antibiotic-resistant genes. An intriguing study revealed discernible disparities between the microbial consortia and their associated antibiotic-resistant genes present in the air, and those found within terrestrial and marine ecosystems.[38] PM has emerged as a principal vector for disseminating antibiotic-resistant genes within the environment.[39,40] Thus, the air could harbor more resistant strains and antibiotic-resistance genes in locales characterized by elevated PM concentrations. Secondarily, PM can incite oxidative stress and elicit inflammatory responses, which could precipitate structural and functional degradation of alveolar epithelial and endothelial cells.[41,42] Furthermore, PM can infiltrate the systemic circulation, provoking vascular dysregulation and systemic inflammation.[43] Such perturbations may aggravate the clinical status of new tuberculosis patients afflicted with chronic pulmonary diseases.[44] This exacerbation might necessitate a complex and protracted diagnostic and treatment regimen, thereby elevating their propensity to develop drug resistance.[45] Lastly, insights gleaned from a molecular epidemiological investigation underscored that the peril of direct transmission of DR-TB distinctly surpasses resistance acquisition attributable to factors such as the injudicious utilization of antibiotics.[46] This implies that PM, laden with resistant strains and antibiotic-resistant genes, could potentially bolster the aerial propagation of drug-resistant

Mycobacterium tuberculosis.

This study has several limitations. First, we estimated PM exposure relying on stationary monitoring data, which may not accurately reflect individual exposure. Future research should utilize mobile monitoring devices or geographic information systems (GIS) for more precise assessments. Second, we only measured the drug resistance to rifampicin and isoniazid, restricting our analysis of the risk of resistance to other antituberculosis drugs. Expanding the sample size to include a broader range of drug-resistant tuberculosis is essential for elucidating the relationship between PM exposure and resistance mechanisms. Third, besides air pollution, other factors, such as tobacco smoking, alcohol consumption, and socioeconomic status, may also affect the association between PM and drug resistance. Future studies should integrate these variables to provide a comprehensive understanding of the multifactorial influences of PM on drug resistance in PTB patients.

Conclusion

In conclusion, our study demonstrated a statistically significant positive association between outdoor PM_{10} and $PM_{2.5}$ concentrations and DR-TB among workers and farmers predominantly engaged in outdoor occupations. Our findings underscore the critical role of reducing ambient particulate matter levels in mitigating the burden of infectious diseases. To further validate this association and evaluate the long-term health outcomes of air pollution interventions, future research should prioritize in vitro mechanistic studies to investigate the biological pathways linking PM exposure to DR-TB, longitudinal cohort studies with extended follow-up periods to assess cumulative effects, and economic evaluations of public health interventions targeting air quality improvements.

Data availability statement

Data are available upon reasonable request. Data are available upon reasonable requests by contacting the corresponding author through the following email address: gsdx_zxl@163.com.

Ethics statements

Patient consent for publication

Not required.

Ethical approval

The present study was approved by the Ethics Committee of Nanjing Medical University. It is a secondary analysis of retrospective, non-identifiable data employing anonymized, pre-existing public health records without direct interaction or intervention with the participants. Given the low-risk nature of this research and the inability to trace the data back to individual subjects, the Ethics Committee granted a waiver for the requirement of informed consent (SZJKJFS2023-001).

Contributors

Xiaolong Zhang: Conceptualization, Methodology, Data Curation, Software, Formal analysis, Writing - Original Draft, Visualization. Zhongqi Li: Conceptualization, Formal analysis, Writing-Review & Editing. Bilin Tao: Formal analysis, Software, Visualization. Ying Fu: Data Curation, Methodology. Caiyan Cui, Feixian Wang ,Yun Li and Yu Wang: Data Curation. Jun Jiang: Conceptualization, Project administration. Jianming Wang: Conceptualization, Resources, Visualization, Writing-Review & Editing, Project administration, Supervision, Funding acquisition. Xiaolong Zhang is responsible for the overall content as guarantor.

Funding

This study was funded by the National Natural Science Foundation of China (82473693, 81973103) and Suzhou Health Youth Backbone Talent "National Tutor System" Training Project (Gngg2022031). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research

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Figure legends

Figure 1. Time-series plots of outdoor air pollutants and meteorological factors in Suzhou City between 2017 and 2021.

Figure 2. Percentage changes in the risk of drug-resistant tuberculosis and their 95% CIs for each 10-unit increase in PM_{10} concentration in Suzhou City between 2017 and 2021.

Figure 3. Percentage changes in the risk of drug-resistant tuberculosis and their 95% CIs for each 10-unit increase in $PM_{2.5}$ concentration in Suzhou City between 2017 and 2021.

