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

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1 **Outdoor particulate matter and risk of drug resistance for workers**
2 **and farmers with pulmonary tuberculosis**
3

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1 **Abstract**

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

6
7 **Methods:** We collected the registration information of pulmonary tuberculosis (PTB)
8 in Suzhou, China, from 2017 to 2021, as well as data on air pollutants and
9 meteorological factors. The generalized additive model was utilized to estimate the
10 effects of outdoor PM on the drug resistance risk of workers and farmers with PTB.

11
12 **Results:** Despite no association between PM₁₀ and drug resistant risk in the overall
13 analysis, subgroup analysis found a significant positive association in winter at all lag
14 days. Similarly, PM_{2.5} was significantly associated with drug resistance risk among
15 males at a lag of 0-3 days, cases ≤ 60 years with a lag of 0-7 days, and in winter at a
16 lag of 0-7 days, 0-15 days, 0-90 days, and 0-180 days.

17
18 **Conclusions:** The concentrations of outdoor PM₁₀ and PM_{2.5} were positively related to
19 the drug resistance risk of workers and farmers with PTB, indicating that reducing
20 ambient PM concentrations might decrease the burden of tuberculosis.

21
22 **Key words:** Pulmonary tuberculosis; Drug resistance; Particulate matter; Risk

1 **Strengths and limitations**

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

15

1 Introduction

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

16

17 The detrimental effects of outdoor air pollutants on human health have been widely
18 corroborated, with particulate matter (PM) emerging as a particularly pernicious and
19 pervasive air pollutant that has attracted significant public concern. The most common
20 PMs are inhalable particles (PM₁₀) and fine particles (PM_{2.5}), characterized by
21 aerodynamic diameters of ≤ 10 micrometers and 2.5 micrometers, respectively. Studies
22 have shown that PM exposure not only exacerbates the prevalence of non-

1 communicable diseases, such as asthma, chronic obstructive pulmonary disease
2 (COPD), and cardiovascular disease, but also intensifies the risk of infectious diseases
3 like coronavirus disease 2019, influenza, and tuberculosis⁸⁻¹². Notably, a study in Jinan
4 identified, for the first time, the association between increased PM concentrations and
5 elevated risk of drug resistance among tuberculosis patients¹³. In contrast, a recent study
6 presented conflicting results¹⁴. The evidence regarding the connection between PM
7 concentration and drug resistance risk of patients with tuberculosis is limited and
8 inconclusive, warranting further research.

9
10 Outdoor workers and farmers are more vulnerable to air pollution and have more
11 significant opportunities to contact patients with tuberculosis, placing them at a greater
12 risk of tuberculosis infection. Although this issue is substantial, there is a scarcity of
13 research exploring the effect of PM on drug-resistance risk among outdoor workers and
14 farmers with pulmonary tuberculosis (PTB). To address this research gap, we
15 performed a time-series analysis in eastern China.

17 **Methods**

18 **Study population**

19 We extracted information on PTB cases diagnosed between 2017 and 2021 from the
20 Suzhou Center for Disease Control and Prevention. All patients were registered in the
21 National Tuberculosis Online Registration System. We collected epidemiological data
22 from each case, including gender, age, ethnicity, current address, occupation,

1 comorbidities, pathogen examination, drug resistance, and treatment classification.
2 Drug susceptibility testing, primarily on isoniazid and rifampicin, was conducted at the
3 Fifth People's Hospital of Suzhou, a designated tuberculosis treatment facility in the
4 city.

5
6 We excluded patients with other respiratory-related disorders, immunodeficiencies,
7 prior tuberculosis treatment, and those who experienced changes in their current
8 address during the treatment period to minimize exposure misclassification. In this
9 investigation, DR-TB included either mono-resistant to isoniazid, mono-resistant to
10 rifampicin, or multidrug-resistant to at least isoniazid and rifampicin. Individuals
11 employed in manufacturing, construction, mining, and transportation were identified as
12 workers. Meanwhile, those engaged in agriculture, forestry, animal husbandry, and
13 fishery were defined as farmers.

14 15 **Data on air pollutant concentrations and meteorological factors**

16 From the China Meteorological Data Sharing Center (<http://data.cma.cn/>), we collected
17 data on meteorological factors in Suzhou City between January 1, 2017, and December
18 31, 2021, including daily average temperature (°C), average wind speed (m/s), and
19 relative humidity (%). Additionally, daily average concentrations of six environmental
20 pollutants, namely PM₁₀, PM_{2.5}, sulfur dioxide (SO₂), nitrogen dioxide (NO₂), carbon
21 monoxide (CO), and ozone (O₃), during the same period were retrieved from the
22 National Urban Air Quality Real-Time Reporting Platform

1 (http://106.37.208.233:20035/). The pollutant concentrations were reported in units of
2 $\mu\text{g}/\text{m}^3$, except for CO, which was reported in the unit of mg/m^3 .

3 4 **Statistical analysis**

5 We used a binomial distributed generalized additive model (GAM) to examine the
6 relationship between PM concentration and drug resistance risk of PTB. GAM, with
7 additive smoothing functions, is a powerful analytical tool capable of analyzing
8 complex environmental health data that may exhibit nonlinear or non-monotonic
9 relationships^{15,16}. To control the impacts of potential confounding factors, we adjusted
10 some covariates in the model, including sex, age, season, etiological examination,
11 comorbidity, treatment type, average temperature, average wind speed, and average
12 relative humidity. In addition, we utilized a thin plate spline function with a maximum
13 degree of freedom of two to create smooth terms for three meteorological factors to
14 control their potential nonlinear effects¹⁵.

15
16 According to previous research, the influence of PM exposure on health may have
17 delayed effects^{16,17}. Thus, we calculated the moving average concentration of PM
18 based on the diagnosis date of PTB patients to estimate their exposure levels. We
19 applied eight different lag days to investigate both short-term and relatively long-term
20 effects of PM exposure on the drug resistance risk of PTB, ranging from 0-3 days to 0-
21 180 days. For example, PM concentration with a lag of 0-3 days represented the mean
22 value of the daily average PM concentration on the day of diagnosis and the previous

1 three days. The strength of the association between PM concentration and drug
2 resistance risk of PTB patients was expressed as percentage changes in drug resistance
3 risk and their corresponding 95% confidence intervals (CIs) for every 10-unit increase
4 in PM concentration. Additionally, we conducted subgroup analyses to evaluate the
5 associations in different populations and seasons.

6
7 We performed two sensitivity analyses to assess the robustness of the associations. First,
8 we estimated the associations at different lag days, as mentioned earlier. Second, we
9 fitted double-pollutant models, each incorporating adjustment for one of four gas
10 pollutants while maintaining the same parameter settings as the primary model. This
11 approach allowed us to determine if other gas pollutants influenced the relationship
12 between PM concentration and drug resistance risk of patients.

13
14 All statistical analyses were carried out using R software version 4.2.0 ([https://www.r-](https://www.r-project.org/)
15 [project.org/](https://www.r-project.org/)), and model fitting was achieved using the mgcv package. Statistical tests
16 were two-tailed, with a significance level set at 0.05.

17 18 **Results**

19 **Patient characteristics**

20 The characteristics of study subjects are listed in Table 1. Of the 7868 cases, 241 (3.06%)
21 had DR-TB, with a higher drug resistance rate in males (3.35%) than in females (2.20%)
22 ($\chi^2 = 6.533$, $P = 0.011$). No significant difference was observed in the drug resistance

1 rate between age or ethnic groups. Sputum smear-positive cases had a higher drug
2 resistance rate (5.92%) than sputum smear negative cases (0.03%) ($\chi^2 = 229.556$, P
3 < 0.001). Comorbidities, including HIV/AIDS, diabetes, or pneumoconiosis, did not
4 significantly affect the drug resistance rate. However, newly treated cases had a lower
5 drug resistance rate (2.59%) compared to those with antituberculosis treatment history
6 (11.11%) ($\chi^2 = 101.913$, $P < 0.001$).

7

8 **Outdoor air pollutants and meteorological factors**

9 The median concentrations and interquartile ranges (IQR) of daily outdoor air
10 pollutants and meteorological factors in Suzhou City from 2017 to 2021 are shown in
11 Table 2. The pollutants under observation, including PM₁₀, PM_{2.5}, SO₂, NO₂, CO, and
12 O₃, exhibited median concentrations of 50.00 µg/m³ (IQR: 36.00-74.00), 30.00 µg/m³
13 (IQR: 20.00-46.00), 6.00 µg/m³ (IQR: 5.00-9.00), 37.00 µg/m³ (IQR: 27.00-51.00),
14 0.70 mg/m³ (IQR: 0.50-0.80), and 92.00 µg/m³ (IQR: 65.00-132.00), respectively.

15 Within the same timeframe, the median (IQR) temperature, wind speed, and relative
16 humidity were calculated as 18.40 °C (10.20-25.50), 2.40 m/s (1.90-3.20), and 73.00%
17 (64.00-83.00), respectively. The temporal trends of air pollutant concentrations and
18 meteorological factors are visually represented in Figure 1.

19

20 **PM₁₀ and drug resistance risk**

21 No significant association was observed between PM₁₀ concentration and drug
22 resistance risk across the whole case (Figure 2). However, the association was

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4 1 significant during the winter season on all lag days. The magnitude of this relationship
5
6 2 augmented as the lag interval expanded, culminating in the most salient effects at lag
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9 3 0-180 days, as a 10-unit increment in PM₁₀ concentration was associated with a 231.24%
10
11
12 4 increased risk of drug resistance (95% CI: 35.79, 708.04).
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17 6 In double-pollutant models, PM₁₀ concentration and drug resistance risk remained
18
19 7 significant at lag 0-60 days after adjusting for each of the four gaseous pollutants
20
21
22 8 (Tables S1).
23
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25 9

10 **PM_{2.5} and drug resistance risk**

11 Similarly, no significant relationship was found between PM_{2.5} concentration and drug
12
13 resistance risk among the cases (Figure 3). However, the subgroup analyses disclosed
14
15 that a 10-unit elevation in PM_{2.5} concentration corresponded to a 10.73% (95% CI: 0.49,
16
17 22.02) increased drug resistance risk in male cases at lag 0-3 days and a 16.28% (95%
18
19 CI: 1.20, 33.59) rise in drug resistance risk in cases under 60 years old at lag 0-7 days.
20
21 A positive correlation emerged between PM_{2.5} concentration and drug resistance risk in
22
23 winter at lag 0-3 days, lag 0-15 days, lag 0-90 days, and lag 0-180 days, with the most
24
25 pronounced impact observed at lag 0-180 days. At this time, the risk of drug resistance
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27 surged by 335.06% for each 10-unit increase in PM_{2.5} concentration (95% CI: 17.71,
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22 In double-pollutant models, the significant association between PM_{2.5} concentration

1 and drug resistance risk persisted in male cases at a lag of 0-3 days and those under 60
2 years old at a lag of 0- 7 days after adjusting for SO₂. Moreover, PM_{2.5} concentration
3 continued to exhibit a significant positive association with drug resistance risk in winter
4 at lag 0-15 days, lag 0-30 days, and lag 0-180 days after adjusting for SO₂; at lag 0-180
5 days after adjusting for CO; at lag 0-7 days, lag 0-15 days, and lag 0-90 days after
6 adjusting for O₃ (Table S2).

7

8 **Discussion**

9 This study examined the relationship between PM concentration and drug resistance
10 risk of workers and farmers with PTB in Suzhou City, a prominent industrial metropolis
11 in eastern China. A positive correlation between PM₁₀ concentration and drug
12 resistance risk was observed throughout all lag days in winter. Moreover, PM_{2.5}
13 concentration was found to be positively correlated with drug resistance risk of male
14 cases at lag 0-3 days, cases under 60 years old at lag 0-7 days, and all cases at some lag
15 days during the winter season. To our knowledge, this is the first study to evaluate the
16 relationship between PM concentration and drug resistance risk of PTB cases in specific
17 demographics in China.

18

19 The existing body of literature exploring the association between PM concentration and
20 drug resistance risk of tuberculosis patients is scarce and inconclusive. A case-control
21 study identified a positive association between PM concentration and drug resistance
22 risk of tuberculosis patients¹³. Specifically, PM₁₀ was shown to significantly impact

1 this risk from lag 0-90 days to lag 0-540 days, while PM_{2.5} had a notable effect up to
2 lag 0-540 days. A green environment could mitigate mortality risk of DR-TB patients
3 ^{18,19}. In contrast, another study suggested a protective effect of PM_{2.5} and PM₁₀ against
4 drug resistance risk ¹⁴. In the current, we selected outdoor workers and farmers as the
5 study subjects and did not uncover a significant association between PM concentration
6 and drug resistance risk in the overall analyses. This disparity might stem from
7 differences in PM concentration and composition characteristics ^{13,14}. Other factors
8 such as geography, meteorological conditions, economic level, population density, and
9 *Mycobacterium tuberculosis* strains might influence the relationship between PM and
10 drug resistance risk ²⁰.

