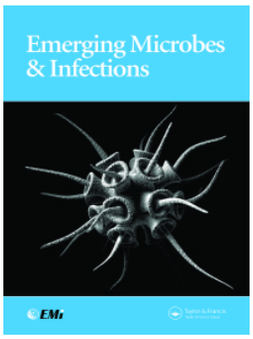

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Impact of fine particulate matter on latent tuberculosis infection and active tuberculosis in older adults: a population-based multicentre cohort study

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ABSTRACT

Evidence showed that air pollution was associated with an increased risk of tuberculosis (TB). This study aimed to study the impact of long-term exposure to ambient particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) on the acquisition of LTBI and on the risk of subsequent active disease development among rural older adults from a multicentre cohort, which have not yet been investigated to date. A total of 4790 older adults were included in a population-based, multicentre, prospective cohort study (LATENTTB-NSTM) from 2013 to 2018. The level of long-term exposure to $PM_{2.5}$ for each participant was assessed by aggregating satellite-based estimates. Logistic regression and time-varying Cox proportional hazards models with province-level random intercepts were employed to assess associations of long-term exposures to $PM_{2.5}$ with the risk of LTBI and subsequent development of active TB, respectively. Out of 4790 participants, 3284 were LTBI-free at baseline, among whom 2806 completed the one-year follow-up and 127 developed newly identified LTBI. No significant associations were identified between $PM_{2.5}$ and the risk of LTBI. And among 1506 participants with LTBI at baseline, 30 active TB cases were recorded during the 5-year follow-up. Particularly, an increment of 5 $\mu g/m^3$ in 2-year moving averaged $PM_{2.5}$ was associated with a 50.6% increased risk of active TB (HR = 1.506, 95% CI: 1.161-1.955). Long-term air pollution might be a neglected risk factor for active TB development from LTBI, especially for those living in developing or less-developed areas where the air quality is poor.

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KEYWORDS Latent tuberculosis infection; tuberculosis; $PM_{2.5}$; air pollution; time dependent Cox regression

1. Introduction

Tuberculosis (TB) caused by the infection of bacillus *Mycobacterium tuberculosis* (MTB) is a major public health challenge caused 1.6 million deaths worldwide in 2021 [1]. More crucially, eight countries in the 30 high TB burden countries accounted for more than two-thirds of all estimated incident cases worldwide, among which China is the third highest burden country [1]. Nearly a quarter of the world's population is infected with MTB, and the lifetime risk of developing TB for those with latent TB infection (LTBI) is estimated to be 5%−10% [2,3]. Therefore, the identification of potential predictors or risk factors for MTB infection and progression to active disease is necessary for TB prevention and control. The global high TB burden is fueled by well-established risk factors including human immunodeficiency virus (HIV) infection, malnutrition, and emerging risk factors including diabetes, indoor air pollution, and smoking [4]. Meanwhile, age, sex and history of close contact with a patient with active TB are found to be associated with LTBI in our previous study [5]. China is challenged by the shifting of TB from the younger to the older due to the ageing population, longer life expectancy and reactivation disease [6-8]. WHO estimated that the percentage of people aged 60 years or over in China is expected to increase from 12.4% (168 million people) in 2010–28.0% (402 million) in

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2040 [7]. Our previous multicentre studies also reported that the prevalence of LTBI and the annual risk of MTB infection acquisition were both higher among older individuals [5,9].

Air pollution has become a global public health problem [10,11]. Previous studies have suggested that ambient air pollution especially fine particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) could result in adverse health outcomes, even in developed countries that have low-level air pollution [10,12–15]. Among previous studies that investigated the effects of $PM_{2.5}$ on the risk of TB, inconsistent results were observed [16–18]. Increasing evidence suggests that ambient air pollution particularly $PM_{2.5}$, which may inhibit cellular immunity to MTB, is associated with an increased risk of TB [16,17]. In contrast, Xiang K and colleagues have found no statistically significant associations between $PM_{2.5}$ and the risk of TB in general populations, but they still found the association was significant in the subgroup of older adults [18,19]. In addition, the association of long-term exposure to $PM_{2.5}$ with the risk of LTBI is unclear and with the risk of active TB development from LTBI is little. Given that older adults living in rural areas are a vulnerable population to TB and air pollution-related health outcomes, studies are worthwhile to reveal the impact of air pollution on their risk of LTBI and subsequent development of active TB. To fill this knowledge gap, based on a multicentre cohort study, we explore the associations of long-term exposure to $PM_{2.5}$ with LTBI and active TB in older adults living in rural areas in China.