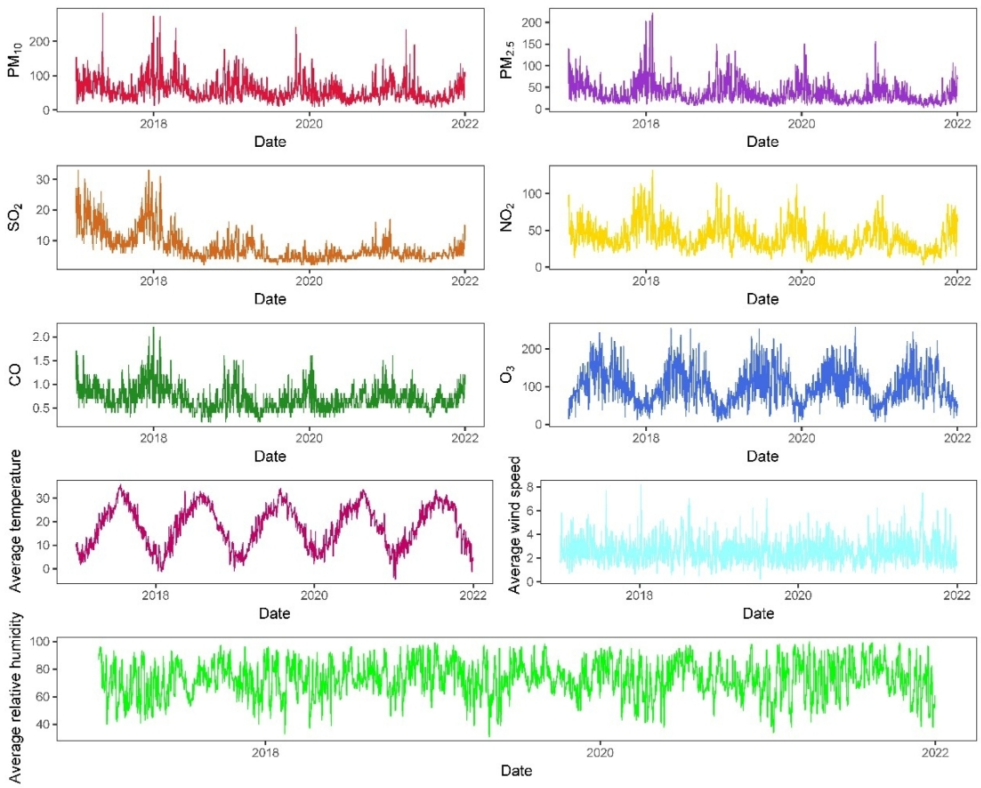
Table 1. Characteristics of study subjects.

Variables	Drug resistance		χ^2	*P*
	Sensitive n (%)	Resistant n (%)		
Sex				
Male	5715 (96.65)	198 (3.35)	6.533	0.011
Female	1912 (97.80)	43 (2.20)		
Age (years)				
<60	5532 (96.93)	175 (3.07)	0.001	0.978
≥60	2095 (96.95)	66 (3.05)		
Ethnic groups				
Han	7531 (96.96)	236 (3.04)	0.668	0.414
Others	96 (95.05)	5 (4.95)		
Sputum smear test				
Positive	3817 (94.08)	240 (5.92)	229.556	<0.001
Negative	3810 (99.97)	1 (0.03)		
Comorbidity*				
Yes	182 (95.79)	8 (4.21)	0.863	0.353
No	7445 (96.97)	233 (3.03)		
Treatment history				
No	7235 (97.41)	192 (2.59)	101.913	<0.001
Yes	392 (88.89)	49 (11.11)		

*: HIV/AIDS, diabetes, or pneumoconiosis.

Table 2. Characteristics of daily average outdoor air pollutant concentrations and meteorological factors in Suzhou City between 2017 and 2021.

Variables	Minimum	Q_{25}	Median	Mean	Q_{75}	Maximum
Outdoor air pollutants						
PM_{10} (μg/m^3)	7.00	36.00	50.00	58.89	74.00	283.00
$PM_{2.5}$ (μg/m^3)	3.00	20.00	30.00	37.15	46.00	222.00
SO_2 (μg/m^3)	2.00	5.00	6.00	7.84	9.00	33.00
NO_2 (μg/m^3)	3.00	27.00	37.00	40.63	51.00	132.00
CO (mg/m^3)	0.20	0.50	0.70	0.70	0.80	2.20
O_3 (μg/m^3)	6.00	65.00	92.00	100.55	132.00	257.00
Meteorological factors						
Average temperature (℃)	-4.50	10.20	18.40	17.94	25.50	35.70
Average wind speed (m/s)	0.20	1.90	2.40	2.61	3.20	8.20
Average relative humidity (%)	31.00	64.00	73.00	72.91	83.00	99.80



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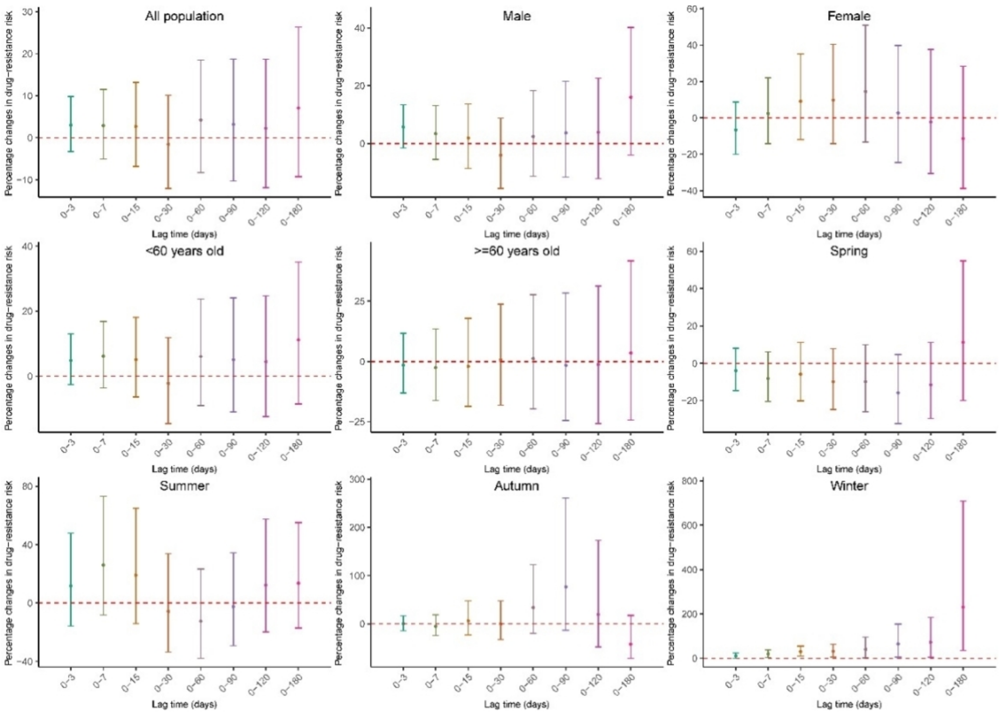