11
12 Our findings indicated that elevated levels of PM₁₀ and PM_{2.5} during winter
13 significantly contributed to the drug resistance risk of workers and farmers with PTB.
14 This observation aligned with previous studies highlighting increased health risks from
15 winter PM exposure. For example, a time-series study from 202 counties in the United
16 States revealed the strongest correlation between PM_{2.5} concentration and daily
17 hospitalization rates for cardiovascular and respiratory systems during winter ²¹.
18 Another study from Wuhan, China, suggested that PM had a more pronounced impact
19 on overall mortality, cardiovascular, stroke, and respiratory system mortality rates in
20 winter²². Animal experiments demonstrated that winter exposure to PM_{2.5} caused more
21 severe cardiac toxicity than summer exposure²³, and wintertime PM exhibited higher
22 endotoxin levels than springtime PM ²⁴. PM samples collected in Italy during winter

1 produced more acute toxicity in mouse models than summer-collected samples ²⁵.
2 Seasonality has been recognized as a crucial modifier when evaluating the impact of
3 air pollution on human health. The potential influence of wintertime PM on the drug
4 resistance risk of tuberculosis might be attributed to high concentrations of pollutants,
5 as demonstrated by our time-series graphs. Increased atmospheric boundary layer
6 stability and reduced vertical mixing tendencies result in pollutant retention and
7 regional accumulation, contributing to this phenomenon primarily observed during
8 winters^{26,27}.

9
10 Although Suzhou lacks coal heating systems, low wind speeds and temperatures
11 exacerbate ground-level pollutant accumulation ²⁷. Nonetheless, the rising demand for
12 heating systems may influence this phenomenon through regional transmission and
13 accumulation from northern parts of China ²⁸. Furthermore, PM_{2.5} has a more
14 significant impact than PM₁₀, consistent with studies on air pollutants related to the
15 onset risk of PTB^{29,30}. This observation can be ascribed to smaller particles penetrating
16 deeper into the alveoli and bronchi, resulting in more severe biological toxicity
17 reactions³¹.

18
19 Our study uncovered a relationship between PM_{2.5} and drug resistance risk of male PTB
20 patients at a lag of 0-3 days and a similar association among patients under 60 years old
21 at a lag of 0-7 days. However, no association was observed in these two subgroups at
22 other lag days, necessitating cautious interpretation of the results. Thus, further research

1 is required to determine their biological plausibility. Gender differences may stem from
2 various factors, including lifestyle habits (e.g., smoking), social behaviors (e.g.,
3 engaging in group activities), and physiological differences, which collectively might
4 render men more susceptible to DR-TB ³²⁻³⁴. Previous research has indicated that
5 patients with DR-TB tend to be younger than those with drug-sensitive infections. For
6 example, a systematic review reported that the incidence of drug resistance was 2.53
7 times higher among PTB cases under 65 years old compared to those aged 65 and
8 above³⁵. This finding suggested that older individuals might develop DR-TB due to
9 latent infections acquired before the emergence of drug resistance, while a younger age
10 represents a risk factor for recent transmission³⁶.

11
12 Escalating PM levels could potentially amplify PTB patients' drug resistance risk. The
13 exact machinations driving this phenomenon are yet to be entirely comprehended;
14 however, several contributory factors can be hypothesized. Primarily, the composition
15 of PM extends beyond mere physiochemical elements, encapsulating biological
16 constituents such as microbes and antibiotic-resistant genes. An intriguing study
17 revealed discernible disparities between the microbial consortia and their associated
18 antibiotic-resistant genes present in the air, and those found within terrestrial and
19 marine ecosystems ³⁷. PM has emerged as a principal vector for disseminating
20 antibiotic-resistant genes within the environment ^{38,39}. Thus, the air could harbor more
21 resistant strains and antibiotic-resistance genes in locales characterized by elevated PM
22 concentrations. Secondly, PM can incite oxidative stress and elicit inflammatory

1 responses, which could precipitate structural and functional degradation of alveolar
2 epithelial and endothelial cells ^{40,41}. Furthermore, PM can infiltrate the systemic
3 circulation, provoking vascular dysregulation and systemic inflammation. Such
4 perturbations may aggravate the clinical status of new tuberculosis patients afflicted
5 with chronic pulmonary diseases. This exacerbation might necessitate a complex and
6 protracted diagnostic and treatment regimen, thereby elevating their propensity to
7 develop drug resistance ⁴². Lastly, insights gleaned from a molecular epidemiological
8 investigation underscored that the peril of direct transmission of DR-TB distinctly
9 surpasses resistance acquisition attributable to factors such as the injudicious utilization
10 of antibiotics⁴³. This implies that PM, laden with resistant strains and antibiotic-
11 resistant genes, could potentially bolster the aerial propagation of drug-resistant
12 *Mycobacterium tuberculosis*.

13
14 In conclusion, our results demonstrated that PM concentration might positively
15 correlate with the drug resistance risk of workers and farmers with PTB. Reducing
16 outdoor PM concentration was likely to decrease the burden of tuberculosis.

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

2

3 **Competing interests**

4 None declared.

5

6 **Patient consent for publication**

7 Not required.

8

9 **Data availability statement**

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

12

13 **Author contributions**

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

21

22 **Ethical approval**

23 The present study was approved by the Ethics Committee of Nanjing Medical
24 University, which recognized it as a secondary analysis of retrospective, non-

1 identifiable data employing anonymized, pre-existing public health records, without
2 any direct interaction or intervention with the participants. Given the low-risk nature of
3 this research and the inability to trace the data back to individual subjects, the Ethics
4 Committee granted a waiver for the requirement of informed consent.

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19 *Respiratory medicine* 2015; **3**(12): 963-72.

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

Variables	Drug sensitivity n (%)	Drug resistance n (%)	χ^2	<i>P</i>
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)		

4 *: HIV/AIDS, diabetes, or pneumoconiosis.

5

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	58.55	74.00	283.00
PM _{2.5} (µg/m ³)	3.00	20.00	30.00	37.51	46.00	222.00
SO ₂ (µg/m ³)	2.00	5.00	6.00	7.51	9.00	33.00
NO ₂ (µg/m ³)	3.00	27.00	37.00	40.55	51.00	132.00
CO (mg/m ³)	0.20	0.50	0.70	0.81	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	17.54	25.50	35.70
Average wind speed (m/s)	0.20	1.90	2.40	2.51	3.20	8.20
Average relative humidity (%)	31.00	64.00	73.00	72.51	83.00	99.80

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1

2 **Figure legends**

3

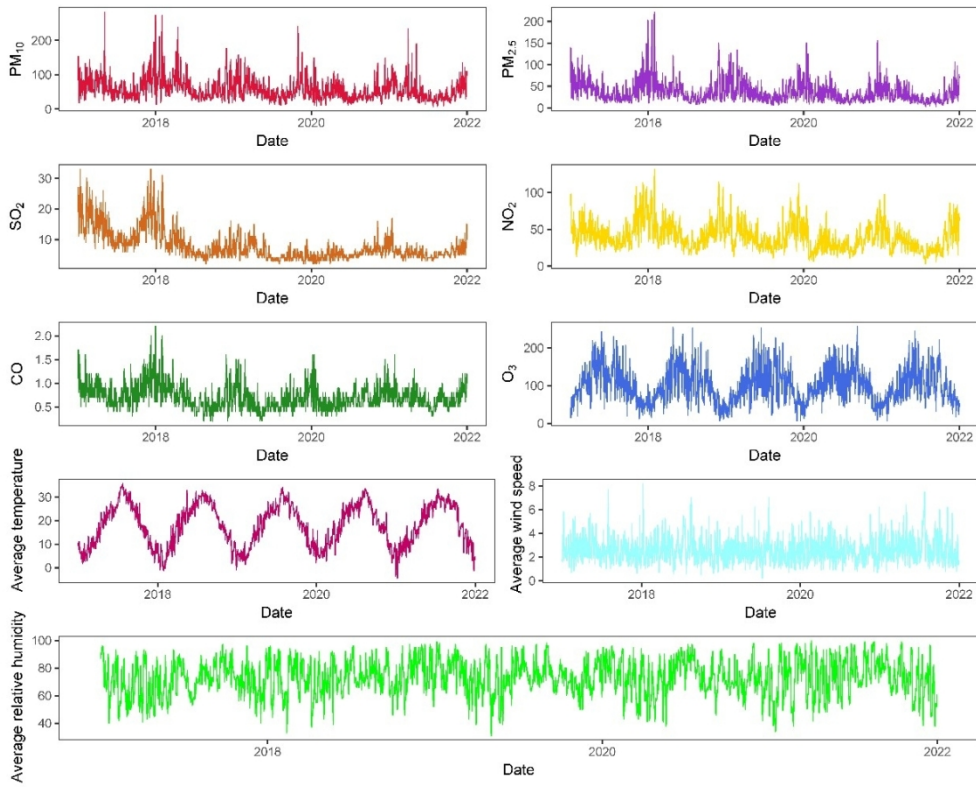
4 Figure 1. The time-series plots of outdoor air pollutant concentrations and
5 meteorological factors in Suzhou City between 2017 and 2021.

6

7 Figure 2. Percentage changes in the risk of drug resistance and their 95% CIs for each
8 10-unit increase in PM₁₀ concentration among workers and farmers with pulmonary
9 tuberculosis in Suzhou City between 2017 and 2021.

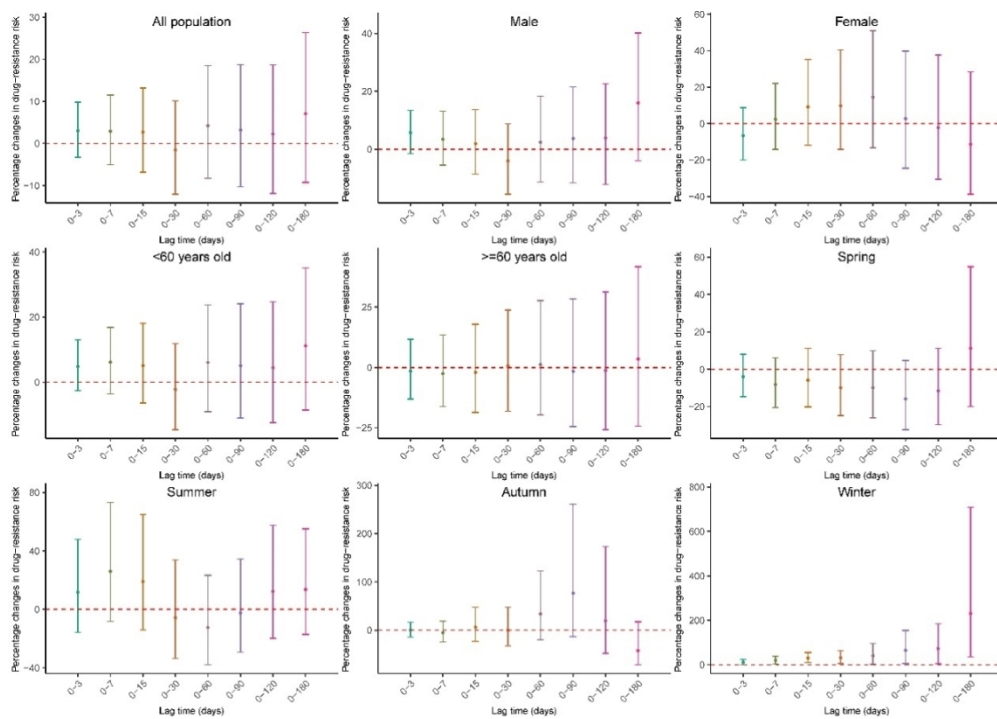
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11 Figure 3. Percentage changes in the risk of drug resistance and their 95% CIs for each
12 10-unit increase in PM_{2.5} concentration among workers and farmers with pulmonary
13 tuberculosis in Suzhou City between 2017 and 2021.