2. Methods

2.1 Study design and participants

A population-based, prospective cohort study (LATENTTB-NSTM) addressing TB infection and active disease development was conducted at four study sites: Xiangtan (6 villages), Hunan province; Longxi (3 villages), Gansu province; Danyang (2 villages), Jiangsu province; and Zhongmu (6 villages), Henan province (Figure 1a), selected based on a wide range of local TB epidemiology, economic conditions and geographic diversity, in rural China during 2013–2018. Registered rural inhabitants (5 years older) with a continuous residence at the study site for 6 months or longer in the past year were the target population of the study. Detailed information about the target, design, organization and implementation of the study has been described previously [5,6,20]. As we focused on older adults, the present study was restricted to older adults (≥60 years old) in the cohort study. Out of 4793 eligible older adults, we included 4790 participants in this study with available information on potential covariates. The baseline survey was conducted between July 1st and September 30th, 2013, screening participants for LTBI. One year later, between July 1 and September 30, 2014, the only yearly follow-up survey (sub-cohort 1, Figure S1) was undertaken to estimate the incidence of TB infection in participants without LTBI. For those with LTBI at baseline (sub-cohort 2, Figure S1), quarterly follow-ups for a duration of 5 years were carried out to track the development of active disease, till the final visit between July 1 and September 30, 2018. The study protocol was approved by the ethics committee of the Institute of Pathogen Biology, Chinese Academy of Medical Sciences in Beijing, China (IPB-2013-5), and written informed consent was obtained from all participants, or their legal guardians if necessary.

2.2 Procedures

For each participant who participated in our cohort, different types of data were collected in 3 main stages: baseline survey, 1-year follow-up survey, and 5-year follow-up survey. At the baseline survey, a standardized questionnaire was used to collect sociodemographic information and self-reported health status by trained interviewers. Examination of height, weight, pulse, and digital chest radiography for participants was done by physicians. Venous blood samples were collected for interferon-γ release assay (IGRA) (QuantiFERON-TB Gold In-Tube assay) which was done as recommended by the manufacturer (Qiagen) with a cutoff value of ≥ 0.35 IU/mL. After the IGRA test, TST was done immediately using the Mantoux method on the left forearm as the first choice, injection of 0.1 mL of 5 tuberculin units of purified protein derivative (Xiangrui; Beijing, China) [21]. Tuberculin reaction size (induration) was measured 48–72 h later in mm of placement by trained study staff. IGRA result was used to determine TB infection status in the present study because our previous results proved TST results were affected by several factors including old age [5]. The 1-year follow-up survey aiming at investigating the risk of TB infection was conducted in parallel at the four study sites among individuals without LTBI from July to September 2014.

Based on baseline survey, individuals with positive results (IGRA+) were included in the 5-year follow-up surveys. During the follow-up period between 2014-2018, quarterly follow-up interviews were conducted by trained staff through telephone or door-to-door surveys for active case finding according to suspected symptoms screening in local study sites. Participants were invited and encouraged to a closing survey for active case finding based on suspected symptoms and digital chest radiography results unless they had migrated out of the site or area, refused to be surveyed, or had died, after being followed up 2 and 5 years,

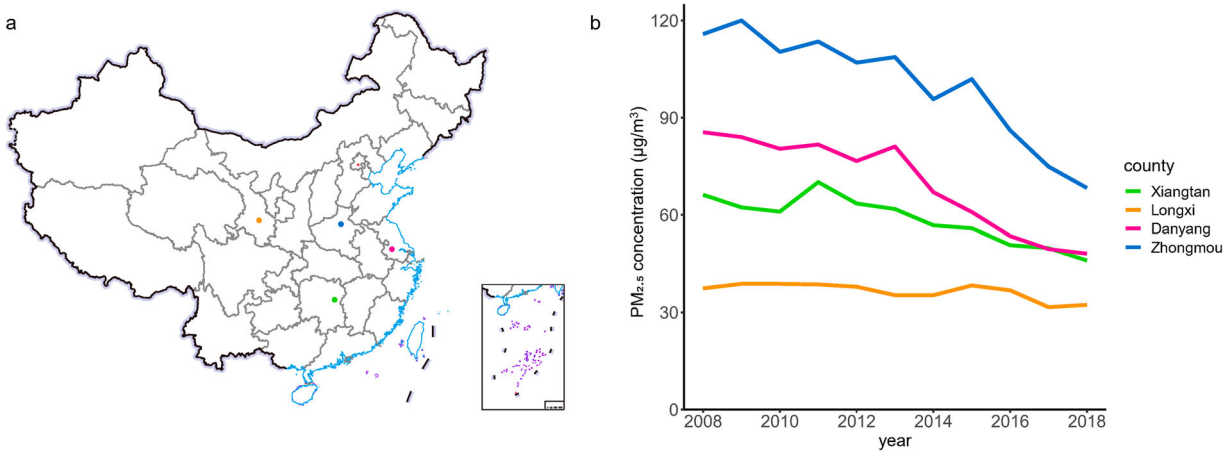

Figure 1. The study sites (a) and (b) levels of annual average particulate matter with an aerodynamic diameter of less than 2.5 μm in the four sites from 2008 to 2018

respectively. All participants who were suspected of having TB based on clinical symptoms or radiographic abnormalities were referred for further diagnosis according to the national guidelines [22]. During the study, TB preventive therapy was not provided to participants with positive IGRA results, exposure to TB, or other risk factors.

