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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 in Suzhou, China

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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 patients with PTB and meteorological factors were extracted from the National Tuberculosis Online Registration System and the China Meteorological Data Sharing Center.

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

Methods The generalised additive model was used 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used a generalised 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 non-linear or non-monotonic relationships.

⇒ 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 history of antituberculosis therapy and infection with 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,[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 patients with tuberculosis.[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 hypothesise 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 patients with PTB 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 minimise 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 1 January 2017 and 31 December 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}, $PM_{2.5}$, sulphur 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 (106.37.208.233:20035/). The pollutant concentrations were reported in units of $\mu g/m^3$, except for CO, which was reported in the unit of mg/m^3.

Statistical analysis

We used a binomial distributed generalised 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 analysing complex environmental health data that may exhibit non-linear or non-monotonic relationships.[15 16] To control the impacts of potential confounding factors, we adjusted covariates, including sex, age, season, aetiological examination, comorbidity, treatment type, average temperature, average wind speed and average relative humidity. In addition, we used a thin-plate spline function with a maximum degree of freedom of 2 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 patients with PTB 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 patients with PTB was expressed as percentage changes in drug resistance risk and their corresponding 95% 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

Table 1 Characteristics of study subjects.

Variables	Drug resistance		χ^2	P value
	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.

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 V.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 AIDS, diabetes or pneumoconiosis, did not significantly affect the drug resistance rate. However, those with 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 IQRs 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/m^3 (IQR: 36.00–74.00), 30.00 µg/m^3 (IQR: 20.00–46.00), 6.00 µg/m^3 (IQR: 5.00–9.00), 37.00 µg/m^3 (IQR: 27.00–51.00), 0.70 mg/m^3 (IQR: 0.50–0.80) and 92.00 µg/m^3 (IQR: 65.00–132.00), respectively. Within the same time frame, 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

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

CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; pSO_2, sulphur dioxide.

0–60 days after adjusting for each of the four gaseous pollutants (online supplemental 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