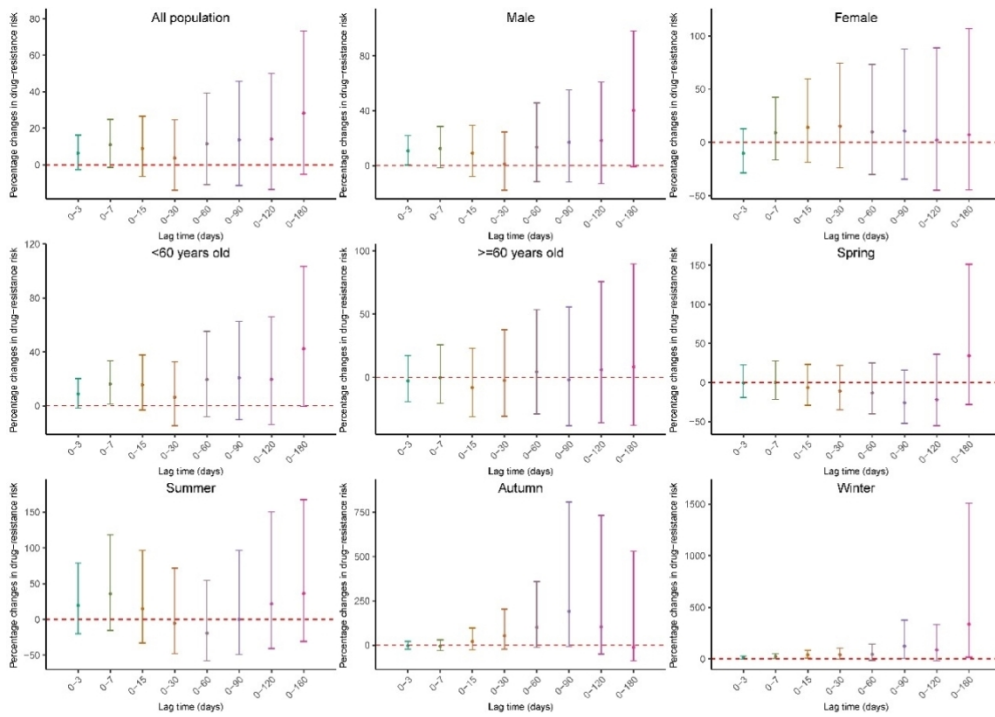


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Supplementary Tables

Table S1. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in PM₁₀ 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)	1.95 (-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)	-2.47 (-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)	0.77 (-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)	-1.74 (-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)	21.29 (-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)	12.29 (-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)	10.70 (-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)	14.39 (-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)	5.32 (-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)	-4.02 (-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)	-3.74 (-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)	-12.42 (-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)	7.44 (-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)	-1.99 (-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)	3.50 (-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)	13.98 (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)	-6.88 (-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)	8.68 (-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)	28.57 (-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)	48.37 (-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)	90.05 (-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)	85.70 (-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)	43.55 (-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)	17.40 (-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)	4.43 (-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)	2.73 (-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)	5.03 (-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)	-6.11 (-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)	24.82 (-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)	16.94 (-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)	35.23 (-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)	32.82 (-9.90, 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)	-3.24 (-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)	-13.44 (-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)	-6.76 (-23.25, 21.67)	-1.91 (-18.63, 18.26)

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	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
Spring	0-30 days	0.67 (-18.13, 23.80)	-5.76 (-26.34, 20.56)	6.60 (-25.70, 52.93)	-3.29 (-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)	1.86 (-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)	3.36 (-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)	1.44 (-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)	1.41 (-29.14, 57.25)	1.86 (-25.93, 40.08)
	0-3 days	-3.97 (-14.66, 8.06)	0.74 (-11.52, 14.71)	-0.69 (-14.90, 15.90)	1.41 (-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)	1.28 (-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)	1.33 (-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)	1.00 (-31.65, 22.77)	-15.66 (-31.25, 3.46)
Summer	0-60 days	-9.83 (-26.02, 9.89)	4.75 (-27.62, 51.58)	52.69 (-18.20, 185.01)	1.00 (-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)	1.00 (-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)	1.54 (-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)	1.09 (-1.13, 206.19)	11.02 (-20.10, 54.25)
	0-3 days	11.69 (-15.67, 47.94)	18.64 (-13.87, 63.43)	3.14 (-29.78, 51.49)	1.03 (-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)	1.44 (-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)	1.00 (-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)	1.00 (-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)	1.02 (-33.51, 83.04)	2.39 (-29.95, 49.67)
Autumn	0-90 days	-2.45 (-29.24, 34.50)	-6.26 (-36.80, 39.04)	-30.37 (-71.47, 69.89)	1.05 (-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)	1.07 (-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)	1.07 (-52.47, 62.27)	14.25 (-17.88, 58.96)
	0-3 days	0.01 (-14.36, 16.80)	-1.13 (-16.46, 17.01)	-6.14 (-26.56, 19.96)	1.01 (-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)	1.03 (-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)	1.03 (-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)	1.09 (-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)	1.04 (-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)	1.04 (-12.77, 333.62)	124.11 (-20.43, 531.22)
Winter	0-120 days	19.11 (-48.07, 173.18)	21.29 (-51.53, 203.53)	-62.48 (-93.36, 112.00)	1.04 (-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)	1.01 (-68.50, 82.86)	-56.28 (-83.71, 17.28)
	0-3 days	11.21 (0.02, 23.65)	10.78 (-3.15, 26.70)	13.19 (-3.58, 32.87)	1.08 (-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)	1.08 (-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)	1.08 (-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)	1.02 (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)	1.05 (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)	1.09 (-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)	1.08 (-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)	1.03 (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

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5 humidity at the same lag time.

6 Model 2: Based on model 1, additionally adjusted for SO₂ at the same lag time.

7 Model 3: Based on model 1, additionally adjusted for NO₂ at the same lag time.

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

9 Model 5: Based on model 1, additionally adjusted for O₃ at the same lag time.
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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)	6.58 (-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)	10.61 (-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)	10.28 (-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)	8.86 (-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)	33.74 (-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)	40.19 (-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)	63.22 (-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)	101.31 (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)	11.39 (-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)	9.88 (-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)	8.47 (-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)	2.45 (-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)	34.65 (-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)	36.06 (-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)	54.74 (-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)	65.88 (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)	-10.25 (-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)	24.50 (-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)	32.33 (-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)	39.30 (-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)	27.75 (-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)	65.29 (-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)	72.41 (-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)	436.86 (-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)	9.17 (-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)	17.40 (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)	20.30 (-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)	13.45 (-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)	39.89 (-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)	59.26 (-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)	99.29 (-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)	171.59 (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)	-5.01 (-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)	-8.85 (-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)	-14.10 (-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)	-1.26 (-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)	23.09 (-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)	0.43 (-44.06, 65.99)	0.16 (-36.01, 56.78)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
Spring	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)	11.11 (-41.98, 112.78)	8.41 (-37.92, 89.32)
	0-3 days	-0.43 (-19.17, 22.66)	9.52 (-12.95, 37.79)	7.80 (-16.04, 38.40)	5.48 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-82.14, 46.56)	-23.57 (-56.43, 34.05)
Summer	0-180 days	34.39 (-28.11, 151.23)	141.37 (-8.21, 534.66)	163.90 (-14.57, 715.14)	5.25 (-2.10, 467.17)	19.03 (-38.83, 131.61)
	0-3 days	19.61 (-20.00, 78.83)	27.39 (-17.91, 97.71)	10.78 (-31.04, 77.98)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (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)	5.25 (-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)	5.25 (-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)	5.25 (-24.08, 25.21)
0-7 days		25.29 (3.69, 51.39)	26.69 (-1.46, 62.90)	20.17 (-7.58, 56.24)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (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 SO₂ at the same lag time.

Model 3: Based on model 1, additionally adjusted for NO₂ at the same lag time.

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

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Model 5: Based on model 1, additionally adjusted for O₃ at the same lag time.

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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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4 1 **Outdoor particulate matter and risk of drug resistance for workers**
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6 2 **and farmers with pulmonary tuberculosis: a population-based time**
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9 3 **series study**
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14 5 Xiaolong Zhang^{1,2,3#}, Zhongqi Li^{2#}, Bilin Tao^{2#}, Ying Fu¹, Caiyan Cui¹, Feixian

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4 28 **Abstract**

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6 29 **Objectives:** The detrimental effects of particulate matter (PM) on human health have
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8
9 30 been widely corroborated. We sought to examine the association of outdoor PM with
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11 31 drug-resistance risk among workers and farmers with pulmonary tuberculosis (PTB).
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17 33 **Design:** We performed a population-based time series study using routinely collected
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19 34 meteorological and TB surveillance data.
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24 36 **Setting:** We selected Suzhou City, China, as the study area. Data on PTB patients and
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27 37 meteorological factors were extracted from the National Tuberculosis Online
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29 38 Registration System and the China Meteorological Data Sharing Center.
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35 40 **Participants:** This study included 7868 PTB patients diagnosed from January 2017 to
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37 41 December 2021 in Suzhou.
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43 43 **Methods:** The generalized additive model was utilized to estimate the effects of
44
45 44 outdoor PM on the drug resistance risk of TB among workers and farmers who usually
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48 45 work outside. Additionally, we conducted subgroup analyses to evaluate the
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50 46 associations in different populations and seasons.
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56 48 **Results:** Despite no significant association between PM with an aerodynamic diameter
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58 49 $\leq 10 \mu\text{m}$ (PM₁₀) and drug-resistant risk in the overall analysis, subgroup analysis
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4 50 observed a significant positive association in the winter season. Similarly, PM with an
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6 51 aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) was significantly associated with drug
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9 52 resistance risk among males at a lag of 0-3 days, people ≤ 60 years with a lag of 0-7
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11 53 days, and in the winter season at a lag of 0-7 days, 0-15 days, 0-90 days, or 0-180 days.
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16
17 55 **Conclusions:** Outdoor PM_{10} and $\text{PM}_{2.5}$ were positively related to the drug resistance
18
19 56 risk of workers and farmers with PTB. Reducing ambient PM pollution may decrease
20
21 57 the burden of TB. Further investigations are needed to verify the association via vitro
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23 58 experiments and extensive cohort studies.
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30 60 **Key words:** tuberculosis; particulate matter; ambient pollutin; drug resistance
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4 62 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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9 64 **STRENGTHS**

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12 65 • This is the first study to evaluate the relationship between PM concentration and
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14 66 drug resistance of TB among the outside working population in eastern China with
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17 67 a large sample size and reliable data.
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22 69 **LIMITATIONS**

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25 70 • PM exposure levels estimated based on the fixed monitoring sites may not
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27 71 accurately represent individual exposure.
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30 72 • This is an observational study, and the specific substances that produce biological
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32 73 effects in air pollutants are unclear.
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75 Introduction

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

90
91 The detrimental effects of outdoor air pollutants on human health have been widely
92 corroborated, with particulate matter (PM) emerging as a particularly pernicious and
93 pervasive air pollutant that has attracted significant public concern.¹⁰ The most common
94 particles are inhalable PMs with an aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) and $2.5 \mu\text{m}$
95 (PM_{2.5}), respectively. Studies have shown that PM exposure not only exacerbates the
96 prevalence of non-communicable diseases, such as chronic obstructive pulmonary

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4 97 disease (COPD),¹¹ but also intensifies the risk of infectious diseases like COVID-19
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6 98 and tuberculosis.^{12,13} A study in Jinan identified an association between increased PM
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9 99 concentrations and the elevated risk of drug resistance among tuberculosis patients¹³.
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12 100 In contrast, a recent study presented conflicting results.¹⁴ The evidence regarding the
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14 101 connection between PM concentration and drug resistance risk of patients with
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17 102 tuberculosis is limited and inconclusive, warranting further research.
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104 Outdoor workers and farmers are more vulnerable to air pollution and have more
105 significant opportunities to contact patients with tuberculosis, placing them at a greater
106 risk of tuberculosis infection. Although this issue is substantial, there is a scarcity of
107 research exploring the effect of PM on drug-resistance risk among outdoor workers
108 with pulmonary tuberculosis (PTB). To address this research gap, we hypothesize that
109 prolonged exposure to elevated concentrations of PM_{2.5} and PM₁₀ is positively
110 correlated with an increased risk of developing DR-TB. To test this hypothesis, we
111 conducted a time-series analysis in eastern China by selecting an outdoor working
112 population in eastern China to compare the correlation between air pollutant levels and
113 DR-TB.
114

115 **Methods**

116 **Study population**

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

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4 119 Tuberculosis Online Registration System and the China Meteorological Data Sharing
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6 120 Center, respectively. We collected epidemiological data from each case, including
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9 121 gender, age, ethnicity, current address, occupation, comorbidities, pathogen
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12 122 examination, drug resistance, and treatment classification. Drug susceptibility testing,
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14 123 primarily on isoniazid and rifampicin, was conducted at the Fifth People's Hospital of
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17 124 Suzhou, a designated tuberculosis treatment facility in the city.
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22 126 PTB diagnosis refers to the national standard of the People's Republic of China (WS-
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24 127 288). We only recruited PTB cases who were workers or farmers working outside and
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27 128 excluded patients with other respiratory-related disorders, and those who experienced
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30 129 changes in their current address during the treatment period to minimize exposure
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33 130 misclassification. We defined DR-TB as mono-resistant to isoniazid, mono-resistant to
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35 131 rifampicin, or multidrug-resistant to at least isoniazid and rifampicin. Individuals
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38 132 employed in manufacturing, construction, mining, and transportation were identified as
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41 133 workers. Meanwhile, those engaged in agriculture, forestry, animal husbandry, and
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43 134 fishery were defined as farmers.
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45 135 46 47 48 136 **Data on air pollutant concentrations and meteorological factors**

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51 137 From the China Meteorological Data Sharing Center (<http://data.cma.cn/>), we collected
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53 138 data on meteorological factors in Suzhou City between January 1, 2017, and December
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56 139 31, 2021, including daily average temperature (°C), average wind speed (m/s), and
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59 140 relative humidity (%). Additionally, daily average concentrations of six environmental
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4 141 pollutants, namely PM₁₀, PM_{2.5}, sulfur dioxide (SO₂), nitrogen dioxide (NO₂), carbon
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6 142 monoxide (CO), and ozone (O₃), during the same period were retrieved from the
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9 143 National Urban Air Quality Real-Time Reporting Platform
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11 144 (<http://106.37.208.233:20035/>). The pollutant concentrations were reported in units of
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14 145 µg/m³, except for CO, which was reported in the unit of mg/m³.
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19 147 **Statistical analysis**