In the present study, active TB cases was defined as individuals with microbiologically or clinically diagnosed TB. Microbiologically confirmed cases were defined as individuals with positive results for any of 3 kinds of bacteriological evidence including sputum smear with acid-fast bacillus microscopy, BACTEC culture, and GeneXpert MTB/RIF assay. Two-week diagnostic antibiotic therapy (not including anti-TB drugs) was suggested for patients who had negative results with all 3 tests above. If the individual showed no response to the antibiotic therapy treatment, a diagnosis of clinically diagnosed TB would be given and retrospectively confirmed by the responses to subsequent anti-TB treatment. In addition, active cases registered in the national network reporting system were also included in our study. A panel that consisted of three radiologists, two physicians, and one laboratory expert, was responsible for active TB diagnosis.

2.3 Exposure assessments

The daily gridded $PM_{2.5}$ concentrations at a 1 km resolution with complete coverage from 2000 to the present were downloaded from the widely used, near real-time, complete space-covering air pollutant concentration database, Tracking Air Pollution in China (TAP, http://tapdata.org.cn/, last access: 22nd December 2022). The details of the $PM_{2.5}$ prediction model have been published elsewhere [23,24]. Briefly, the 1 km resolution $PM_{2.5}$ predictions fuse MAIAC satellite aerosol optical depth (AOD) retrievals, TAP $PM_{2.5}$ products at a 10 km resolution, satellite normalized difference vegetation index (NDVI) products, and land use variables including road maps, population distribution, artificial impervious area, and vegetation index with a random forest model. The annual model, with training data for each corresponding year from 2015 to 2020, had an out-of-bag R^2 (the coefficient of determination of the linear regression between measurements and predictions from trees that did not include each of these measurements for training) ranging between 0.80 and 0.84, and the hindcast model, with training data from 2013 to 2020 to predict historical $PM_{2.5}$ concentrations from 2000 to 2014, had a by-year cross-validation R^2 of 0.76. The 10 km resolution $PM_{2.5}$ predictions fuse ground $PM_{2.5}$ measurements, Community Multiscale Air Quality (CMAQ) $PM_{2.5}$ simulations, Moderate Resolution Imaging Spectroradiometer (MODIS) level-2 AOD retrievals, Modern-Era Retrospective analysis for Research and Applications, Version 2 (MERRA-2) meteorology parameters, and land use information with a two-stage random forest model.

The centre of each participant's village was geocoded into latitude and longitude data. As a surrogate, we assigned estimated ambient $PM_{2.5}$ concentrations to each participant based on the geocoded latitude and longitude. The aggregate $PM_{2.5}$ concentration during the different four exposure windows, including moving averages of 1, 2 years, 3, and 5 years before the date of measurement of the LTBI status, were estimated separately for participants at baseline and in sub-cohort 1. As for participants in sub-cohort 2, the 1, 2, 3 and 5-year moving averages of the previous $PM_{2.5}$ exposure till the last quarter were estimated for each quarter of follow-up. Corresponding aggregate temperature values were estimated in the same way accordingly using hourly gridded 2 m temperature (temperature of the air at 2 metres above the surface of land, sea or in-land waters) data from the European Centre for Medium-Range Weather

Forecasts (ECMWF) Reanalysis v5 (ERA5) Land dataset at a resolution of 0.1° x 0.1° [25].

2.4 Statistical analysis

We first performed logistic regression models to investigate the associations of the prevalent LTBI at baseline with long-term exposure to ambient $PM_{2.5}$, which increasingly adjusted for priori selected potential covariates. Model 1 adjusted for age, sex, and temperature using a spline term with 3 degrees of freedom; Model 2 additionally adjusted for sociodemographic factors and lifestyles (BMI, education, family income, smoking status, and alcohol drinking); Model 3 further adjusted for TB risk factors (family history of TB, close contact with TB patients, immune disorders (including hyperthyroidism, diabetes I, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and AIDS), and type 2 diabetes (self-reported or with a fasting plasma glucose value no less than 7.0 mmol/L[26])). We incorporated province-level random intercepts into modelling analyses to account for potential spatial variations between provinces. Subsequently, among baseline LTBI-free participants, we evaluated their long-term exposure to $PM_{2.5}$ with their incident LTBI during the 1-year follow-up using the same models.