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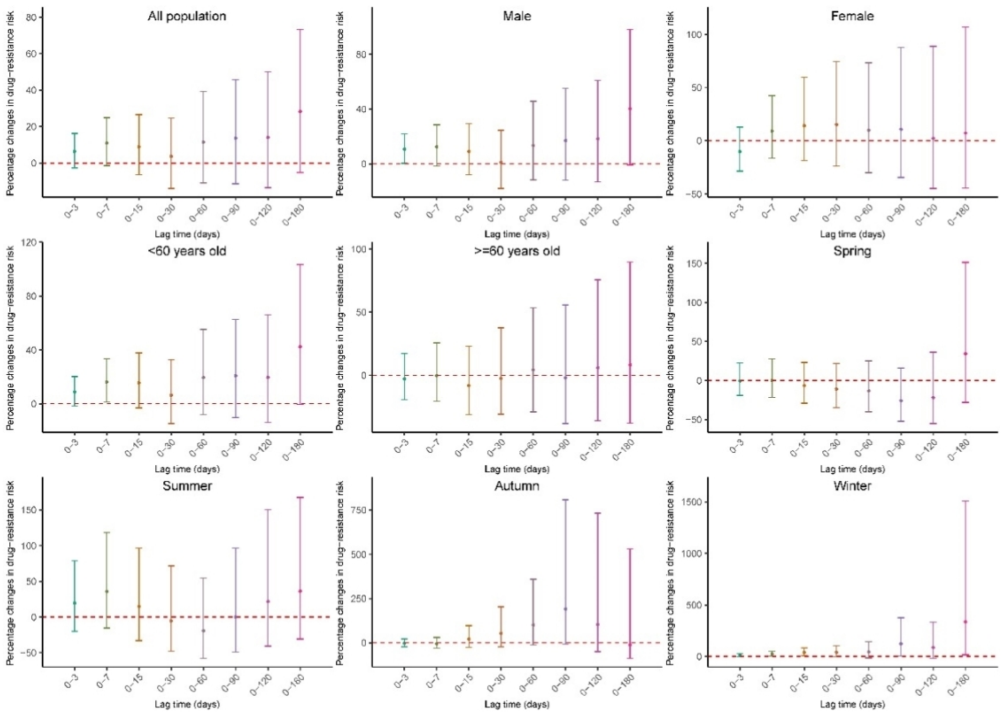