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22 148 We used a binomial distributed generalized additive model (GAM) to examine the
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24 149 relationship between PM and drug resistance risk of PTB. GAM, with additive
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26 150 smoothing functions, is a powerful analytical tool capable of analyzing complex
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28 151 environmental health data that may exhibit nonlinear or non-monotonic relationships¹⁵
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30 152 ¹⁶. To control the impacts of potential confounding factors, we adjusted covariates,
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33 153 including sex, age, season, etiological examination, comorbidity, treatment type,
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35 154 average temperature, average wind speed, and average relative humidity. In addition,
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38 155 we utilized a thin plate spline function with a maximum degree of freedom of two to
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40 156 create smooth terms for three meteorological factors to control their potential nonlinear
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43 157 effects.¹⁵
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51 159 According to previous research, the influence of PM exposure on health may have
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53 160 delayed effects.^{16 17} Thus, we calculated the moving average concentration of PM based
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56 161 on the diagnosis date of PTB patients to estimate their exposure levels. We applied eight
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59 162 different lag days to investigate both short-term and relatively long-term effects of PM
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4 163 exposure on the drug resistance risk of PTB, ranging from 0-3 days to 0-180 days. For
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6 164 example, PM concentration with a lag of 0-3 days represented the mean value of the
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9 165 daily average PM concentration on the day of diagnosis and the previous three days.
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12 166 The strength of the association between PM concentration and drug resistance risk of
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14 167 PTB patients was expressed as percentage changes in drug resistance risk and their
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17 168 corresponding 95% confidence intervals (CIs) for every 10-unit increase in PM
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20 169 concentration. Additionally, we conducted subgroup analyses to evaluate the
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22 170 associations in different populations and seasons.
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27 172 We performed two sensitivity analyses to assess the robustness of the association. First,
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30 173 we estimated the association at different lag days, as mentioned above. Second, we
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33 174 fitted double-pollutant models, each incorporating adjustment for one of four gas
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35 175 pollutants while maintaining the same parameter settings as the primary model. This
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38 176 approach allowed us to determine if other gas pollutants influenced the relationship
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40 177 between PM concentration and drug resistance risk of patients.
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44
45 179 All statistical analyses were carried out using R software version 4.2.0 ([https://www.r-](https://www.r-project.org/)
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47
48 180 [project.org/](https://www.r-project.org/)), and model fitting was achieved using the mgcv package. Statistical tests
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51 181 were two-tailed, with a significance level set at 0.05.
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56 183 **Results**

58 184 **Patient characteristics**

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4 185 The characteristics of study subjects are shown in Table 1. Of the 7868 PTB cases, 241
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6 186 (3.06%) had DR-TB, with a higher drug resistance rate in males (3.35%) than in females
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9 187 (2.20%) ($\chi^2 = 6.533$, $P = 0.011$). No significant difference was observed in the drug
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11
12 188 resistance rate between age or ethnic groups. Sputum smear-positive cases had a higher
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15 189 drug resistance rate (5.92%) than sputum smear-negative cases (0.03%) ($\chi^2 = 229.556$,
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17 190 $P < 0.001$). Comorbidities, including HIV or Acquired Immune Deficiency Syndrome
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19 191 (AIDS), diabetes, or pneumoconiosis, did not significantly affect the drug resistance
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21
22 192 rate. However, those with previous antituberculosis treatment history had an increased
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25 193 risk of drug resistance (11.11% vs. 2.59%, $\chi^2 = 101.913$, $P < 0.001$).
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195 **Outdoor air pollutants and meteorological factors**

196 The median concentrations and interquartile ranges (IQR) of daily outdoor air
197 pollutants and meteorological factors in Suzhou City from 2017 to 2021 are shown in
198 Table 2. The pollutants under observation, including PM₁₀, PM_{2.5}, SO₂, NO₂, CO, and
199 O₃, exhibited median concentrations of 50.00 µg/m³ (IQR: 36.00-74.00), 30.00 µg/m³
200 (IQR: 20.00-46.00), 6.00 µg/m³ (IQR: 5.00-9.00), 37.00 µg/m³ (IQR: 27.00-51.00),
201 0.70 mg/m³ (IQR: 0.50-0.80), and 92.00 µg/m³ (IQR: 65.00-132.00), respectively.
202 Within the same timeframe, the median (IQR) temperature, wind speed, and relative
203 humidity were calculated as 18.40 °C (10.20-25.50), 2.40 m/s (1.90-3.20), and 73.00%
204 (64.00-83.00), respectively. The temporal trends of air pollutant concentrations and
205 meteorological factors are visually represented in Figure 1.
206

207 **PM₁₀ and drug resistance risk**

208 No significant association was observed between PM₁₀ concentration and drug
209 resistance risk across the whole case (Figure 2). However, the association was
210 significant during the winter season on all lag days. The magnitude of this relationship
211 augmented as the lag interval expanded, culminating in the most salient effects at lag
212 0-180 days, as a 10-unit increment in PM₁₀ concentration was associated with a 231.24%
213 increased risk of drug resistance (95% CI: 35.79, 708.04).

214
215 In double-pollutant models, PM₁₀ concentration and drug resistance risk remained
216 significant at a lag of 0-60 days after adjusting for each of the four gaseous pollutants
217 (Table S1).

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219 **PM_{2.5} and drug resistance risk**

220 Similarly, the overall analysis found no significant relationship between PM_{2.5} and drug
221 resistance risk (Figure 3). However, the subgroup analyses disclosed that a 10-unit
222 elevation in PM_{2.5} concentration corresponded to a 10.73% (95% CI: 0.49, 22.02)
223 increased drug resistance risk in male cases at lag 0-3 days and a 16.28% (95% CI: 1.20,
224 33.59) rise in drug resistance risk in cases under 60 years old at lag 0-7 days. A positive
225 correlation emerged between PM_{2.5} concentration and drug resistance risk in winter at
226 lag 0-3 days, lag 0-15 days, lag 0-90 days, and lag 0-180 days, with the most
227 pronounced impact observed at lag 0-180 days. At this time, the risk of drug resistance
228 surged by 335.06% for each 10-unit increase in PM_{2.5} concentration (95% CI: 17.71,

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9 231 In double-pollutant models, the significant association between PM_{2.5} concentration
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11 232 and drug resistance risk persisted in male cases at a lag of 0-3 days and those under 60
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13 233 years old at a lag of 0-7 days after adjusting for SO₂. Moreover, PM_{2.5} concentration
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15 234 continued to exhibit a significant positive association with drug resistance risk in winter
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17 235 at lag 0-15 days, lag 0-30 days, and lag 0-180 days after adjusting for SO₂; at lag 0-180
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19 236 days after adjusting for CO; at lag 0-7 days, lag 0-15 days, and lag 0-90 days after
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21 237 adjusting for O₃ (Table S2).

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28 29 30 239 **Discussion**

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32 240 This study examined the relationship between PM concentration and drug resistance
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34 241 risk of workers and farmers with PTB in Suzhou City, a prominent industrial metropolis
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36 242 in eastern China. A positive correlation between PM₁₀ concentration and drug
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38 243 resistance risk was observed throughout all lag days in winter. Moreover, PM_{2.5}
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40 244 concentration was found to be positively correlated with drug resistance risk of male
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42 245 cases at lag 0-3 days, cases under 60 years old at lag 0-7 days, and all cases at some lag
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44 246 days during the winter season. To our knowledge, this is the first study to evaluate the
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46 247 relationship between PM concentration and drug resistance of PTB among the outside
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48 248 working populations in China. This study emphasizes the importance of air quality in
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50 249 the prevention and control of infectious diseases. It is necessary to take a comprehensive,
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52 250 cross-sectoral approach to effectively control air pollution and reduce the burden of
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4 251 drug resistance in tuberculosis. We suggest combining air quality control measures with
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6 252 the existing tuberculosis prevention and control programs, such as strengthening
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9 253 screening and protection of high-risk groups in seasons with severe air pollution, to
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11 254 facilitate the early detection and management of drug-resistant tuberculosis.
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17 256 The existing body of literature exploring the association between PM concentration and
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19 257 drug resistance risk of tuberculosis patients is scarce and inconclusive. A case-control
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22 258 study identified a positive association between PM concentration and drug resistance
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24 259 risk of tuberculosis patients.¹³ Specifically, PM₁₀ was shown to significantly impact this
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26 260 risk from lag 0-90 days to lag 0-540 days, while PM_{2.5} had a notable effect up to lag 0-
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28 261 540 days. A green environment could mitigate mortality risk of DR-TB patients.^{18,19} In
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30 262 contrast, another study suggested a protective effect of PM_{2.5} and PM₁₀ against drug
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32 263 resistance risk.¹⁴ In the current study, we selected outdoor workers and farmers as the
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34 264 study subjects and did not uncover a significant association between PM concentration
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36 265 and drug resistance risk in the overall analyses. This disparity might stem from
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38 266 differences in PM concentration and composition characteristics.^{13,14} Other factors such
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40 267 as geography, meteorological conditions, economic level, population density, and
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42 268 *Mycobacterium tuberculosis* strains might influence the relationship between PM and
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44 269 drug resistance risk.²⁰
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56 271 Our findings indicated that elevated levels of PM₁₀ and PM_{2.5} during winter
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58 272 significantly contributed to the drug resistance risk of workers and farmers with PTB.
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4 273 This observation aligned with previous studies highlighting increased health risks from
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6 274 winter PM exposure. For example, a time-series study from 202 counties in the United
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9 275 States revealed the strongest correlation between PM_{2.5} concentration and daily
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11 276 hospitalization rates for cardiovascular and respiratory systems during winter.²¹
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14 277 Another study from Wuhan, China, suggested that PM had a more pronounced impact
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16 278 on overall mortality, cardiovascular, stroke, and respiratory system mortality rates in
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18 279 winter²². Animal experiments demonstrated that winter exposure to PM_{2.5} caused more
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20 280 severe cardiac toxicity than summer exposure,²³ and wintertime PM exhibited higher
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22 281 endotoxin levels than springtime PM.²⁴ PM samples collected in Italy during winter
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24 282 produced more acute toxicity in mouse models than summer-collected samples.²⁵
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26 283 Seasonality has been recognized as a crucial modifier when evaluating the impact of air
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28 284 pollution on human health. The potential influence of wintertime PM on the drug
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30 285 resistance risk of tuberculosis might be attributed to high concentrations of pollutants,
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32 286 as demonstrated by our time-series graphs. Studies have indicated that increased
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34 287 atmospheric boundary layer stability and reduced vertical mixing tendencies in winter
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36 288 result in pollutant retention and regional accumulation; this may account for the
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38 289 increased risk of resistance observed in winter.^{26,27}
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50 291 Although Suzhou lacks coal heating systems, low wind speeds and temperatures
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52 292 exacerbate ground-level pollutant accumulation.²⁷ Nonetheless, the rising demand for
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54 293 heating systems may influence this phenomenon through regional transmission and
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56 294 accumulation from northern parts of China.²⁸ Furthermore, PM_{2.5} has a more significant
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4 295 impact than PM₁₀, consistent with studies on air pollutants related to the onset risk of
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6 296 PTB.^{29,30} This observation can be ascribed to smaller particles penetrating deeper into
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9 297 the alveoli and bronchi, resulting in more severe biological toxicity reactions.³¹
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14 299 Our study uncovered a relationship between PM_{2.5} and drug resistance risk of male PTB
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17 300 patients at a lag of 0-3 days and a similar association among patients under 60 years old
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19 301 at a lag of 0-7 days. However, no association was observed in these two subgroups at
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21
22 302 other lag days, necessitating cautious interpretation of the results. Thus, further research
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24 303 is required to determine their biological plausibility. The difference in different lag days
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26 304 may be related to individual immunity. For example, individuals with poor immunity
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28 305 may be exposed for a few weeks to increase the risk of developing resistance, while
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30 306 those with better immunity may take longer.³² Gender differences may stem from
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33 307 various factors, including lifestyle habits (e.g., smoking), social behaviors (e.g.,
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35 308 engaging in group activities), and physiological differences, which collectively might
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38 309 render men more susceptible to DR-TB.³³⁻³⁵ Previous research has indicated that
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40 310 patients with DR-TB tend to be younger than those with drug-sensitive infections. For
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43 311 example, a systematic review reported that the incidence of drug resistance was 2.53
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45 312 times higher among PTB cases under 65 years old compared to those aged 65 and
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47 313 above.³⁶ This finding suggested that older individuals might develop DR-TB due to
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49 314 latent infections acquired before the emergence of drug resistance, while a younger age
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52 315 represents a risk factor for recent transmission.³⁷
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4 317 Escalating PM levels could potentially amplify PTB patients' drug resistance risk. The
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6 318 exact machinations driving this phenomenon are yet to be entirely comprehended;
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9 319 however, several contributory factors can be hypothesized. Primarily, the composition
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11 320 of PM extends beyond mere physiochemical elements, encapsulating biological
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14 321 constituents such as microbes and antibiotic-resistant genes. An intriguing study
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17 322 revealed discernible disparities between the microbial consortia and their associated
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20 323 antibiotic-resistant genes present in the air, and those found within terrestrial and
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23 324 marine ecosystems.³⁸ PM has emerged as a principal vector for disseminating
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26 325 antibiotic-resistant genes within the environment.^{39,40} Thus, the air could harbor more
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29 326 resistant strains and antibiotic-resistance genes in locales characterized by elevated PM
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32 327 concentrations. Secondly, PM can incite oxidative stress and elicit inflammatory
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35 328 responses, which could precipitate structural and functional degradation of alveolar
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38 329 epithelial and endothelial cells.^{41,42} Furthermore, PM can infiltrate the systemic
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41 330 circulation, provoking vascular dysregulation and systemic inflammation.⁴³ Such
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44 331 perturbations may aggravate the clinical status of new tuberculosis patients afflicted
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47 332 with chronic pulmonary diseases.⁴⁴ This exacerbation might necessitate a complex and
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50 333 protracted diagnostic and treatment regimen, thereby elevating their propensity to
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53 334 develop drug resistance.⁴⁵ Lastly, insights gleaned from a molecular epidemiological
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56 335 investigation underscored that the peril of direct transmission of DR-TB distinctly
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59 336 surpasses resistance acquisition attributable to factors such as the injudicious utilization
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337 of antibiotics.⁴⁶ This implies that PM, laden with resistant strains and antibiotic-
338 resistant genes, could potentially bolster the aerial propagation of drug-resistant