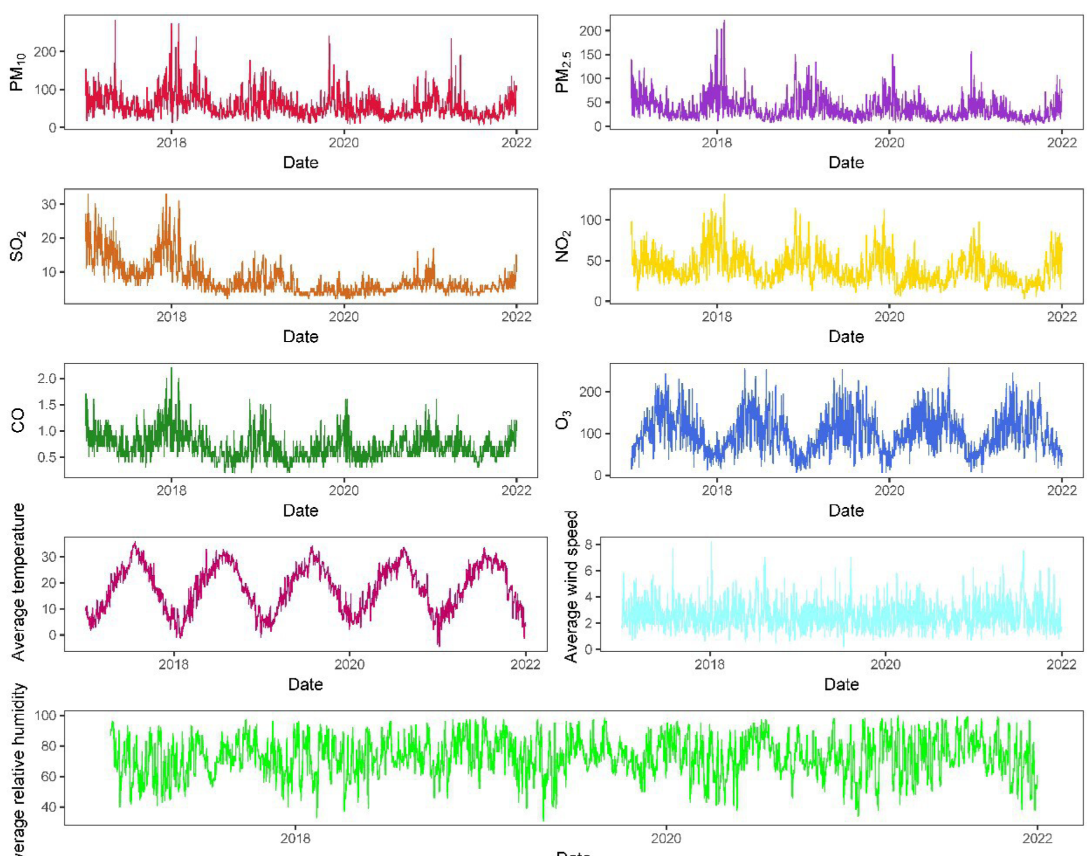

Figure 1 Time-series plots of outdoor air pollutants and meteorological factors in Suzhou City between 2017 and 2021. CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; pSO_2, sulphur dioxide.

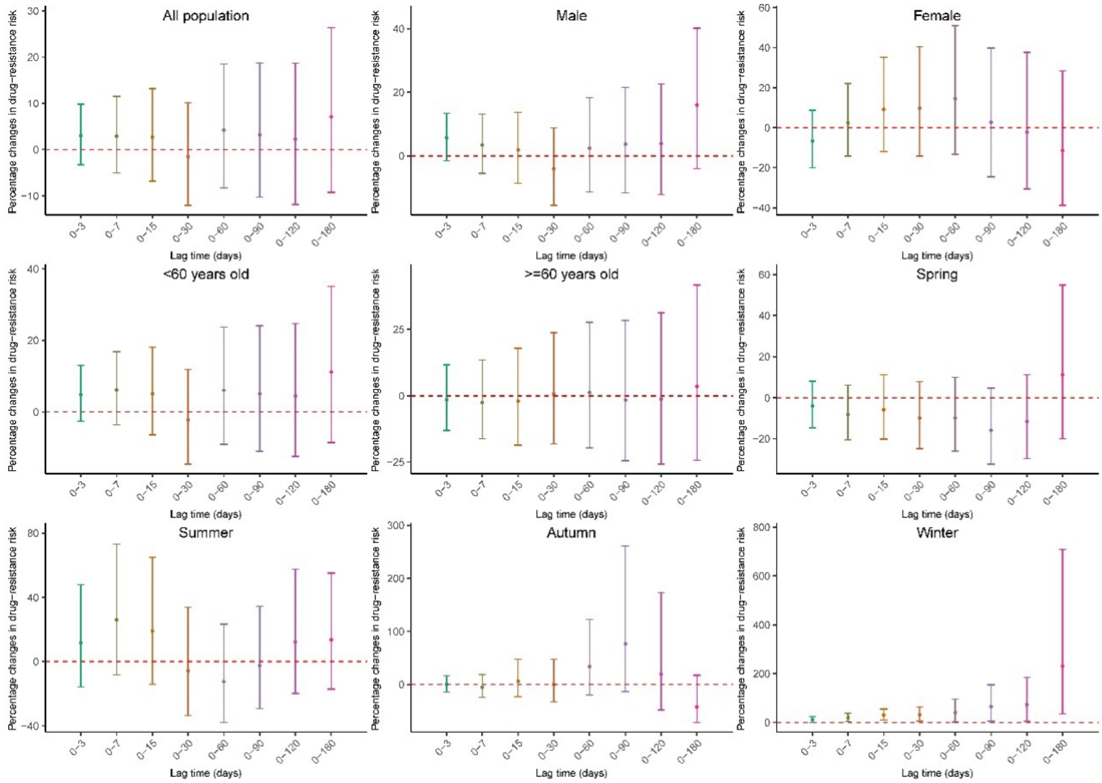

Figure 2 Percentage changes in the risk of drug-resistant tuberculosis and their 95% CIs for each 10-unit increase in PM_{10} concentration in Suzhou City between 2017 and 2021.