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Supplementary Tables

Table S1. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in PM_{10} concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
All population	0-3 days	3.02 (-3.34, 9.79)	3.89 (-3.35, 11.67)	1.95 (-7.20, 11.99)	1.87 (-6.26, 10.70)	3.16 (-3.23, 9.96)
	0-7 days	2.89 (-5.07, 11.51)	3.35 (-5.57, 13.12)	-2.47 (-14.10, 10.73)	1.[illegible]2 (-8.61, 11.66)	2.83 (-5.14, 11.47)
	0-15 days	2.66 (-6.87, 13.17)	4.14 (-6.79, 16.36)	0.77 (-14.50, 18.76)	3.[illegible]1 (-8.03, 16.26)	2.80 (-6.77, 13.35)
	0-30 days	-1.60 (-12.07, 10.11)	-1.02 (-13.33, 13.03)	-1.74 (-19.52, 19.97)	0.[illegible]6 (-13.25, 13.99)	-1.52 (-12.03, 10.24)
	0-60 days	4.24 (-8.32, 18.52)	9.58 (-6.39, 28.28)	21.29 (-7.26, 58.63)	12.41 (-4.37, 32.13)	5.98 (-6.97, 20.73)
	0-90 days	3.19 (-10.33, 18.74)	7.69 (-10.73, 29.91)	12.29 (-22.71, 63.15)	9.[illegible]8 (-7.96, 30.94)	3.40 (-10.21, 19.08)
	0-120 days	2.25 (-11.91, 18.70)	4.36 (-15.27, 28.53)	10.70 (-28.56, 71.52)	9.[illegible]7 (-9.07, 32.03)	2.09 (-12.14, 18.63)
	0-180 days	7.08 (-9.27, 26.37)	8.38 (-14.35, 37.14)	14.39 (-34.45, 99.60)	17.45 (-4.06, 43.78)	8.62 (-8.12, 28.40)
Male	0-3 days	5.66 (-1.58, 13.42)	6.58 (-1.69, 15.54)	5.32 (-4.96, 16.73)	3.[illegible]9 (-5.28, 13.95)	5.88 (-1.38, 13.68)
	0-7 days	3.38 (-5.54, 13.15)	3.21 (-6.77, 14.26)	-4.02 (-16.75, 10.64)	1.[illegible]2 (-9.40, 13.31)	3.36 (-5.61, 13.19)
	0-15 days	1.93 (-8.65, 13.73)	3.23 (-8.81, 16.85)	-3.74 (-20.00, 15.82)	2.[illegible]7 (-10.33, 16.41)	2.13 (-8.50, 14.00)
	0-30 days	-4.13 (-15.51, 8.79)	-4.20 (-17.45, 11.17)	-12.42 (-30.50, 10.38)	-3.[illegible]2 (-17.20, 12.42)	-3.86 (-15.32, 9.15)
	0-60 days	2.44 (-11.29, 18.31)	8.68 (-8.77, 29.46)	7.44 (-20.73, 45.61)	10.45 (-7.76, 32.24)	4.57 (-9.71, 21.10)
	0-90 days	3.65 (-11.57, 21.48)	10.10 (-10.47, 35.41)	-1.99 (-35.81, 49.66)	10.48 (-9.24, 34.50)	4.03 (-11.37, 22.10)
	0-120 days	3.82 (-12.06, 22.56)	9.11 (-12.88, 36.64)	3.50 (-36.50, 68.70)	11.88 (-8.98, 37.52)	4.21 (-11.84, 23.18)
	0-180 days	15.99 (-3.98, 40.13)	22.55 (-5.30, 58.60)	13.98 (-38.57, 111.50)	30.12 (3.33, 63.85)	17.26 (-3.19, 42.03)
Female	0-3 days	-6.73 (-19.99, 8.73)	-6.50 (-21.31, 11.09)	-7.00 (-26.58, 17.79)	-6.[illegible]8 (-23.38, 14.38)	-6.90 (-20.21, 8.61)
	0-7 days	2.31 (-14.19, 21.99)	4.30 (-14.15, 26.72)	8.68 (-17.93, 43.92)	0.40 (-19.82, 25.73)	2.46 (-14.07, 22.17)
	0-15 days	9.10 (-11.93, 35.16)	11.24 (-13.46, 42.98)	28.57 (-11.81, 87.45)	12.[illegible]8 (-13.90, 48.00)	9.26 (-11.79, 35.34)
	0-30 days	9.76 (-14.18, 40.38)	14.03 (-15.17, 53.29)	48.37 (-3.13, 127.25)	17.[illegible]8 (-14.47, 60.55)	8.58 (-15.18, 39.00)
	0-60 days	14.44 (-13.26, 50.99)	17.80 (-17.83, 68.88)	90.05 (4.94, 244.18)	23.[illegible]8 (-13.95, 77.77)	11.85 (-14.95, 47.10)
	0-90 days	2.72 (-24.52, 39.80)	-4.82 (-38.91, 48.29)	85.70 (-19.72, 329.53)	7.78 (-28.17, 61.71)	3.42 (-23.86, 40.46)
	0-120 days	-2.23 (-30.51, 37.57)	-17.93 (-51.04, 37.57)	43.55 (-47.44, 292.02)	0.[illegible]3 (-34.87, 55.47)	-3.06 (-31.35, 36.90)
	0-180 days	-11.32 (-38.74, 28.37)	-31.17 (-62.16, 25.20)	17.40 (-68.64, 339.42)	-10.00 (-42.80, 41.60)	-10.22 (-38.25, 30.53)
<60 years old	0-3 days	4.91 (-2.58, 12.98)	7.81 (-0.79, 17.16)	4.43 (-6.56, 16.72)	5.[illegible]0 (-4.65, 15.84)	4.85 (-2.67, 12.94)
	0-7 days	6.13 (-3.62, 16.88)	9.90 (-1.16, 22.21)	2.73 (-11.81, 19.67)	6.90 (-5.06, 20.36)	6.11 (-3.65, 16.87)
	0-15 days	5.14 (-6.39, 18.09)	10.05 (-3.35, 25.30)	5.03 (-13.88, 28.09)	7.[illegible]2 (-6.53, 22.99)	5.14 (-6.39, 18.10)
	0-30 days	-2.25 (-14.59, 11.88)	2.03 (-12.87, 19.49)	-6.11 (-26.38, 19.73)	1.[illegible]7 (-13.67, 19.51)	-2.15 (-14.56, 12.07)
	0-60 days	6.09 (-9.06, 23.75)	15.67 (-3.94, 39.28)	24.82 (-9.01, 71.21)	17.[illegible]9 (-3.03, 42.12)	7.35 (-8.19, 25.53)
	0-90 days	5.06 (-11.07, 24.12)	16.12 (-6.81, 44.70)	16.94 (-24.76, 81.73)	16.09 (-5.62, 42.79)	5.01 (-11.11, 24.05)
	0-120 days	4.49 (-12.44, 24.70)	14.78 (-10.20, 46.71)	35.23 (-19.25, 126.46)	15.71 (-7.03, 44.02)	5.28 (-11.88, 25.77)
	0-180 days	11.15 (-8.57, 35.11)	21.46 (-7.93, 60.24)	32.82 (-30.65, 154.35)	25.49 (-0.90, 58.92)	13.90 (-6.44, 38.66)
≥60 years old	0-3 days	-1.44 (-13.04, 11.71)	-5.28 (-18.14, 9.60)	-3.24 (-19.27, 15.97)	-4.[illegible]1 (-18.96, 12.28)	-0.93 (-12.60, 12.31)
	0-7 days	-2.49 (-16.21, 13.47)	-9.58 (-24.29, 7.98)	-13.44 (-31.87, 9.98)	-9.[illegible]1 (-25.62, 10.10)	-2.10 (-16.07, 14.18)
	0-15 days	-2.06 (-18.61, 17.87)	-9.57 (-27.02, 12.04)	-6.76 (-31.15, 26.28)	-3.[illegible]6 (-23.25, 21.67)	-1.91 (-18.63, 18.26)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