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9 341 This study has several limitations. First, we estimated PM exposure relying on
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11 342 stationary monitoring data, which may not accurately reflect individual exposure.
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13 343 Future research should utilize mobile monitoring devices or geographic information
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15 344 systems (GIS) for more precise assessments. Second, we only measured the drug
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17 345 resistance to rifampicin and isoniazid, restricting our analysis of the risk of resistance
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19 346 to other antituberculosis drugs. Expanding the sample size to include a broader range
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21 347 of drug-resistant tuberculosis is essential for elucidating the relationship between PM
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23 348 exposure and resistance mechanisms. Third, besides air pollution, other factors, such as
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25 349 tobacco smoking, alcohol consumption, and socioeconomic status, may also affect the
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27 350 association between PM and drug resistance. Future studies should integrate these
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29 351 variables to provide a comprehensive understanding of the multifactorial influences of
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31 352 PM on drug resistance in PTB patients.
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43 354 **Conclusion**

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45 355 In conclusion, our study demonstrated a positive association between outdoor PM₁₀ and
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47 356 PM_{2.5} concentrations and drug-resistant tuberculosis among workers and farmers who
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49 357 usually work outside. Our findings indicate the role of reducing ambient PM levels in
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51 358 alleviating the burden of infectious disease. Further research, including in vitro
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53 359 experiments and extensive cohort studies, is needed to confirm the association and
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55 360 explore the long-term effects of air pollution intervention measures.
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361 **Data availability statement**

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

366 **Ethics statements**

367 **Patient consent for publication**

368 Not required.

369 **Ethical approval**

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

377 **Contributors**

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

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

386

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

394

395 **Competing interests**

396 None declared.

397

398 **Patient and public involvement**

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

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4 578 **Figure legends**

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9 580 Figure 1. Time-series plots of outdoor air pollutants and meteorological factors in
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12 581 Suzhou City between 2017 and 2021.

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17 583 Figure 2. Percentage changes in the risk of drug-resistant tuberculosis and their 95%
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20 584 CIs for each 10-unit increase in PM₁₀ concentration in Suzhou City between 2017 and
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27 587 Figure 3. Percentage changes in the risk of drug-resistant tuberculosis and their 95%
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30 588 CIs for each 10-unit increase in PM_{2.5} concentration in Suzhou City between 2017 and
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591 Table 1. Characteristics of study subjects.

Variables	Drug resistance		χ^2	<i>P</i>
	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)		

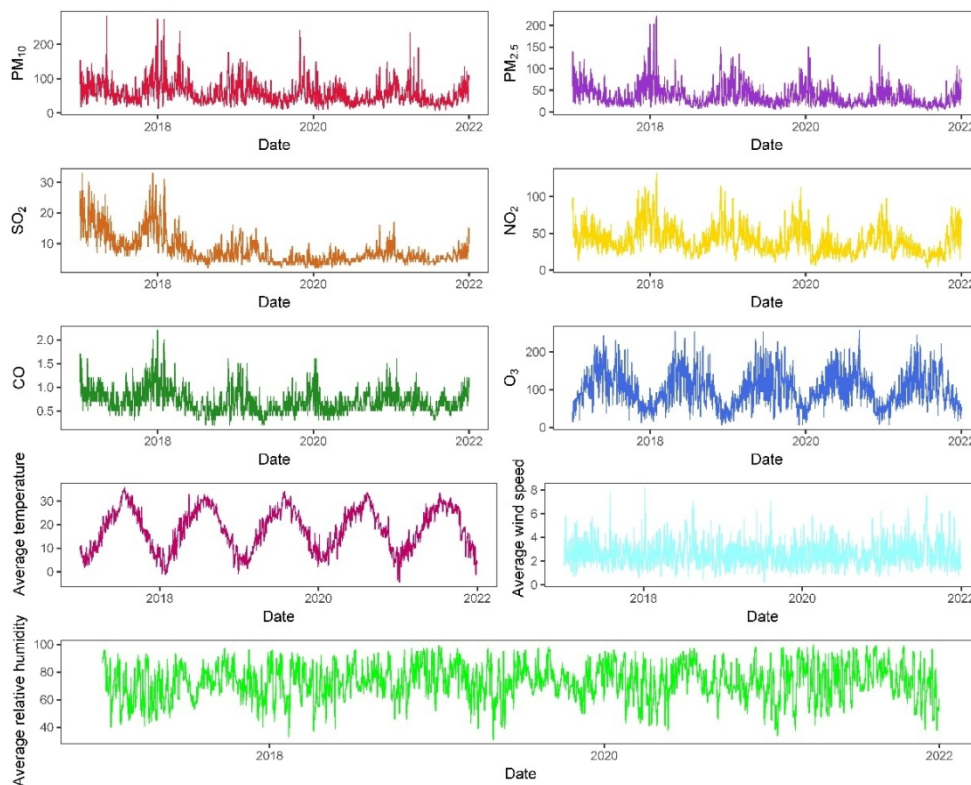
592 *: HIV/AIDS, diabetes, or pneumoconiosis.

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

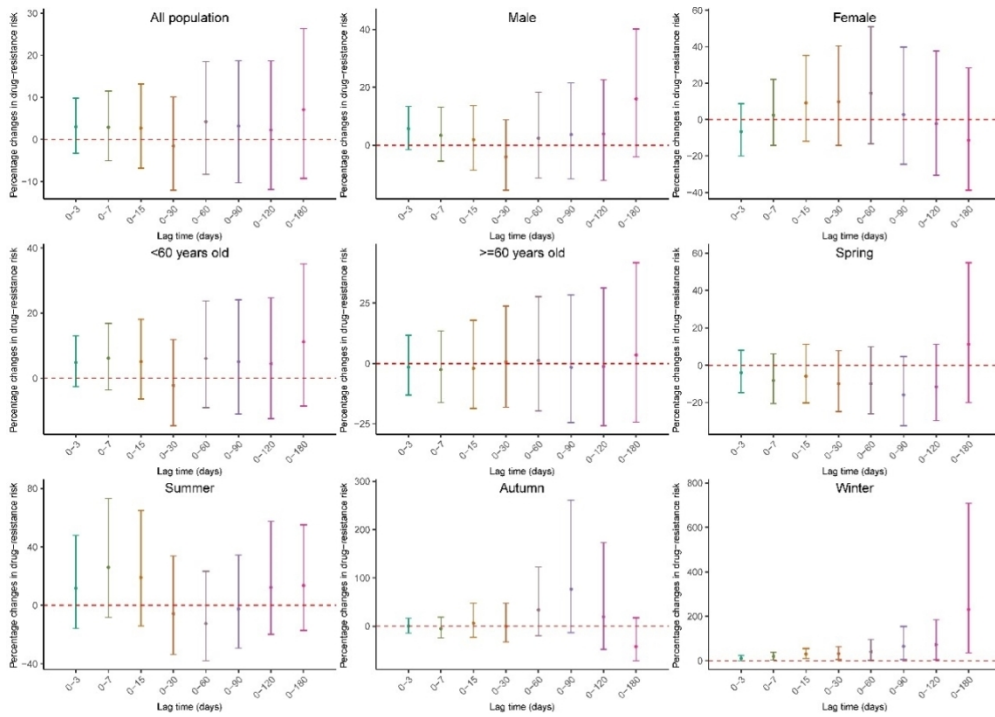
Variables	Minimum	Q25	Median	Mean	Q75	Maximum
Outdoor air pollutants						
PM ₁₀ (µg/m ³)	7.00	36.00	50.00	58.89	74.00	283.00
PM _{2.5} (µg/m ³)	3.00	20.00	30.00	37.15	46.00	222.00
SO ₂ (µg/m ³)	2.00	5.00	6.00	7.84	9.00	33.00
NO ₂ (µg/m ³)	3.00	27.00	37.00	40.63	51.00	132.00
CO (mg/m ³)	0.20	0.50	0.70	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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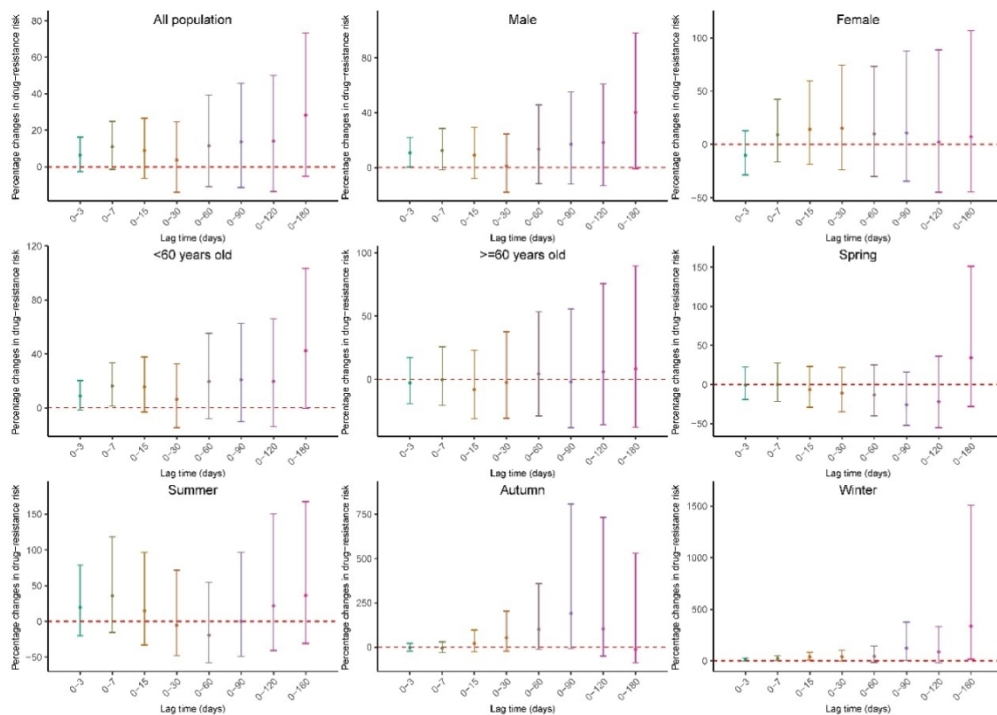


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146x103mm (220 x 220 DPI)



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 PM₁₀ 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)	2.82 (-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)	1.11 (-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)	1.16 (-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)	1.41 (-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)	1.88 (-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)	1.67 (-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)	1.15 (-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)	1.19 (-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)	1.12 (-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)	1.11 (-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)	-3.19 (-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)	1.15 (-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)	1.18 (-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)	1.18 (-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)	3.12 (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)	-6.18 (-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)	0.19 (-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)	12.18 (-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)	23.18 (-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)	7.11 (-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)	0.11 (-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)	-10.10 (-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)	6.10 (-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)	7.12 (-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)	1.17 (-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)	17.19 (-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)	1.19 (-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)	1.11 (-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)	2.19 (-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)	-4.11 (-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)	-9.11 (-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)	-3.16 (-23.25, 21.67)	-1.91 (-18.63, 18.26)

	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5
Spring	0-30 days	0.67 (-18.13, 23.80)	-5.76 (-26.34, 20.56)	6.60 (-25.70, 52.93)	-3.29 (-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)	1.86 (-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)	3.36 (-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)	1.44 (-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)	1.41 (-29.14, 57.25)	1.86 (-25.93, 40.08)
	0-3 days	-3.97 (-14.66, 8.06)	0.74 (-11.52, 14.71)	-0.69 (-14.90, 15.90)	1.41 (-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)	1.28 (-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)	1.33 (-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)	1.00 (-31.65, 22.77)	-15.66 (-31.25, 3.46)
Summer	0-60 days	-9.83 (-26.02, 9.89)	4.75 (-27.62, 51.58)	52.69 (-18.20, 185.01)	1.00 (-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)	1.00 (-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)	1.54 (-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)	1.19 (-1.13, 206.19)	11.02 (-20.10, 54.25)
	0-3 days	11.69 (-15.67, 47.94)	18.64 (-13.87, 63.43)	3.14 (-29.78, 51.49)	1.23 (-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)	1.44 (-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)	1.40 (-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)	1.20 (-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)	1.02 (-33.51, 83.04)	2.39 (-29.95, 49.67)
Autumn	0-90 days	-2.45 (-29.24, 34.50)	-6.26 (-36.80, 39.04)	-30.37 (-71.47, 69.89)	1.35 (-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)	1.17 (-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)	1.17 (-52.47, 62.27)	14.25 (-17.88, 58.96)
	0-3 days	0.01 (-14.36, 16.80)	-1.13 (-16.46, 17.01)	-6.14 (-26.56, 19.96)	1.01 (-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)	1.28 (-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)	1.43 (-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)	1.19 (-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)	1.34 (-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)	1.94 (-12.77, 333.62)	124.11 (-20.43, 531.22)
Winter	0-120 days	19.11 (-48.07, 173.18)	21.29 (-51.53, 203.53)	-62.48 (-93.36, 112.00)	1.40 (-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)	1.41 (-68.50, 82.86)	-56.28 (-83.71, 17.28)
	0-3 days	11.21 (0.02, 23.65)	10.78 (-3.15, 26.70)	13.19 (-3.58, 32.87)	1.18 (-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)	1.25 (-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)	1.30 (-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)	1.22 (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)	1.20 (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)	1.19 (-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)	1.18 (-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)	1.13 (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

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humidity at the same lag time.