We finally used Cox regression models with time-dependent covariate [27,28] to analyze the associations between long-term exposure to ambient $PM_{2.5}$ and the incident TB among baseline LTBI participants, controlling for aforementioned baseline individual risk factors and potential confounders, with province-level random intercepts [29]. The timescale used in the models was time-in-study (follow-up time) [30]. Only the exposure was treated as the time-dependent variate to account for the changes in $PM_{2.5}$ exposure during the study period. Hazard ratios (HRs) and 95% CIs were calculated for each 5-μg/m^3 increase in $PM_{2.5}$. Subgroup analyses were also conducted based on the demographic factors and TB risk factors of the participants at baseline. We performed data analyses separately within each subgroup using the Cox regression models with time-dependent $PM_{2.5}$ exposure to derive the stratum-specific HR, and assessed effect modification by those factors using interaction terms.

Additional sensitivity analyses were conducted by (1) using a village-level random intercept in analysis for incident TB, (2) restricting to active TB cases who were diagnosed with microbiologically TB, (3) removing participants who were lost during follow-up, (4) additionally adjusting for history of immune suppression, self-reported cancer and pneumonia, and (5) including PM_{10} from another source, CHAP [31], in two-pollutant models to test the independent effect of $PM_{2.5}$ from the copollutant.

All the statistical analyses were performed using R 4.1.3 (R Core Team, Vienna, Austria). We used "lm4" and "coxme" packages to fit logistic and Cox models with random intercept term, respectively. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

3.1 Participants' characteristics and $PM_{2.5}$ pollution distributions

As shown in Table 1, the age (mean ± standard deviation [SD]) of all the participants at baseline was 68.3 ± 6.9 years and 36.1% of them were no less than 70 years old. Roughly half of the participants were male and 38.2% of them were overweight. Nearly

Table 1. Baseline characteristics of the participants.

Characteristics	Total $N = 4790$	Sub cohort 1 $n = 2806$	Sub cohort 2 $n = 1506$
Age (years)			
Mean (SD)	68.3 (6.9)	68.2 (6.9)	68.3 (6.6)
Age group			
60~69	3061 (63.9%)	1846 (65.8%)	947 (62.9%)
≥70	1729 (36.1%)	960 (34.2%)	559 (37.1%)
Sex			
Male	2280 (47.6%)	1230 (43.8%)	837 (55.6%)
Female	2510 (52.4%)	1576 (56.2%)	669 (44.4%)
BMI			
Non-overweight	2962 (61.8%)	1715 (61.1%)	915 (60.8%)
Overweight	1828 (38.2%)	1091 (38.9%)	591 (39.2%)
Education			
No schooling	1820 (38.0%)	1070 (38.1%)	518 (34.4%)
Primary school or higher	2970 (62.0%)	1736 (61.9%)	988 (65.6%)
Family income per head (RMB)			
<6000	3313 (69.2%)	1904 (67.9%)	1042 (69.2%)
≥6000	1477 (30.8%)	902 (32.1%)	464 (30.8%)
Smoking status			
Never	3287 (68.6%)	2009 (71.6%)	923 (61.3%)
Ever (current and former)	1503 (31.4%)	797 (28.4%)	583 (38.7%)
Alcohol drinking			
No	3852 (80.4%)	2267 (80.8%)	1171 (77.8%)
Yes	938 (19.6%)	539 (19.2%)	335 (22.2%)
Family history of TB			
No	4634 (96.7%)	2721 (97.0%)	1444 (95.9%)
Yes	156 (3.3%)	85 (3.0%)	62 (4.1%)
Close contact with TB patients			
No	4574 (95.5%)	2684 (95.7%)	1428 (94.8%)
Yes	216 (4.5%)	122 (4.3%)	78 (5.2%)
Immune disorders			
No	4674 (97.6%)	2728 (97.2%)	1482 (98.4%)
Yes	117 (2.4%)	78 (2.8%)	24 (1.6%)
Type 2 diabetes			
No	4440 (92.7%)	2598 (92.6%)	1395 (92.6%)
Yes	350 (7.3%)	208 (7.4%)	111 (7.4%)
Province			
Hunan	1429 (29.8%)	804 (28.7%)	480 (31.9%)
Gansu	858 (17.9%)	396 (14.1%)	295 (19.6%)
Jiangsu	1650 (34.4%)	1086 (38.7%)	456 (30.3%)
Henan	853 (17.8%)	520 (18.5%)	275 (18.3%)

Note: Data are n (%), unless otherwise specified. The sub cohort 1 focused on the people without LTBI (latent tuberculosis infection) at baseline, while the sub cohort 2 focused on the people with LTBI at baseline. Abbreviations: SD, standard deviation; TB, tuberculosis.