	0-30 days	0.67 (-18.13, 23.80)	-5.76 (-26.34, 20.56)	6.60 (-25.70, 52.93)	-3.19 (-24.98, 24.91)	0.65 (-18.16, 23.79)
	0-60 days	1.26 (-19.71, 27.71)	-5.30 (-29.16, 26.60)	23.35 (-24.80, 102.33)	1.76 (-24.86, 37.79)	2.78 (-18.75, 30.02)
	0-90 days	-1.53 (-24.49, 28.41)	-11.63 (-38.27, 26.50)	-1.69 (-52.18, 102.13)	-3.76 (-31.67, 35.26)	-1.63 (-24.63, 28.39)
	0-120 days	-1.29 (-25.74, 31.21)	-11.16 (-41.01, 33.80)	-34.12 (-71.99, 54.95)	0.74 (-31.05, 44.06)	-2.43 (-26.45, 29.42)
	0-180 days	3.56 (-24.35, 41.76)	-11.44 (-44.69, 41.79)	-18.98 (-73.51, 147.78)	6.56 (-29.14, 57.25)	1.86 (-25.93, 40.08)
Spring	0-3 days	-3.97 (-14.66, 8.06)	0.74 (-11.52, 14.71)	-0.69 (-14.90, 15.90)	-2.24 (-15.25, 12.54)	-3.14 (-14.19, 9.33)
	0-7 days	-8.12 (-20.49, 6.18)	-2.51 (-17.59, 15.33)	-10.79 (-28.41, 11.18)	-7.83 (-23.46, 10.99)	-6.78 (-19.40, 7.82)
	0-15 days	-5.81 (-20.22, 11.20)	6.59 (-12.57, 29.96)	3.28 (-23.79, 39.96)	2.33 (-21.82, 22.02)	-5.50 (-20.17, 11.87)
	0-30 days	-9.91 (-24.80, 7.93)	1.11 (-21.31, 29.90)	14.91 (-22.28, 69.90)	8.40 (-31.65, 22.77)	-15.66 (-31.25, 3.46)
	0-60 days	-9.83 (-26.02, 9.89)	4.75 (-27.62, 51.58)	52.69 (-18.20, 185.01)	17.49 (-32.82, 105.50)	-11.01 (-27.41, 9.09)
	0-90 days	-15.80 (-32.33, 4.79)	-16.91 (-46.23, 28.40)	35.67 (-46.56, 244.43)	-34.70 (-62.68, 14.27)	-18.73 (-35.18, 1.91)
	0-120 days	-11.58 (-29.71, 11.24)	-5.71 (-43.60, 57.62)	19.42 (-57.99, 239.53)	-37.54 (-62.45, 3.88)	-10.86 (-28.98, 11.87)
	0-180 days	11.25 (-20.09, 54.86)	82.40 (-4.98, 250.14)	155.97 (-6.63, 601.71)	73.39 (-1.13, 206.19)	11.02 (-20.10, 54.25)
Summer	0-3 days	11.69 (-15.67, 47.94)	18.64 (-13.87, 63.43)	3.14 (-29.78, 51.49)	14.93 (-17.47, 59.76)	18.64 (-11.31, 58.69)
	0-7 days	26.12 (-8.15, 73.19)	35.16 (-4.65, 91.58)	22.26 (-23.89, 96.40)	32.84 (-7.17, 90.08)	31.57 (-4.27, 80.82)
	0-15 days	19.11 (-13.98, 64.93)	29.02 (-9.98, 84.89)	26.02 (-25.66, 113.61)	37.80 (-10.76, 83.03)	19.45 (-13.05, 64.09)
	0-30 days	-5.73 (-33.66, 33.96)	-5.11 (-37.09, 43.11)	-10.09 (-50.02, 61.73)	1.13 (-33.24, 53.19)	-3.87 (-32.57, 37.04)
	0-60 days	-12.47 (-37.86, 23.30)	15.23 (-28.29, 85.16)	-29.53 (-66.08, 46.38)	-10.32 (-33.51, 83.04)	2.39 (-29.95, 49.67)
	0-90 days	-2.45 (-29.24, 34.50)	-6.26 (-36.80, 39.04)	-30.37 (-71.47, 69.89)	13.95 (-29.18, 80.46)	-1.66 (-29.58, 37.32)
	0-120 days	12.37 (-19.90, 57.63)	57.82 (-11.10, 180.17)	32.33 (-49.50, 246.78)	70.37 (-2.46, 198.28)	34.50 (-8.45, 97.61)
	0-180 days	13.50 (-17.02, 55.24)	-26.98 (-54.20, 16.40)	7.98 (-72.67, 326.67)	-12.17 (-52.47, 62.27)	14.25 (-17.88, 58.96)
Autumn	0-3 days	0.01 (-14.36, 16.80)	-1.13 (-16.46, 17.01)	-6.14 (-26.56, 19.96)	-0.71 (-17.51, 19.51)	-0.03 (-14.56, 16.98)
	0-7 days	-5.03 (-23.93, 18.56)	-5.19 (-25.19, 20.17)	-12.51 (-38.90, 25.27)	-7.78 (-28.52, 18.97)	-4.97 (-23.90, 18.68)
	0-15 days	6.50 (-23.01, 47.33)	11.56 (-21.45, 58.44)	11.54 (-36.57, 96.13)	4.78 (-26.44, 49.24)	9.74 (-21.08, 52.59)
	0-30 days	-0.43 (-32.79, 47.52)	-0.43 (-34.18, 50.61)	-22.97 (-63.25, 61.43)	-1.99 (-34.49, 47.85)	8.76 (-30.41, 69.97)
	0-60 days	33.66 (-19.76, 122.63)	27.87 (-26.30, 121.88)	17.30 (-55.07, 206.20)	34.15 (-20.37, 125.98)	12.96 (-40.50, 114.47)
	0-90 days	76.72 (-13.39, 260.59)	164.24 (-3.60, 624.33)	141.00 (-61.60, 1412.34)	94.48 (-12.77, 333.62)	124.11 (-20.43, 531.22)
	0-120 days	19.11 (-48.07, 173.18)	21.29 (-51.53, 203.53)	-62.48 (-93.36, 112.00)	40.84 (-41.93, 241.55)	19.71 (-49.18, 181.97)
	0-180 days	-42.20 (-71.52, 17.33)	-42.66 (-71.91, 17.06)	-89.62 (-97.88, -49.29)	-24.11 (-68.50, 82.86)	-56.28 (-83.71, 17.28)
Winter	0-3 days	11.21 (0.02, 23.65)	10.78 (-3.15, 26.70)	13.19 (-3.58, 32.87)	1.78 (-15.38, 22.18)	11.73 (0.65, 24.04)
	0-7 days	19.69 (3.58, 38.29)	21.57 (0.50, 47.07)	19.68 (-6.04, 52.43)	8.86 (-12.44, 35.34)	20.83 (4.58, 39.60)
	0-15 days	30.51 (9.89, 55.00)	49.97 (15.68, 94.43)	32.70 (-4.53, 84.45)	24.80 (-4.68, 63.41)	31.84 (10.65, 57.10)
	0-30 days	31.42 (5.98, 62.97)	60.58 (14.73, 124.74)	42.45 (-11.87, 130.25)	41.22 (0.58, 100.26)	36.11 (7.37, 72.55)
	0-60 days	40.48 (1.23, 94.94)	134.42 (28.84, 326.52)	248.89 (38.62, 778.15)	86.70 (12.89, 208.77)	40.11 (0.12, 96.09)
	0-90 days	64.36 (6.21, 154.36)	102.85 (-13.92, 378.03)	3388.62 (211.56, 38962.49)	97.49 (-0.58, 294.26)	120.81 (34.55, 262.35)
	0-120 days	72.65 (4.55, 185.12)	84.47 (-23.90, 347.18)	275.06 (-60.78, 3486.92)	84.78 (-6.79, 266.32)	44.14 (-12.93, 138.61)
	0-180 days	231.24 (35.79, 708.04)	529.41 (63.91, 2316.96)	3810.34 (10.50, 138283.73)	303.13 (43.69, 1030.45)	171.49 (-15.60, 773.32)