Model 2: Based on model 1, additionally adjusted for SO₂ at the same lag time.

Model 3: Based on model 1, additionally adjusted for NO₂ 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 O₃ at the same lag time.

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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)	6.58 (-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)	10.61 (-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)	10.28 (-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)	8.86 (-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)	33.74 (-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)	40.19 (-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)	63.22 (-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)	101.31 (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)	11.39 (-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)	9.88 (-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)	8.47 (-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)	2.45 (-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)	34.65 (-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)	36.06 (-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)	54.74 (-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)	65.88 (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)	-10.25 (-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)	24.50 (-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)	32.33 (-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)	39.30 (-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)	27.75 (-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)	65.29 (-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)	72.41 (-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)	436.86 (-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)	9.17 (-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)	17.40 (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)	20.30 (-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)	13.45 (-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)	39.89 (-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)	59.26 (-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)	99.29 (-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)	171.59 (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)	-5.01 (-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)	-8.85 (-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)	-14.10 (-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)	-1.26 (-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)	23.09 (-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)	0.43 (-44.06, 65.99)	0.16 (-36.01, 56.78)

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	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5	
Spring	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)	11.11 (-41.98, 112.78)	8.41 (-37.92, 89.32)	
	0-3 days	-0.43 (-19.17, 22.66)	9.52 (-12.95, 37.79)	7.80 (-16.04, 38.40)	5.48 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (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 SO₂ at the same lag time.

Model 3: Based on model 1, additionally adjusted for NO₂ at the same lag time.

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

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Model 5: Based on model 1, additionally adjusted for O₃ at the same lag time.

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BMJ Open

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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Primary Subject Heading:	Epidemiology
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Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES



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4 1 **Outdoor particulate matter and risk of drug resistance for workers**
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6 2 **and farmers with pulmonary tuberculosis: a population-based time**
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9 3 **series study in Suzhou, China**
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14 5 Xiaolong Zhang^{1,2,3#}, Zhongqi Li^{2#}, Bilin Tao^{2#}, Ying Fu¹, Caiyan Cui¹, Feixian

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4 28 **Abstract**

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6 29 **Objectives:** The detrimental effects of particulate matter (PM) on human health have
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8
9 30 been widely corroborated. We aimed to examine the association between outdoor PM
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11 31 and the drug-resistance risk among workers and farmers with pulmonary tuberculosis
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13 32 (PTB).
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19 34 **Design:** We performed a population-based time series study using routinely collected
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21 35 meteorological and TB surveillance data.
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27 37 **Setting:** We selected Suzhou City, China, as the study area. Data on PTB patients and
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29 38 meteorological factors were extracted from the National Tuberculosis Online
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31 39 Registration System and the China Meteorological Data Sharing Center.
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37 41 **Participants:** This study included 7868 PTB patients diagnosed from January 2017 to
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39 42 December 2021 in Suzhou.
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44 44 **Methods:** The generalized additive model was utilized to estimate the effects of
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46 45 outdoor PM on the drug resistance risk of TB among workers and farmers who typically
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48 46 work outdoors. Moreover, subgroup analyses were carried out to evaluate the
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50 47 associations in different populations and seasons.
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56 49 **Results:** Although there was no significant association between PM with an
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4 50 aerodynamic diameter $\leq 10 \mu\text{m}$ (PM_{10}) and drug-resistant risk in the overall analysis,
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7 51 subgroup analysis revealed a significant positive association in the winter season.
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9 52 Similarly, PM with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) was significantly
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12 53 associated with drug resistance risk among males with a lag of 0-3 days, people ≤ 60
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14 54 years with a lag of 0-7 days, and in the winter season with a lag of 0-7 days, 0-15 days,
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17 55 0-90 days, or 0-180 days.
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22 57 **Conclusions:** Outdoor PM_{10} and $\text{PM}_{2.5}$ were positively related to the drug resistance
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24 58 risk of workers and farmers with PTB. Reducing ambient PM pollution might reduce
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27 59 the burden of TB. Further research is required to verify the association through in vitro
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30 60 experiments and extensive cohort studies.
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35 62 **Key words:** tuberculosis; particulate matter; ambient pollutin; drug resistance
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4 64 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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6 65 **STRENGTHS**

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9 66 • This study utilized a generalized additive model to evaluate the relationship
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11 67 between particulate matter concentration and the drug resistance risk of pulmonary
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13 68 tuberculosis among the outdoor working population.
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16 69 • This approach enabled the analysis of complex environmental health data that
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19 70 might present nonlinear or non-monotonic relationships.
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25 72 **LIMITATIONS**

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27 73 • Particulate matter exposure levels estimated based on the fixed monitoring sites
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29 74 may not precisely reflect individual exposure.
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32 75 • As an observational study, the specific substances within air pollutants that
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35 76 generate biological effects remain unclear.
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78 Introduction

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

93
94 The detrimental effects of outdoor air pollutants on human health have been widely
95 corroborated, with particulate matter (PM) emerging as a particularly pernicious and
96 pervasive air pollutant that has attracted significant public concern.¹⁰ The most common
97 particles are inhalable PMs with an aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) and $2.5 \mu\text{m}$
98 (PM_{2.5}), respectively. Studies have shown that PM exposure not only exacerbates the
99 prevalence of non-communicable diseases, such as chronic obstructive pulmonary

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4 100 disease (COPD),¹¹ but also intensifies the risk of infectious diseases like COVID-19
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6 101 and tuberculosis.^{12,13} A study in Jinan identified an association between increased PM
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9 102 concentrations and the elevated risk of drug resistance among tuberculosis patients¹³.
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11 103 However, a recent study presented conflicting results.¹⁴ The evidence regarding the
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14 104 connection between PM concentration and drug resistance risk of patients with
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17 105 tuberculosis is limited and inconclusive, warranting further research.
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22 107 Outdoor workers and farmers are more vulnerable to air pollution and have more
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24 108 significant opportunities to contact patients with tuberculosis, placing them at a greater
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27 109 risk of tuberculosis infection. Although this issue is substantial, there is a scarcity of
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30 110 research exploring the effect of PM on drug-resistance risk among outdoor workers
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32 111 with pulmonary tuberculosis (PTB). To address this research gap, we hypothesize that
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35 112 prolonged exposure to elevated concentrations of PM_{2.5} and PM₁₀ is positively
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38 113 correlated with an increased risk of developing DR-TB. To test this hypothesis, we
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41 114 conducted a time-series analysis in eastern China by selecting an outdoor working
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44 115 population in eastern China to compare the correlation between air pollutant levels and
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46 116 DR-TB.

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118 **Methods**

119 **Study population**

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

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4 122 Tuberculosis Online Registration System and the China Meteorological Data Sharing
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6 123 Center, respectively. We collected epidemiological data from each case, including
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9 124 gender, age, ethnicity, current address, occupation, comorbidities, pathogen
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12 125 examination, drug resistance, and treatment classification. Drug susceptibility testing,
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14 126 primarily on isoniazid and rifampicin, was conducted at the Fifth People's Hospital of
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17 127 Suzhou, a designated tuberculosis treatment facility in the city.
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22 129 PTB diagnosis refers to the national standard of the People's Republic of China (WS-
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24 130 288). We only recruited PTB cases from workers or farmers working outside and
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27 131 excluded patients with other respiratory-related disorders and those who experienced
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30 132 changes in their current address during the treatment period to minimize exposure
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33 133 misclassification. We defined DR-TB as mono-resistant to isoniazid, mono-resistant to
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35 134 rifampicin, or multidrug-resistant to at least isoniazid and rifampicin. Individuals
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38 135 employed in manufacturing, construction, mining, and transportation were identified as
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41 136 workers. Meanwhile, those engaged in agriculture, forestry, animal husbandry, and
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43 137 fishery were defined as farmers.
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45 138 46 47 48 139 **Data on air pollutant concentrations and meteorological factors**

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51 140 From the China Meteorological Data Sharing Center (<http://data.cma.cn/>), we collected
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53 141 data on meteorological factors in Suzhou City between January 1, 2017, and December
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56 142 31, 2021, including daily average temperature (°C), average wind speed (m/s), and
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59 143 relative humidity (%). Additionally, daily average concentrations of six environmental
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4 144 pollutants, namely PM₁₀, PM_{2.5}, sulfur dioxide (SO₂), nitrogen dioxide (NO₂), carbon
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6 145 monoxide (CO), and ozone (O₃), during the same period were retrieved from the
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9 146 National Urban Air Quality Real-Time Reporting Platform
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11 147 (<http://106.37.208.233:20035/>). The pollutant concentrations were reported in units of
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14 148 µg/m³, except for CO, which was reported in the unit of mg/m³.

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19 150 **Statistical analysis**

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22 151 We used a binomial distributed generalized additive model (GAM) to examine the
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24 152 relationship between PM and drug resistance risk of PTB. GAM, with additive
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26 153 smoothing functions, is a powerful analytical tool capable of analyzing complex
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28 154 environmental health data that may exhibit nonlinear or non-monotonic relationships¹⁵
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30 155 ¹⁶. To control the impacts of potential confounding factors, we adjusted covariates,
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33 156 including sex, age, season, etiological examination, comorbidity, treatment type,
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35 157 average temperature, average wind speed, and average relative humidity. In addition,
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38 158 we utilized a thin plate spline function with a maximum degree of freedom of two to
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41 159 create smooth terms for three meteorological factors to control their potential nonlinear
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44 160 effects.¹⁵

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50 162 According to previous research, the influence of PM exposure on health may have
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52 163 delayed effects.^{16 17} Thus, we calculated the moving average concentration of PM based
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55 164 on the diagnosis date of PTB patients to estimate their exposure levels. We applied eight
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58 165 different lag days to investigate both short-term and relatively long-term effects of PM
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4 166 exposure on the drug resistance risk of PTB, ranging from 0-3 days to 0-180 days. For
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6 167 example, PM concentration with a lag of 0-3 days represented the mean value of the
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9 168 daily average PM concentration on the day of diagnosis and the previous three days.
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12 169 The strength of the association between PM concentration and drug resistance risk of
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14 170 PTB patients was expressed as percentage changes in drug resistance risk and their
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17 171 corresponding 95% confidence intervals (CIs) for every 10-unit increase in PM
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20 172 concentration. Additionally, we conducted subgroup analyses to evaluate the
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22 173 associations in different populations and seasons.
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27 175 We performed two sensitivity analyses to assess the robustness of the association. First,
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30 176 we estimated the association at different lag days, as mentioned above. Second, we
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33 177 fitted double-pollutant models, each incorporating adjustment for one of four gas
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35 178 pollutants while maintaining the same parameter settings as the primary model. This
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38 179 approach allowed us to determine if other gas pollutants influenced the relationship
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40 180 between PM concentration and drug resistance risk of patients.
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45 182 All statistical analyses were carried out using R software version 4.2.0 ([https://www.r-](https://www.r-project.org/)
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48 183 [project.org/](https://www.r-project.org/)), and model fitting was achieved using the `mgcv` package. Statistical tests
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51 184 were two-tailed, with a significance level set at 0.05.
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55 186 **Results**

56 187 **Patient characteristics**

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4 188 The characteristics of study subjects are shown in Table 1. Of the 7868 PTB cases, 241
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6 189 (3.06%) had DR-TB, with a higher drug resistance rate in males (3.35%) than in females
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9 190 (2.20%) ($\chi^2 = 6.533$, $P = 0.011$). No significant difference was observed in the drug
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11 191 resistance rate between age or ethnic groups. Sputum smear-positive cases had a higher
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13 192 drug resistance rate (5.92%) than sputum smear-negative cases (0.03%) ($\chi^2 = 229.556$,
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15 193 $P < 0.001$). Comorbidities, including HIV or Acquired Immune Deficiency Syndrome
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17 194 (AIDS), diabetes, or pneumoconiosis, did not significantly affect the drug resistance
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19 195 rate. However, those with previous antituberculosis treatment history had an increased
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21 196 risk of drug resistance (11.11% vs. 2.59%, $\chi^2 = 101.913$, $P < 0.001$).
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30 198 **Outdoor air pollutants and meteorological factors**

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32 199 The median concentrations and interquartile ranges (IQR) of daily outdoor air
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34 200 pollutants and meteorological factors in Suzhou City from 2017 to 2021 are shown in
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36 201 Table 2. The pollutants under observation, including PM₁₀, PM_{2.5}, SO₂, NO₂, CO, and
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38 202 O₃, exhibited median concentrations of 50.00 µg/m³ (IQR: 36.00-74.00), 30.00 µg/m³
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40 203 (IQR: 20.00-46.00), 6.00 µg/m³ (IQR: 5.00-9.00), 37.00 µg/m³ (IQR: 27.00-51.00),
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42 204 0.70 mg/m³ (IQR: 0.50-0.80), and 92.00 µg/m³ (IQR: 65.00-132.00), respectively.
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45 205 Within the same timeframe, the median (IQR) temperature, wind speed, and relative
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47 206 humidity were calculated as 18.40 °C (10.20-25.50), 2.40 m/s (1.90-3.20), and 73.00%
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49 207 (64.00-83.00), respectively. The temporal trends of air pollutant concentrations and
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51 208 meteorological factors are visually represented in Figure 1.
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210 **PM₁₀ and drug resistance risk**

211 No significant association was observed between PM₁₀ concentration and drug
212 resistance risk across the whole case (Figure 2). However, the association was
213 significant during the winter season on all lag days. The magnitude of this relationship
214 augmented as the lag interval expanded, culminating in the most salient effects at lag
215 0-180 days, as a 10-unit increment in PM₁₀ concentration was associated with a 231.24%
216 increased risk of drug resistance (95% CI: 35.79, 708.04).