38% of participants were never educated. Around a third of participants reported having ever smoked. About 43%, 5%, 2% and 7% at baseline had family history of TB, history of close contact with patients with TB, immune disorders, and type 2 diabetes, respectively. Participants were generally evenly distributed across four sites. The annual $PM_{2.5}$ concentrations in all four sites decreased over time from 2008 to 2018 but kept at a relatively high-level ranging from ~30 to ~120 ug/m^3 (Figure 1b).

3.2 Associations of $PM_{2.5}$ with the prevalent and incident LTBI

At baseline, 1506 of the total 4790 participants were with prevalent LTBI. Long-term exposure to $PM_{2.5}$ at different exposure windows was associated with slightly increased odds of LTBI but not statistically significant (Table 2). In crude model 1, a 5 μg/m^3 increase in $PM_{2.5}$ exposure over the preceding year was associated with a 4.2% higher risk of LTBI (OR = 1.042, 95% confidence interval [CI]: 0.986-1.101). When fully adjusted (model 3), the OR was 1.044 (95% CI: 0.987-1.104). Then, for 2806 participants without LTBI at baseline, 127 of them were diagnosed with LTBI at the 1-year follow-up survey. The association of incident LTBI with long-term exposure to $PM_{2.5}$ was similar to prevalent LTBI at baseline (Table 3). The fully adjusted model 3 showed that a 5 μg/m^3 increase in $PM_{2.5}$ exposure over the preceding year was associated with a 6.0% higher risk of incident LTBI (OR = 1.060, 95% CI: 0.962-1.167).

3.3 Association between $PM_{2.5}$ and incident active TB

Among 1506 participants with LTBI, with a median follow-up of 5 years, 362 (24.0%) of them were lost, and 30 developed active TB during the follow-up from 2014 to 2018, of whom 8 (26.7%) were microbiologically confirmed and 22 (73.3%) were clinically diagnosed and confirmed by their responses to the subsequent anti-tuberculosis treatment. We observed significant positive associations between long-term exposure to $PM_{2.5}$ and incident active TB (Table 4). Generally, there was a trend of increased risk of active TB associated with 1-year to 3-year exposure to $PM_{2.5}$ but the risk was slightly mitigated in response to 5-year moving-average exposure. In the crude model 1, a 5 μg/m^3 increment of 2-year average $PM_{2.5}$ was significantly associated with a 55.9% higher risk of active TB for the individuals with LTBI (hazard ratio [HR] = 1.559, 95% CI: 1.206-2.015). When fully adjusted for all potential covariates, the risk remained statistically significant (HR = 1.506, 95% CI: 1.161-1.955).

We further conducted subgroup analyses using the fully adjusted model with a 2-year exposure window which yielded the most robust association with incident active TB (Figure 2). No significant modifying effects were observed with interaction p-values > 0.05. Specifically, sex-specific analyses indicated a higher risk of active TB incidence in women (HR = 2.242, 95% CI: 1.167-4.306) than in men (HR = 1.354, 95% CI: 1.007-1.820), but not significantly (Table S1). Long-term $PM_{2.5}$ exposure tended to have a stronger association with the development of active TB in participants with a higher education level (HR = 1.624, 95% CI: 1.169-2.257) and drinking alcohol (HR = 2.007, 95% CI: 1.118-3.604). Other strata also yielded insignificant effect differences with counterparts.

In sensitivity analyses, the results were robust when using a village-level random intercept and some remain significant but with wide CIs for 2- and 3-year moving-average exposure when considering only microbiologically confirmed TB cases (Table S2 and Table S3). Removing participants who failed to be followed up gave robust results (Table S4). Additionally adjusting for history of immune suppression, self-reported cancer and pneumonia yielded highly consistent results (Table S5 and Table S6). Including hetero-source PM_{10} in two-pollutant models gave similar results of association of $PM_{2.5}$ with incident LTBI except for 1-year exposure but made the association of $PM_{2.5}$ with incident TB fade due to multicollinearity (Table S7 and Table S8).

4. Discussion

Leveraging the unique cohort of older rural residents, our study suggests that long-term exposure to $PM_{2.5}$

Table 2. Association between LTBI at baseline and long-term exposure to $PM_{2.5}$.