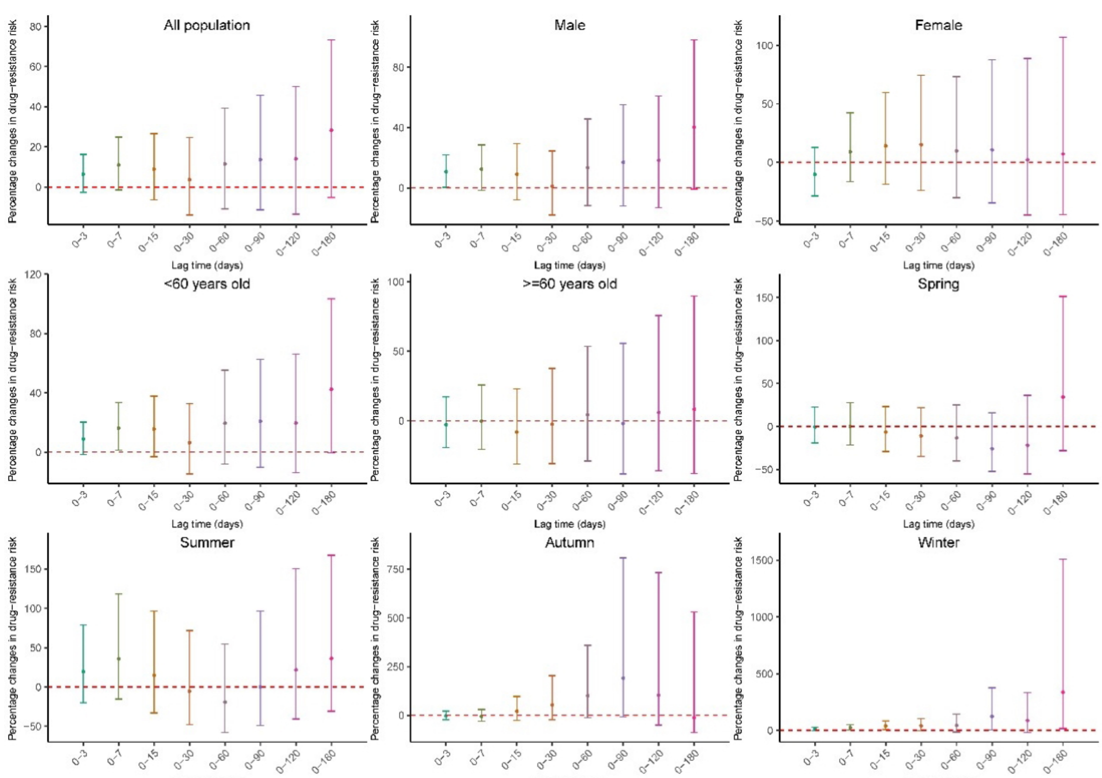

Figure 3 Percentage changes in the risk of drug-resistant tuberculosis and their 95% CIs for each 10-unit increase in $PM_{2.5}$ concentration in Suzhou City between 2017 and 2021.

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 (online supplemental 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 emphasises 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 programmes, such as strengthening screening and protection of high-risk groups in seasons with severe air pollution, to facilitate the early detection and management of DR-TB.

The existing body of literature exploring the association between PM concentration and drug resistance risk of patients with tuberculosis is scarce and inconclusive. A case-control study identified a positive association between PM concentration and drug resistance risk in patients with tuberculosis.[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 patients with DR-TB.[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 USA revealed the strongest correlation between $PM_{2.5}$ concentration and daily hospitalisation 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 recognised 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 patients with PTB 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 (eg, smoking), social behaviours (eg, 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 with 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 drug resistance risk of patients with PTB. The exact machinations driving this phenomenon are yet to be entirely comprehended; however, several contributory factors can be hypothesised. 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 harbour more resistant strains and antibiotic resistance genes in locales characterised 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 patients with tuberculosis and 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 utilisation of antibiotics.[46] This implies that PM, laden with resistant strains and antibiotic-resistant genes, could potentially bolster the aerial propagation of drug-resistant *M. 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 use mobile monitoring devices or geographic information systems 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 DR-TB 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 socio-economic 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 patients with PTB.

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 PM 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 prioritise 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.

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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.

Patient consent for publication Not applicable.

Ethics 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 anonymised, 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).

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