Model 1: Adjusted for sex, age, season, etiological examination, comorbidity, treatment type, and average temperature, average wind speed, and average relative

humidity at the same lag time.
Model 2: Based on model 1, additionally adjusted for SO_2 at the same lag time.
Model 3: Based on model 1, additionally adjusted for NO_2 at the same lag time.
Model 4: Based on model 1, additionally adjusted for CO at the same lag time.
Model 5: Based on model 1, additionally adjusted for O_3 at the same lag time.

Table S2. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in $PM_{2.5}$ concentration among workers and farmers with pulmonary tuberculosis in Suzhou City between 2017 and 2021.

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
All population	0-3 days	6.41 (-2.62, 16.29)	8.45 (-1.97, 19.97)	6.48 (-5.25, 19.66)	6.28 (-5.72, 19.80)	7.41 (-1.93, 17.64)
	0-7 days	10.95 (-1.41, 24.86)	13.25 (-0.63, 29.06)	10.21 (-6.10, 29.35)	11.61 (-3.68, 29.31)	12.13 (-0.46, 26.30)
	0-15 days	8.93 (-6.29, 26.62)	12.69 (-4.88, 33.51)	10.17 (-9.81, 34.58)	12.08 (-6.15, 33.85)	9.95 (-5.59, 28.03)
	0-30 days	3.66 (-13.83, 24.70)	7.14 (-13.67, 32.98)	8.86 (-14.48, 38.57)	7.30 (-13.21, 32.65)	4.10 (-13.71, 25.58)
	0-60 days	11.53 (-10.70, 39.30)	22.29 (-6.87, 60.58)	33.74 (-1.35, 81.30)	19.98 (-7.05, 54.89)	16.00 (-6.63, 44.12)
	0-90 days	13.66 (-11.31, 45.65)	29.09 (-7.84, 80.81)	40.19 (-7.91, 113.42)	24.13 (-6.65, 65.07)	12.86 (-11.97, 44.68)
	0-120 days	13.97 (-13.42, 50.02)	27.69 (-12.89, 87.19)	63.22 (-4.85, 179.99)	25.47 (-8.03, 71.16)	13.60 (-13.82, 49.75)
	0-180 days	28.23 (-5.16, 73.38)	41.24 (-6.65, 113.69)	101.31 (2.93, 293.73)	45.53 (3.93, 103.80)	28.09 (-5.36, 73.37)
Male	0-3 days	10.73 (0.49, 22.02)	12.92 (1.08, 26.13)	11.39 (-1.78, 26.33)	10.28 (-3.31, 25.79)	11.78 (1.28, 23.37)
	0-7 days	12.51 (-1.48, 28.48)	14.03 (-1.59, 32.13)	9.88 (-8.08, 31.35)	13.13 (-4.04, 33.37)	14.34 (-0.01, 30.75)
	0-15 days	9.18 (-7.84, 29.33)	13.01 (-6.48, 36.56)	8.47 (-13.36, 35.80)	11.82 (-8.17, 36.16)	11.23 (-6.36, 32.14)
	0-30 days	1.18 (-17.79, 24.55)	4.36 (-17.88, 32.64)	2.45 (-22.43, 35.30)	[illegible] (-17.49, 31.99)	2.92 (-16.56, 26.96)
	0-60 days	13.50 (-11.61, 45.73)	28.25 (-5.45, 73.95)	34.65 (-4.32, 89.49)	23.32 (-7.28, 64.00)	18.60 (-7.23, 51.63)
	0-90 days	17.06 (-11.76, 55.29)	38.13 (-5.21, 101.29)	36.06 (-15.64, 119.43)	28.00 (-7.05, 76.27)	15.59 (-12.93, 53.44)
	0-120 days	18.35 (-12.97, 60.96)	40.97 (-7.51, 114.88)	54.74 (-15.78, 184.33)	31.65 (-6.91, 86.19)	18.84 (-12.79, 61.96)
	0-180 days	40.26 (-0.76, 98.24)	63.09 (2.07, 160.58)	65.88 (-21.56, 250.78)	59.06 (8.46, 133.26)	40.27 (-0.87, 98.47)
Female	0-3 days	-10.26 (-28.62, 12.82)	-10.11 (-30.60, 16.43)	-10.25 (-34.90, 23.72)	-10.16 (-33.67, 21.70)	-10.89 (-29.26, 12.26)
	0-7 days	9.12 (-16.42, 42.46)	13.30 (-15.35, 51.66)	24.50 (-15.75, 83.97)	9.40 (-22.09, 53.60)	8.41 (-17.02, 41.62)
	0-15 days	14.01 (-18.57, 59.61)	16.44 (-20.77, 71.14)	32.33 (-19.59, 117.77)	19.05 (-21.69, 80.99)	11.97 (-19.96, 56.64)
	0-30 days	15.23 (-23.87, 74.41)	22.08 (-26.94, 103.99)	39.30 (-19.43, 140.86)	23.48 (-25.78, 105.45)	9.90 (-27.96, 67.66)
	0-60 days	10.04 (-30.08, 73.18)	4.78 (-42.78, 91.85)	27.75 (-34.32, 148.47)	13.38 (-35.67, 99.82)	5.79 (-32.96, 66.92)
	0-90 days	10.83 (-34.53, 87.63)	2.91 (-52.42, 122.56)	65.29 (-31.44, 298.51)	20.62 (-36.53, 128.84)	11.07 (-34.59, 88.61)