	Model 1		Model 2		Model 3	
Exposure duration	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
1 year	1.042 (0.986, 1.101)	0.143	1.045 (0.988, 1.105)	0.125	1.044 (0.987, 1.104)	0.131
2 years	1.037 (0.976, 1.102)	0.240	1.038 (0.976, 1.103)	0.235	1.037 (0.976, 1.103)	0.242
3 years	1.037 (0.976, 1.102)	0.240	1.039 (0.977, 1.104)	0.220	1.038 (0.977, 1.104)	0.229
5 years	1.033 (0.975, 1.094)	0.268	1.034 (0.976, 1.095)	0.256	1.033 (0.975, 1.094)	0.267

Note: Adjusted ORs (95% CIs) of LTBI (latent tuberculosis infection) are presented by per 5 μg/m^3 increment in moving average ambient $PM_{2.5}$ concentrations in different durations. Model 1: adjusted for age, sex, and temperature. Model 2: additionally adjusted for BMI, education, family income, smoking status, and alcohol drinking. Model 3: additionally adjusted for family history of TB, close contact with TB patients, immune disorders, and type 2 diabetes. Abbreviations: HR, hazard ratio; CI, confidence interval; TB, tuberculosis; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm.

Table 3. Association between incidence of LTBI and long-term exposure to $PM_{2.5}$.

	Model 1		Model 2		Model 3	
Exposure duration	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
1 year	1.048 (0.961, 1.144)	0.291	1.068 (0.970, 1.175)	0.182	1.060 (0.962, 1.167)	0.237
2 years	1.011 (0.885, 1.156)	0.871	1.021 (0.890, 1.170)	0.767	1.022 (0.891, 1.172)	0.759
3 years	0.998 (0.837, 1.190)	0.984	1.003 (0.840, 1.199)	0.972	1.007 (0.842, 1.204)	0.938
5 years	1.011 (0.829, 1.232)	0.915	1.015 (0.832, 1.239)	0.883	1.020 (0.835, 1.247)	0.843

Note: Adjusted ORs (95% CIs) of incidence of LTBI (latent tuberculosis infection) are presented by per 5 μg/m^3 increment in moving average ambient $PM_{2.5}$ concentrations in different durations. Model 1: adjusted for age, sex, and temperature. Model 2: additionally adjusted for BMI, education, family income, smoking status, and alcohol drinking. Model 3: additionally adjusted for family history of TB, close contact with TB patients, immune disorders, and type 2 diabetes. Abbreviations: HR, hazard ratio; CI, confidence interval; TB, tuberculosis; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm.

Table 4. Association between incidence of TB and long-term exposure to $PM_{2.5}$.

	Model 1		Model 2		Model 3	
Exposure duration	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
1 year	1.304 (1.084, 1.568)	0.005	1.286 (1.062, 1.556)	0.010	1.278 (1.055, 1.548)	0.012
2 years	1.559 (1.206, 2.015)	0.001	1.522 (1.173, 1.975)	0.002	1.506 (1.161, 1.955)	0.002
3 years	1.591 (1.179, 2.147)	0.002	1.551 (1.148, 2.095)	0.004	1.534 (1.136, 2.071)	0.005
5 years	1.444 (1.059, 1.968)	0.020	1.423 (1.048, 1.934)	0.024	1.411 (1.040, 1.915)	0.027

Note: Adjusted HRs (95% CIs) of incidence of TB are presented by per 5 μg/m^3 increment in moving average ambient $PM_{2.5}$ concentrations in different durations. Model 1: adjusted for age, sex, and temperature. Model 2: additionally adjusted for BMI, education, family income, smoking status, and alcohol drinking. Model 3: additionally adjusted for family history of TB, close contact with TB patients, immune disorders, and type 2 diabetes. Abbreviations: HR, hazard ratio; CI, confidence interval; TB, tuberculosis; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm.

was associated with an increased risk of developing active TB from LTBI individuals though there was no robust association of $PM_{2.5}$with the prevalence or incidence of LTBI. Our finding implied that for older adults with LTBI living, air pollution control is highly warranted to mitigate the local burden of active TB.

Only a few previous studies have assessed associations between household fuel use and LTBI among the general population. In a previous case–control