217
218 In double-pollutant models, PM₁₀ concentration and drug resistance risk remained
219 significant at a lag of 0-60 days after adjusting for each of the four gaseous pollutants
220 (Table S1).

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222 **PM_{2.5} and drug resistance risk**

223 Similarly, the overall analysis found no significant relationship between PM_{2.5} and drug
224 resistance risk (Figure 3). However, the subgroup analyses disclosed that a 10-unit
225 elevation in PM_{2.5} concentration corresponded to a 10.73% (95% CI: 0.49, 22.02)
226 increased drug resistance risk in male cases at lag 0-3 days and a 16.28% (95% CI: 1.20,
227 33.59) rise in drug resistance risk in cases under 60 years old at lag 0-7 days. A positive
228 correlation emerged between PM_{2.5} concentration and drug resistance risk in winter at
229 lag 0-3 days, lag 0-15 days, lag 0-90 days, and lag 0-180 days, with the most
230 pronounced impact observed at lag 0-180 days. At this time, the risk of drug resistance
231 surged by 335.06% for each 10-unit increase in PM_{2.5} concentration (95% CI: 17.71,

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9 234 In double-pollutant models, the significant association between PM_{2.5} concentration
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11 235 and drug resistance risk persisted in male cases at a lag of 0-3 days and those under 60
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13 236 years old at a lag of 0-7 days after adjusting for SO₂. Moreover, PM_{2.5} concentration
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15 237 continued to exhibit a significant positive association with drug resistance risk in winter
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17 238 at lag 0-15 days, lag 0-30 days, and lag 0-180 days after adjusting for SO₂; at lag 0-180
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19 239 days after adjusting for CO; at lag 0-7 days, lag 0-15 days, and lag 0-90 days after
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21 240 adjusting for O₃ (Table S2).
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30 242 **Discussion**

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32 243 This study examined the relationship between PM concentration and drug resistance
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34 244 risk of workers and farmers with PTB in Suzhou City, a prominent industrial metropolis
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36 245 in eastern China. A positive correlation between PM₁₀ concentration and drug
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38 246 resistance risk was observed throughout all lag days in winter. Moreover, PM_{2.5}
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40 247 concentration was found to be positively correlated with drug resistance risk of male
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42 248 cases at lag 0-3 days, cases under 60 years old at lag 0-7 days, and all cases at some lag
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44 249 days during the winter season. To our knowledge, this is the first study to evaluate the
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46 250 relationship between PM concentration and drug resistance of PTB among the outside
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48 251 working populations in China. This study emphasizes the importance of air quality in
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50 252 the prevention and control of infectious diseases. It is necessary to take a comprehensive,
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52 253 cross-sectoral approach to effectively control air pollution and reduce the burden of
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4 254 drug resistance in tuberculosis. We suggest combining air quality control measures with
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6 255 the existing tuberculosis prevention and control programs, such as strengthening
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9 256 screening and protection of high-risk groups in seasons with severe air pollution, to
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11 257 facilitate the early detection and management of drug-resistant tuberculosis.
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17 259 The existing body of literature exploring the association between PM concentration and
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19 260 drug resistance risk of tuberculosis patients is scarce and inconclusive. A case-control
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21 261 study identified a positive association between PM concentration and drug resistance
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23 262 risk of tuberculosis patients.¹³ Specifically, PM₁₀ was shown to significantly impact this
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25 263 risk from lag 0-90 days to lag 0-540 days, while PM_{2.5} had a notable effect up to lag 0-
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27 264 540 days. A green environment could mitigate the mortality risk of DR-TB patients.^{18,19}

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30 265 In contrast, another study suggested a protective effect of PM_{2.5} and PM₁₀ against drug
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32 266 resistance risk.¹⁴ In the current study, we selected outdoor workers and farmers as the
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34 267 study subjects and did not uncover a significant association between PM concentration
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36 268 and drug resistance risk in the overall analyses. This disparity might stem from
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38 269 differences in PM concentration and composition characteristics.^{13,14} Other factors such
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40 270 as geography, meteorological conditions, economic level, population density, and
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42 271 *Mycobacterium tuberculosis* strains might influence the relationship between PM and
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44 272 drug resistance risk.²⁰
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51 274 Our findings indicated that elevated levels of PM₁₀ and PM_{2.5} during winter
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53 275 significantly contributed to the drug resistance risk of workers and farmers with PTB.
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4 276 This observation aligned with previous studies highlighting increased health risks from
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6 277 winter PM exposure. For example, a time-series study from 202 counties in the United
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9 278 States revealed the strongest correlation between PM_{2.5} concentration and daily
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11 279 hospitalization rates for cardiovascular and respiratory systems during winter.²¹
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14 280 Another study from Wuhan, China, suggested that PM had a more pronounced impact
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16 281 on overall mortality, cardiovascular, stroke, and respiratory system mortality rates in
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18 282 winter²². Animal experiments demonstrated that winter exposure to PM_{2.5} caused more
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20 283 severe cardiac toxicity than summer exposure,²³ and wintertime PM exhibited higher
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22 284 endotoxin levels than springtime PM.²⁴ PM samples collected in Italy during winter
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24 285 produced more acute toxicity in mouse models than summer-collected samples.²⁵
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26 286 Seasonality has been recognized as a crucial modifier when evaluating the impact of air
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28 287 pollution on human health. The potential influence of wintertime PM on the drug
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30 288 resistance risk of tuberculosis might be attributed to high concentrations of pollutants,
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32 289 as demonstrated by our time-series graphs. Studies have indicated that increased
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34 290 atmospheric boundary layer stability and reduced vertical mixing tendencies in winter
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36 291 result in pollutant retention and regional accumulation; this may account for the
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38 292 increased risk of resistance observed in winter.^{26,27}
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50 294 Although Suzhou lacks coal heating systems, low wind speeds and temperatures
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52 295 exacerbate ground-level pollutant accumulation.²⁷ Nonetheless, the rising demand for
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54 296 heating systems may influence this phenomenon through regional transmission and
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56 297 accumulation from northern parts of China.²⁸ Furthermore, PM_{2.5} has a more significant
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4 298 impact than PM₁₀, consistent with studies on air pollutants related to the onset risk of
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6 299 PTB.^{29,30} This observation can be ascribed to smaller particles penetrating deeper into
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9 300 the alveoli and bronchi, resulting in more severe biological toxicity reactions.³¹
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14 302 Our study uncovered a relationship between PM_{2.5} and drug resistance risk of male PTB
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17 303 patients at a lag of 0-3 days and a similar association among patients under 60 years old
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20 304 at a lag of 0-7 days. However, no association was observed in these two subgroups at
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22 305 other lag days, necessitating cautious interpretation of the results. Thus, further research
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24 306 is required to determine their biological plausibility. The difference in different lag days
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27 307 may be related to individual immunity. For example, individuals with poor immunity
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30 308 may be exposed for a few weeks to increase the risk of developing resistance, while
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32 309 those with better immunity may take longer.³² Gender differences may stem from
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35 310 various factors, including lifestyle habits (e.g., smoking), social behaviors (e.g.,
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37 311 engaging in group activities), and physiological differences, which collectively might
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40 312 render men more susceptible to DR-TB.³³⁻³⁵ Previous research has indicated that
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43 313 patients with DR-TB tend to be younger than those with drug-sensitive infections. For
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46 314 example, a systematic review reported that the incidence of drug resistance was 2.53
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48 315 times higher among PTB cases under 65 years old compared to those aged 65 and
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51 316 above.³⁶ This finding suggested that older individuals might develop DR-TB due to
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54 317 latent infections acquired before the emergence of drug resistance, while a younger age
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57 318 represents a risk factor for recent transmission.³⁷
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4 320 Escalating PM levels could potentially amplify PTB patients' drug resistance risk. The
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6 321 exact machinations driving this phenomenon are yet to be entirely comprehended;
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9 322 however, several contributory factors can be hypothesized. Primarily, the composition
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11 323 of PM extends beyond mere physiochemical elements, encapsulating biological
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14 324 constituents such as microbes and antibiotic-resistant genes. An intriguing study
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17 325 revealed discernible disparities between the microbial consortia and their associated
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20 326 antibiotic-resistant genes present in the air, and those found within terrestrial and
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22 327 marine ecosystems.³⁸ PM has emerged as a principal vector for disseminating
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25 328 antibiotic-resistant genes within the environment.^{39,40} Thus, the air could harbor more
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28 329 resistant strains and antibiotic-resistance genes in locales characterized by elevated PM
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31 330 concentrations. Secondly, PM can incite oxidative stress and elicit inflammatory
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34 331 responses, which could precipitate structural and functional degradation of alveolar
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37 332 epithelial and endothelial cells.^{41,42} Furthermore, PM can infiltrate the systemic
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40 333 circulation, provoking vascular dysregulation and systemic inflammation.⁴³ Such
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43 334 perturbations may aggravate the clinical status of new tuberculosis patients afflicted
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46 335 with chronic pulmonary diseases.⁴⁴ This exacerbation might necessitate a complex and
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49 336 protracted diagnostic and treatment regimen, thereby elevating their propensity to
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52 337 develop drug resistance.⁴⁵ Lastly, insights gleaned from a molecular epidemiological
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55 338 investigation underscored that the peril of direct transmission of DR-TB distinctly
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58 339 surpasses resistance acquisition attributable to factors such as the injudicious utilization
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60 340 of antibiotics.⁴⁶ This implies that PM, laden with resistant strains and antibiotic-
341 resistant genes, could potentially bolster the aerial propagation of drug-resistant

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4 342 *Mycobacterium tuberculosis*.

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9 344 This study has several limitations. First, we estimated PM exposure relying on
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11 345 stationary monitoring data, which may not accurately reflect individual exposure.
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14 346 Future research should utilize mobile monitoring devices or geographic information
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17 347 systems (GIS) for more precise assessments. Second, we only measured the drug
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19 348 resistance to rifampicin and isoniazid, restricting our analysis of the risk of resistance
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22 349 to other antituberculosis drugs. Expanding the sample size to include a broader range
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25 350 of drug-resistant tuberculosis is essential for elucidating the relationship between PM
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28 351 exposure and resistance mechanisms. Third, besides air pollution, other factors, such as
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30 352 tobacco smoking, alcohol consumption, and socioeconomic status, may also affect the
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33 353 association between PM and drug resistance. Future studies should integrate these
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36 354 variables to provide a comprehensive understanding of the multifactorial influences of
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38 355 PM on drug resistance in PTB patients.

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41 42 357 **Conclusion**

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45 358 In conclusion, our study demonstrated a statistically significant positive association
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48 359 between outdoor PM₁₀ and PM_{2.5} concentrations and DR-TB among workers and
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51 360 farmers predominantly engaged in outdoor occupations. Our findings underscore the
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54 361 critical role of reducing ambient particulate matter levels in mitigating the burden of
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57 362 infectious diseases. To further validate this association and evaluate the long-term
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59 363 health outcomes of air pollution interventions, future research should prioritize in vitro

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4 364 mechanistic studies to investigate the biological pathways linking PM exposure to DR-
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6 365 TB, longitudinal cohort studies with extended follow-up periods to assess cumulative
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9 366 effects, and economic evaluations of public health interventions targeting air quality
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12 367 improvements.

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16 369 **Data availability statement**

19 370 Data are available upon reasonable request. Data are available upon reasonable requests
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21 371 by contacting the corresponding author through the following email address:
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23 372 gndx_zxl@163.com.

24 373

28 374 **Ethics statements**

31 375 **Patient consent for publication**

34 376 Not required.

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38 378 **Ethical approval**

41 379 The present study was approved by the Ethics Committee of Nanjing Medical
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43 380 University. It is a secondary analysis of retrospective, non-identifiable data employing
44
45 381 anonymized, pre-existing public health records without direct interaction or
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47 382 intervention with the participants. Given the low-risk nature of this research and the
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49 383 inability to trace the data back to individual subjects, the Ethics Committee granted a
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51 384 waiver for the requirement of informed consent (SZJKJFS2023-001).
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59 386 **Contributors**

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3 387 Xiaolong Zhang: Conceptualization, Methodology, Data Curation, Software, Formal
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5 388 analysis, Writing - Original Draft, Visualization. Zhongqi Li: Conceptualization,
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7 389 Formal analysis, Writing-Review & Editing. Bilin Tao: Formal analysis, Software,
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9 390 Visualization. Ying Fu: Data Curation, Methodology. Caiyan Cui, Feixian Wang ,Yun
10
11 391 Li and Yu Wang: Data Curation. Jun Jiang: Conceptualization, Project administration.
12
13 392 Jianming Wang: Conceptualization, Resources, Visualization, Writing-Review &
14
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16
17 394 responsible for the overall content as guarantor.
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395

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402 **Competing interests**

403 None declared.
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405 **Patient and public involvement**

406 Patients and/or the public were not involved in the design, or conduct, or reporting, or
407 dissemination plans of this research
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4 585 **Figure legends**
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9 587 Figure 1. Time-series plots of outdoor air pollutants and meteorological factors in
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17 590 Figure 2. Percentage changes in the risk of drug-resistant tuberculosis and their 95%
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20 591 CIs for each 10-unit increase in PM₁₀ concentration in Suzhou City between 2017 and
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27 594 Figure 3. Percentage changes in the risk of drug-resistant tuberculosis and their 95%
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30 595 CIs for each 10-unit increase in PM_{2.5} concentration in Suzhou City between 2017 and
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598 Table 1. Characteristics of study subjects.