	0-120 days	2.13 (-44.74, 88.76)	-18.44 (-67.67, 105.76)	72.41 (-48.12, 472.97)	8.14 (-46.92, 120.46)	0.58 (-45.65, 86.13)
	0-180 days	7.20 (-44.41, 106.73)	4.07 (-60.08, 171.28)	436.86 (2.43, 2713.84)	18.88 (-43.55, 150.36)	8.98 (-43.72, 111.01)
<60 years old	0-3 days	8.84 (-1.58, 20.37)	13.34 (1.26, 26.87)	9.17 (-4.48, 24.78)	10.89 (-3.19, 27.01)	8.80 (-1.77, 20.52)
	0-7 days	16.28 (1.20, 33.59)	23.14 (5.85, 43.25)	17.40 (-2.72, 41.69)	21.08 (2.08, 43.63)	16.98 (1.67, 34.59)
	0-15 days	15.56 (-3.22, 37.98)	24.94 (2.76, 51.92)	20.30 (-5.07, 52.47)	21.13 (-1.27, 48.61)	15.89 (-3.08, 38.57)
	0-30 days	6.43 (-14.66, 32.73)	17.03 (-9.20, 50.84)	13.45 (-15.15, 51.69)	13.87 (-11.33, 46.23)	7.36 (-14.22, 34.39)
	0-60 days	19.52 (-8.00, 55.26)	40.59 (2.23, 93.34)	39.89 (-2.94, 101.62)	33.60 (-0.90, 80.11)	21.40 (-6.72, 57.99)
	0-90 days	20.82 (-10.23, 62.62)	54.81 (3.47, 131.62)	59.26 (-3.13, 161.81)	37.99 (-1.58, 93.48)	21.22 (-9.99, 63.25)
	0-120 days	19.57 (-13.98, 66.20)	52.89 (-3.19, 141.46)	99.29 (3.65, 283.19)	35.66 (-6.12, 96.02)	22.06 (-12.42, 70.13)
	0-180 days	42.34 (-0.39, 103.40)	79.60 (10.12, 192.92)	171.59 (22.57, 501.79)	63.71 (10.33, 142.90)	43.23 (-0.06, 105.28)
≥60 years old	0-3 days	-2.74 (-19.31, 17.23)	-8.63 (-26.85, 14.11)	-5.01 (-25.31, 20.80)	-8.78 (-28.62, 18.10)	-0.62 (-17.74, 20.08)
	0-7 days	-0.19 (-20.72, 25.65)	-9.64 (-31.22, 18.70)	-8.85 (-33.21, 24.39)	-9.21 (-32.88, 23.07)	4.11 (-17.77, 31.81)
	0-15 days	-8.15 (-31.36, 22.92)	-21.29 (-44.61, 11.84)	-14.10 (-41.41, 25.93)	-12.26 (-38.53, 25.24)	-6.02 (-30.10, 26.35)
	0-30 days	-2.51 (-30.91, 37.56)	-15.71 (-45.01, 29.21)	-1.26 (-36.24, 52.91)	-9.23 (-39.69, 36.61)	-2.70 (-31.30, 37.81)
	0-60 days	4.36 (-29.02, 53.44)	-7.06 (-44.34, 55.20)	23.09 (-28.78, 112.74)	5.40 (-34.51, 69.63)	7.40 (-26.67, 57.29)
	0-90 days	-2.01 (-38.27, 55.57)	-22.04 (-59.23, 49.06)	0.43 (-56.00, 129.21)	-3.74 (-44.06, 65.99)	0.16 (-36.01, 56.78)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
	0-120 days	5.96 (-36.09, 75.68)	-5.62 (-55.37, 99.59)	1.16 (-62.68, 174.17)	10.74 (-38.88, 100.65)	6.70 (-35.08, 75.37)
	0-180 days	8.34 (-38.13, 89.72)	-16.17 (-63.31, 91.54)	-3.12 (-73.43, 253.31)	[illegible] (-41.98, 112.78)	8.41 (-37.92, 89.32)
Spring	0-3 days	-0.43 (-19.17, 22.66)	9.52 (-12.95, 37.79)	7.80 (-16.04, 38.40)	[illegible] (-18.12, 34.86)	3.21 (-18.14, 30.13)
	0-7 days	0.15 (-21.49, 27.75)	15.32 (-13.03, 52.90)	6.91 (-21.57, 45.75)	[illegible] (-20.27, 48.26)	9.29 (-16.91, 43.75)
	0-15 days	-6.34 (-28.91, 23.40)	18.34 (-14.71, 64.20)	13.86 (-24.67, 72.10)	[illegible] (-28.77, 47.13)	-5.34 (-29.34, 26.81)
	0-30 days	-10.73 (-34.78, 22.18)	14.32 (-25.88, 76.33)	26.89 (-21.86, 106.04)	[illegible] (-35.46, 50.50)	-25.93 (-48.95, 7.47)
	0-60 days	-13.29 (-39.94, 25.18)	34.81 (-36.16, 184.65)	43.61 (-28.91, 190.10)	[illegible] (-39.33, 105.04)	-19.07 (-47.14, 23.92)
	0-90 days	-25.64 (-52.41, 16.20)	-18.11 (-83.47, 305.76)	14.43 (-52.85, 177.70)	[illegible] (-68.23, 56.08)	-45.63 (-67.52, -9.01)
	0-120 days	-21.67 (-55.02, 36.38)	95.93 (-74.76, 1421.17)	69.48 (-49.61, 469.94)	[illegible] (-82.14, 46.56)	-23.57 (-56.43, 34.05)
	0-180 days	34.39 (-28.11, 151.23)	141.37 (-8.21, 534.66)	163.90 (-14.57, 715.14)	[illegible] (-2.10, 467.17)	19.03 (-38.83, 131.61)
Summer	0-3 days	19.61 (-20.00, 78.83)	27.39 (-17.91, 97.71)	10.78 (-31.04, 77.98)	[illegible] (-22.05, 106.10)	38.00 (-10.54, 112.87)
	0-7 days	35.97 (-15.33, 118.36)	43.39 (-13.14, 136.70)	23.82 (-31.05, 122.34)	[illegible] (-14.27, 162.71)	54.02 (-5.70, 151.56)