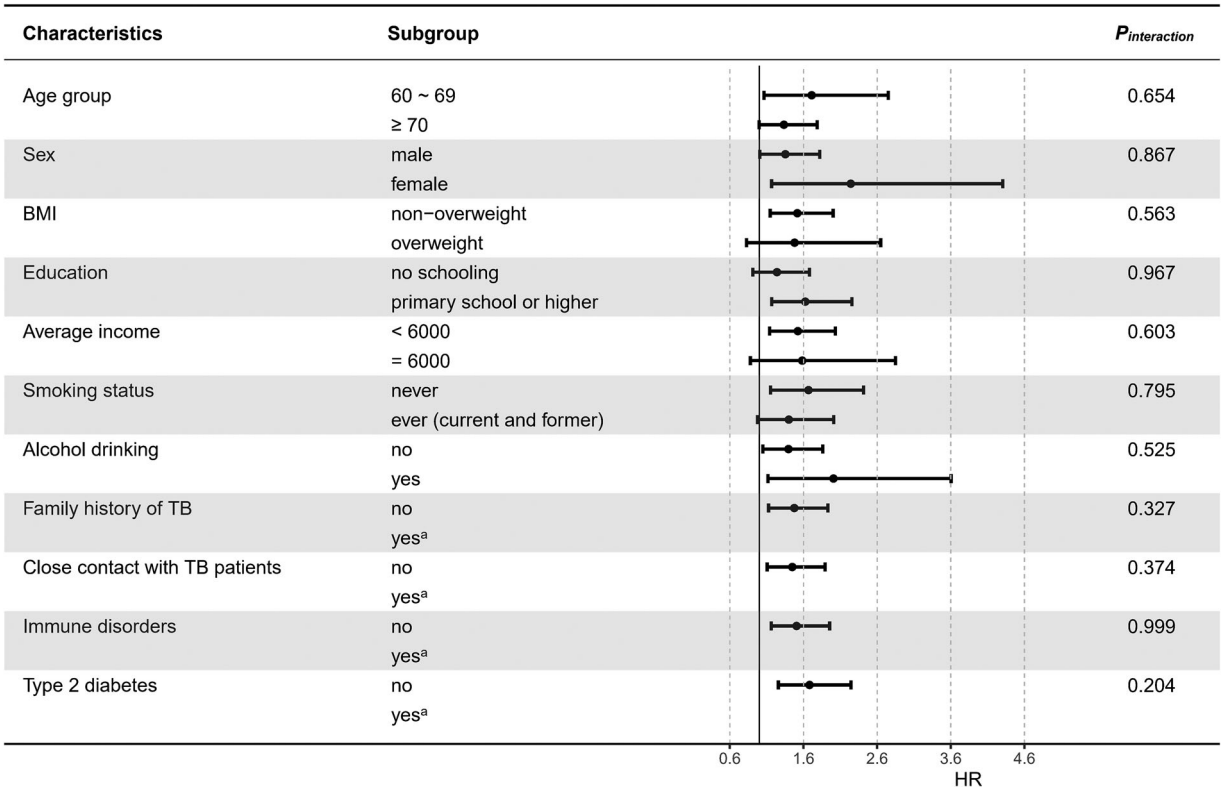

Figure 2. Subgroup analyses of association (HR) between the incidence of TB and 2-year exposure to $PM_{2.5}$. Note: Adjusted HRs (95% CIs) of incidence of TB are presented by per 5 μg/m^3 increment in 2-year moving average ambient $PM_{2.5}$ concentrations in different subgroups. Models were adjusted for temperature, age, sex, BMI, education, and family income, smoking status, alcohol drinking, family history of TB, close contact with TB patients, immune disorders, and type 2 diabetes. Abbreviations: HR, hazard ratio; CI, confidence interval; TB, tuberculosis; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm. [a] The sample size of the subgroup is too small to fitting the model.

study with 1088 participants, no significant association was found between the use of wood for cooking and the risk of LTBI [32]. Although the components of pollutants are different, we did not find an association between $PM_{2.5}$ and the risk of LTBI in our study participants either. MTB infection is mainly due to exposure to patients with active TB. In theory, in the scenario of high risk of MTB exposure, air pollution may increase the risk of MTB infection by increasing the spread of MTB droplets or reducing the immune protection of the respiratory tract of the population. However, in areas with a low risk of exposure to MTB, the impact of air quality on MTB infection transmission will be weakened. This may be the reason why there is no significant association observed in our study. Although larger-scale studies may have more findings, given the current downward trend in the incidence of TB in China, the focus of TB infection control will still be on the control of infectious agents and the promotion of isolation treatment and standardized treatment of active TB patients. Further longitudinal studies with serial LTBI testing in countries or areas with relatively high-level air pollutants to assess the associations between long-term exposure to $PM_{2.5}$ or other air pollutants and LTBI were needed.

To the best of our knowledge, this study is the first population-based, multicentre, prospective study to report that long-term exposure to $PM_{2.5}$ was positively associated with the risk of developing active TB among older adults with LTBI. Consistent with our findings, two recent systematic reviews suggested that long-term exposure to $PM_{2.5}$ was associated with an increased risk of active TB [16,17]. In addition, although a systematic review and meta-analysis did not find a positive association of long-term exposure to $PM_{2.5}$ with TB risk in general populations, it reported a significant association was observed in older adults [18]. Although previous studies have also suggested that long-term $PM_{2.5}$ exposure is associated with the risk of active TB, especially in older adults. However, our study provides stronger evidence. On the one hand, our study directly targets rural older adults, who are the key population of TB control in China. Their relatively stable long-term residence at the research site is more suitable for studying the association between long-term $PM_{2.5}$ exposure and TB. On the other hand, we directly observed the positive association between long-term $PM_{2.5}$ exposure and the risk of TB in the LTBI population rather than the general population. The advantage of this study design is that it is more in line with the characteristics of chronic infectious diseases. The association between exposure and disease is further refined to different disease progression stages such as infection and post-infection, which can more clearly understand the potential mechanism of exposure involved in the pathogenesis.