Variables	Drug resistance		χ^2	<i>P</i>
	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)		

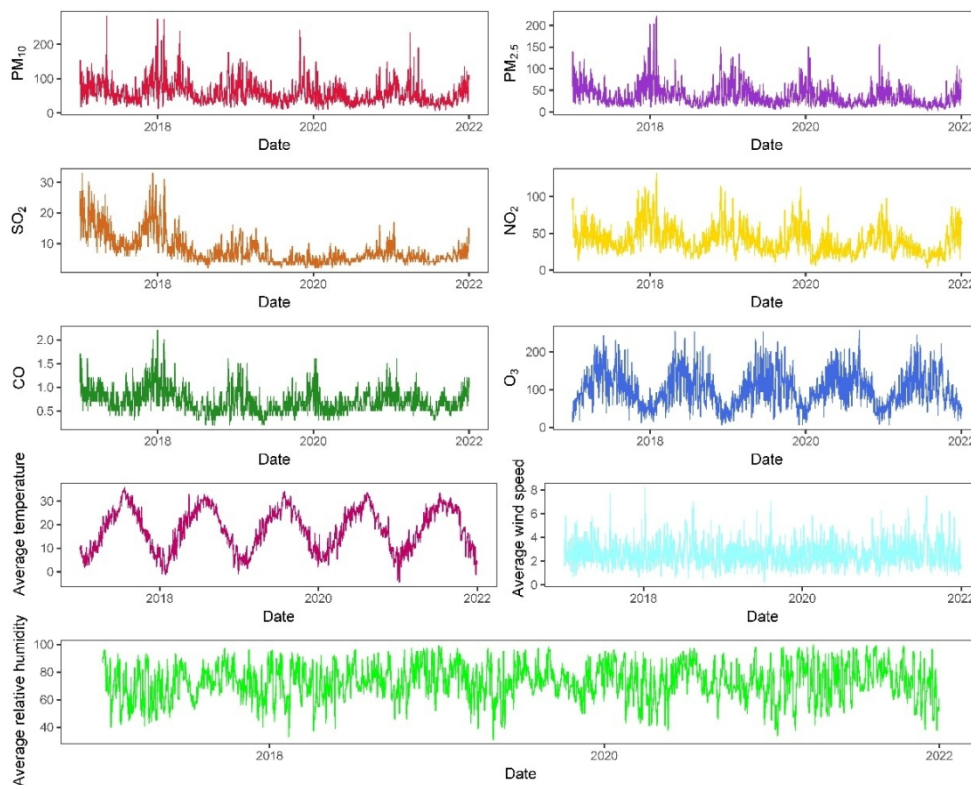
599 *: HIV/AIDS, diabetes, or pneumoconiosis.

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

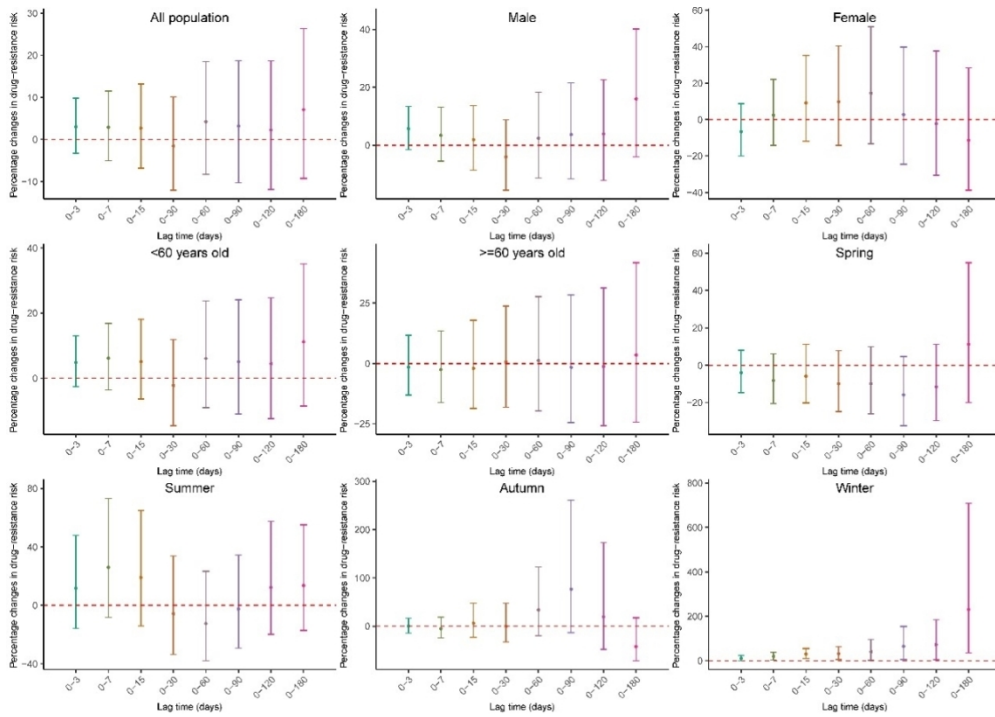
Variables	Minimum	Q ₂₅	Median	Mean	Q ₇₅	Maximum
Outdoor air pollutants						
PM ₁₀ (µg/m ³)	7.00	36.00	50.00	58.89	74.00	283.00
PM _{2.5} (µg/m ³)	3.00	20.00	30.00	37.15	46.00	222.00
SO ₂ (µg/m ³)	2.00	5.00	6.00	7.84	9.00	33.00
NO ₂ (µg/m ³)	3.00	27.00	37.00	40.63	51.00	132.00
CO (mg/m ³)	0.20	0.50	0.70	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 (°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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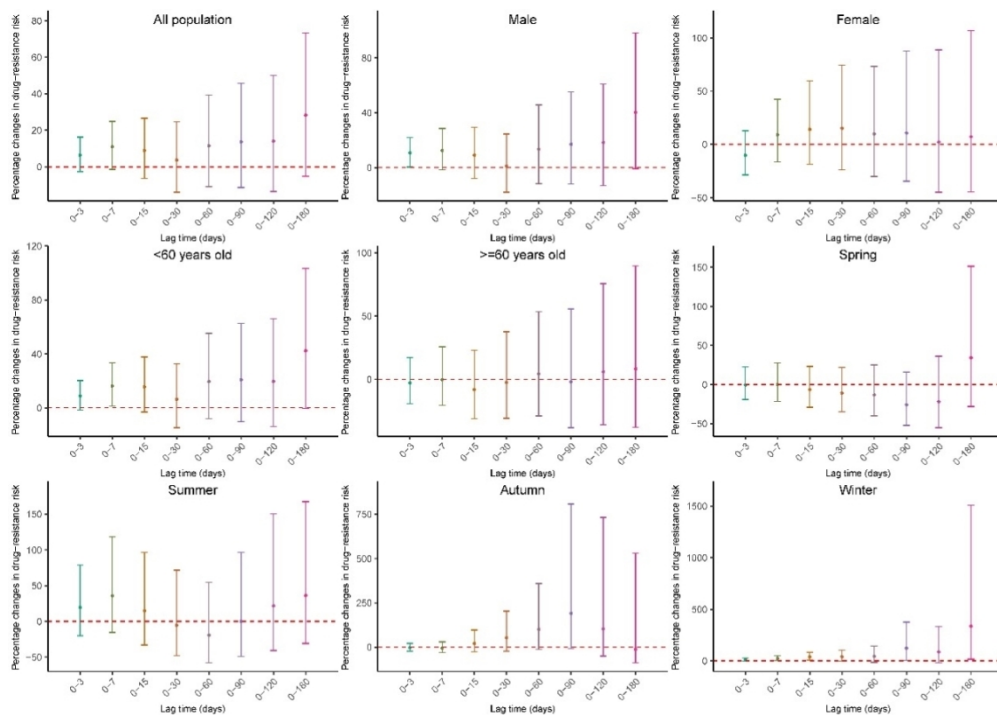


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Supplementary Tables

Table S1. Percentage changes in the risk of drug resistance and their 95% CIs for each 10-unit increase in PM₁₀ 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)	1.95 (-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)	-2.47 (-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)	0.77 (-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)	-1.74 (-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)	21.29 (-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)	12.29 (-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)	10.70 (-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)	14.39 (-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)	5.32 (-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)	-4.02 (-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)	-3.74 (-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)	-12.42 (-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)	7.44 (-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)	-1.99 (-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)	3.50 (-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)	13.98 (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)	-6.88 (-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)	8.68 (-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)	28.57 (-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)	48.37 (-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)	90.05 (-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)	85.70 (-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)	43.55 (-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)	17.40 (-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)	5.20 (-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)	17.99 (-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)	15.99 (-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)	25.99 (-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)	-4.11 (-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)	-9.11 (-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
Spring	0-30 days	0.67 (-18.13, 23.80)	-5.76 (-26.34, 20.56)	6.60 (-25.70, 52.93)	-3.29 (-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)	1.86 (-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)	3.36 (-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)	1.44 (-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)	1.41 (-29.14, 57.25)	1.86 (-25.93, 40.08)
	0-3 days	-3.97 (-14.66, 8.06)	0.74 (-11.52, 14.71)	-0.69 (-14.90, 15.90)	1.41 (-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)	1.28 (-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)	1.33 (-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)	1.00 (-31.65, 22.77)	-15.66 (-31.25, 3.46)
Summer	0-60 days	-9.83 (-26.02, 9.89)	4.75 (-27.62, 51.58)	52.69 (-18.20, 185.01)	1.00 (-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)	1.00 (-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)	1.54 (-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)	1.19 (-1.13, 206.19)	11.02 (-20.10, 54.25)
	0-3 days	11.69 (-15.67, 47.94)	18.64 (-13.87, 63.43)	3.14 (-29.78, 51.49)	1.23 (-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)	1.44 (-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)	1.40 (-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)	1.20 (-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)	1.02 (-33.51, 83.04)	2.39 (-29.95, 49.67)
Autumn	0-90 days	-2.45 (-29.24, 34.50)	-6.26 (-36.80, 39.04)	-30.37 (-71.47, 69.89)	1.35 (-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)	1.07 (-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)	1.17 (-52.47, 62.27)	14.25 (-17.88, 58.96)
	0-3 days	0.01 (-14.36, 16.80)	-1.13 (-16.46, 17.01)	-6.14 (-26.56, 19.96)	1.01 (-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)	1.28 (-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)	1.43 (-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)	1.19 (-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)	1.34 (-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)	1.94 (-12.77, 333.62)	124.11 (-20.43, 531.22)
Winter	0-120 days	19.11 (-48.07, 173.18)	21.29 (-51.53, 203.53)	-62.48 (-93.36, 112.00)	1.40 (-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)	1.41 (-68.50, 82.86)	-56.28 (-83.71, 17.28)
	0-3 days	11.21 (0.02, 23.65)	10.78 (-3.15, 26.70)	13.19 (-3.58, 32.87)	1.18 (-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)	1.25 (-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)	1.30 (-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)	1.22 (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)	1.20 (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)	1.19 (-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)	1.18 (-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)	1.13 (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

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humidity at the same lag time.

Model 2: Based on model 1, additionally adjusted for SO₂ at the same lag time.

Model 3: Based on model 1, additionally adjusted for NO₂ 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 O₃ at the same lag time.

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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)	6.58 (-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)	10.61 (-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)	10.28 (-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)	8.86 (-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)	33.74 (-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)	40.19 (-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)	63.22 (-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)	101.31 (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)	11.39 (-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)	9.88 (-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)	8.47 (-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)	2.45 (-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)	34.65 (-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)	36.06 (-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)	54.74 (-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)	65.88 (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)	-10.25 (-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)	24.50 (-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)	32.33 (-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)	39.30 (-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)	27.75 (-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)	65.29 (-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)	72.41 (-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)	436.86 (-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)	9.17 (-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)	17.40 (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)	20.30 (-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)	13.45 (-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)	39.89 (-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)	59.26 (-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)	99.29 (-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)	171.59 (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)	-5.01 (-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)	-8.85 (-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)	-14.10 (-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)	-1.26 (-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)	23.09 (-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)	0.43 (-44.06, 65.99)	0.16 (-36.01, 56.78)

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	Lag time	Model 1	Model 2	Model 3	Model 4	Model 5	
Spring	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)	11.11 (-41.98, 112.78)	8.41 (-37.92, 89.32)	
	0-3 days	-0.43 (-19.17, 22.66)	9.52 (-12.95, 37.79)	7.80 (-16.04, 38.40)	5.48 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (-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)	5.25 (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 SO₂ at the same lag time.

Model 3: Based on model 1, additionally adjusted for NO₂ at the same lag time.

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

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Model 5: Based on model 1, additionally adjusted for O₃ at the same lag time.

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