	0-15 days	14.87 (-32.96, 96.82)	19.54 (-32.29, 111.06)	5.43 (-47.99, 113.73)	[illegible] (-29.67, 144.56)	27.58 (-25.97, 119.88)
	0-30 days	-5.28 (-47.79, 71.85)	-3.39 (-48.76, 82.14)	-4.36 (-57.47, 115.04)	[illegible] (-46.20, 116.64)	-1.22 (-46.25, 81.56)
	0-60 days	-19.21 (-57.74, 54.48)	7.48 (-48.04, 122.35)	-24.55 (-72.16, 104.49)	[illegible] (-51.77, 125.88)	-0.97 (-50.52, 98.20)
	0-90 days	0.15 (-49.00, 96.64)	-2.98 (-53.49, 102.38)	-17.26 (-80.07, 243.47)	[illegible] (-46.79, 153.50)	0.98 (-48.77, 99.03)
	0-120 days	21.65 (-40.85, 150.21)	47.32 (-40.95, 267.54)	25.59 (-74.96, 529.99)	[illegible] (-37.13, 218.01)	59.56 (-26.32, 245.54)
	0-180 days	36.13 (-30.70, 167.42)	-23.97 (-79.46, 181.45)	64.64 (-78.83, 1180.42)	-1.04 (-66.55, 192.75)	38.33 (-31.72, 180.24)
Autumn	0-3 days	-2.96 (-22.65, 21.76)	-4.56 (-25.17, 21.73)	-13.09 (-37.73, 21.29)	[illegible] (-28.09, 24.59)	-3.32 (-23.79, 22.64)
	0-7 days	-4.54 (-29.95, 30.11)	-4.35 (-30.52, 31.69)	-9.72 (-42.76, 42.40)	[illegible] (-35.10, 31.65)	-4.18 (-30.14, 31.41)
	0-15 days	20.70 (-26.12, 97.21)	25.42 (-24.08, 107.19)	34.63 (-32.59, 168.89)	[illegible] (-29.82, 103.26)	18.87 (-27.36, 94.52)
	0-30 days	53.45 (-22.46, 203.68)	57.14 (-22.00, 216.59)	95.52 (-29.40, 441.48)	[illegible] (-24.92, 205.45)	62.34 (-19.95, 229.20)
	0-60 days	100.47 (-12.31, 358.31)	97.05 (-21.63, 395.49)	161.05 (-36.72, 976.90)	[illegible] (-12.31, 421.85)	72.09 (-34.92, 355.02)
	0-90 days	191.09 (-6.67, 807.96)	715.97 (41.58, 4602.55)	604.03 (-50.03, 9819.71)	[illegible] (1.26, 1443.03)	326.51 (-11.66, 1959.17)
	0-120 days	103.34 (-50.34, 732.58)	132.47 (-52.28, 1032.58)	20.48 (-88.06, 1115.85)	[illegible] (-34.81, 1393.11)	101.34 (-51.02, 727.62)
	0-180 days	-11.86 (-87.69, 531.11)	-15.79 (-87.99, 490.57)	-73.47 (-98.60, 401.41)	[illegible] (-90.11, 726.57)	-23.90 (-91.96, 620.34)
Winter	0-3 days	13.03 (-0.83, 28.82)	11.89 (-5.11, 31.95)	12.24 (-5.61, 33.47)	[illegible] (-24.08, 25.21)	12.30 (-1.43, 27.94)
	0-7 days	25.29 (3.69, 51.39)	26.69 (-1.46, 62.90)	20.17 (-7.58, 56.24)	[illegible] (-22.14, 46.43)	25.00 (3.59, 50.83)
	0-15 days	40.39 (7.36, 83.57)	59.14 (8.51, 133.39)	22.28 (-17.08, 80.32)	[illegible] (-23.64, 84.09)	40.44 (7.36, 83.71)
	0-30 days	41.89 (-1.21, 103.79)	90.32 (3.90, 248.61)	16.65 (-32.60, 101.90)	[illegible] (-25.37, 168.71)	41.60 (-1.73, 104.04)
	0-60 days	44.33 (-14.72, 144.26)	81.16 (-20.73, 314.01)	20.99 (-61.70, 282.17)	[illegible] (-20.38, 302.26)	41.84 (-16.57, 141.13)
	0-90 days	122.73 (4.15, 376.34)	105.16 (-40.77, 610.68)	319.34 (-57.56, 4043.11)	[illegible] (-15.94, 615.14)	307.07 (54.14, 975.03)
	0-120 days	88.39 (-17.81, 331.78)	14.55 (-70.70, 347.80)	-78.30 (-96.99, 56.42)	[illegible] (-44.00, 399.20)	39.86 (-38.48, 217.93)
	0-180 days	335.06 (17.71, 1507.95)	537.94 (16.80, 3384.40)	-84.34 (-99.93, 3336.70)	[illegible] (17.64, 1935.72)	138.49 (-59.37, 1299.84)

Model 1: Adjusted for sex, age, season, etiological examination, comorbidity, treatment type, and average temperature, average wind speed, and average relative humidity at the same lag time.
Model 2: Based on model 1, additionally adjusted for SO_2 at the same lag time.
Model 3: Based on model 1, additionally adjusted for NO_2 at the same lag time.
Model 4: Based on model 1, additionally adjusted for CO at the same lag time.

Model 5: Based on model 1, additionally adjusted for O_3 at the same lag time.