There are several possible biological mechanisms underlying the association between long-term exposure to $PM_{2.5}$ and the risk of active TB. First, ambient air pollution was associated with reducing immunity by interfering with lung defense functions, which would contribute to the development of pulmonary diseases [33]. Furthermore, oxidative stress in macrophages and epithelial cells and inflammation caused by particulate matter or other pollutants can reduce the immune response and increase susceptibility to TB [34,35]. Therefore, particulate matter such as $PM_{2.5}$ may accelerate the progression of TB. Second, it is well known that microbial growth or survival requires iron. The elevated $PM_{2.5}$ level consisting of transition metals increases the accumulation of iron, which may accelerate iron availability and provide a good environment for MTB proliferation [36–38]. Third, $PM_{2.5}$ exposure or diesel exhaust particles (DEP) could result in the inflammation of cytotoxicity of T cells through a macrophage-dependent manner and reduce the expression of IFN-γ, TNF-α in a DEP dose-dependent manner that might contribute to the progression of MTB infection [39,40]. Therefore, all described above suggest that exposure to $PM_{2.5}$ can reduce lung immunity and accelerate the progression of active TB. However, further studies on the precise mechanisms underlying associations between exposure to $PM_{2.5}$ and active TB are therefore required.

Preventive treatment for older adults with LTBI is a necessary intervention to reduce the occurrence of active TB, especially for older adults, since the above mechanism may be more prominent in this vulnerable population. Together with previous studies, immune aging, comorbidity, and environmental factors may lead to a higher risk of TB for older adults with LTBI. Our previous study suggested that the incidence of TB in rural communities may decrease by 30% if effective LTBI intervention is performed on individuals with a history of TB and age > 50 years [41]. This only accounts for 3% of the rural population, but it has greatly improved the cost-effectiveness of targeted interventions at the community level. Beyond older adults, high-risk populations such as HIV patients and children who are household contacts of patients with pulmonary TB also have contributions to the burden of TB. Therefore, besides the prevention of incident TB cases resulting from LTBI individuals, further understanding of the determinants of LTBI in older adults is conducive to the establishment of a new preventive treatment strategy under the guidance of risk classification suitable for China's national conditions.

4.1. Strengths and limitations

Compared with previous studies, the strengths of this study include a multicentre, prospective study design,

large sample size, and well control for established and potential confounding factors associated with the risk of active TB. However, our study also has several limitations. First, as with recent studies on the associations between air pollution and TB, our study is based on a satellite-based comprehensive model and assigned $PM_{2.5}$ levels according to the residents' addresses at the village level, which could not completely represent the real air pollution level of each resident; meanwhile, information about the participants' activity time spent outdoors and the indoor use of solid fuels was not collected. These issues might cause misclassification of the exposure and further studies using personal wearable devices could exclude this misclassification bias [42,43]. Second, we did not stratify the participants according to other air pollution exposures such as NO2, SO2, and CO which were not available during the follow-up period. Therefore, we were unable to access the modification effect of the abovementioned factors. Third, although we have adjusted several potential confounding factors in our multivariable model, confounding bias could not be completely excluded because of the unknown and unmeasured residual confounding factors. Fourth, the time when participants with LTBI at baseline were infected was unclear which might lead to potential bias on the association and further causal link between air pollution and incident active TB developed from LTBI. Finally, the proportion of non-microbially confirmed cases was high, which was due to the discovery of active cases based on chest radiography screening and might lead to potential bias from misclassification of disease status. However, the estimates of HRs of incident TB with 2- and 3-y moving-average $PM_{2.5}$ exposure were even bigger and significant when considering microbiologically confirmed TB only and the clinical cases count a lot as well for public health.

5. Conclusion

Based on the first large-scale, population-based, multicentre, prospective study, we uniquely posed out that long-term air pollution could be considered as a neglected risk factor for active TB development from LTBI. It shed some light on scaling up preventive treatment for individuals with LTBI, especially for those living in developing or less-developed areas where the air quality is poor. Meanwhile, no associations between long-term air pollution and LTBI were found. Our study contributes to the understanding of outdoor air pollutants exposures and the risk of active TB development from LTBI and suggests that studies investigating the benefits of improvement of air quality on TB control are warranted particularly for areas with high TB burden.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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