Alveolar deposition of inhaled fine particulate matter increased risk of severity of pulmonary tuberculosis in the upper and middle lobes

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To the Editor:

The chest radiograph (CXR) is still an important examination in the diagnosis of pulmonary tuberculosis in low- and middle-income countries [1]. The degree of abnormalities on the CXR reflects the overall disease severity in culture-positive pulmonary tuberculosis patients and is independently predictive of outcome [2]. Previous studies have shown that exposure to ambient air pollution was associated with an increased risk of *Mycobacterium tuberculosis* infection [3, 4]. However, the association between inhaled particulate matter (PM) deposition in the lungs and the severity of pulmonary tuberculosis at the lung lobar level is still poorly understood. We investigated the association between lung lobe-deposited dose of inhaled fine PM, $PM_{2.5}$ (particle size <2.5 µm in aerodynamic diameter), and CXR abnormalities in different lung lobes of pulmonary tuberculosis patients.

We conducted a retrospective study between April 2014 and November 2022 in culture-positive pulmonary tuberculosis patients between 18 and 95 years of age who underwent posteroanterior CXR during admission to the Chest Department of New Taipei Hospital in Taipei, Taiwan. We included patients who had been diagnosed with pulmonary tuberculosis with *M. tuberculosis* detected by culture-positive sputum samples [5] that were processed in the Infectious Disease and Clinical Microbiology section. Concentrated acid-fast bacilli fluorescence microscopy and mycobacterial culture were used to test the centrifuged sputum deposit. We used the MGIT TBc identification test to identify *M. tuberculosis* in the culture-positive isolates. Patients with nontuberculous mycobacteria infections and HIV were excluded from this study. The patient's smoking habit was ascertained through a narrated questionnaire. This study was approved by the Ethics Committee of the Taipei Medical University-Joint Institutional Review Board (IRB approval No. N202107075).

Deposition fraction of inhaled $PM_{2.5}$ in different lung lobes was derived from individual $PM_{2.5}$ exposures estimated using land use regression (LUR) models [6, 7]. $PM_{2.5}$ concentrations were collected from 20 measurement sites using European Study of Cohorts for Air Pollution Effects (ESCAPE) criteria (http://www.escapeproject.eu/manuals/) [8]. The residential addresses were collected and transformed into geocoded information using Taiwan Geospatial One Stop (www.tgos.tw). The Geographic Information System (ESRI ArcGIS v.10.8) analysis was conducted to calculate $PM_{2.5}$. Finally, the individual 1-year $PM_{2.5}$ exposure concentration was estimated following the LUR models using R software (R version 3.6.3). Next, we utilised the Multiple-Path Particle Dosimetry Model (MPPD version 3.04; Applied Research Associated, Raleigh, NC, USA) to estimate the deposition of $PM_{2.5}$ in different regions of the lung [6]. Calculating the alveolar regions in both lungs as symmetrical, we estimated 2500 mL for functional residual capacity, 500 mL of upper respiratory tract volume and each patient's tidal volume, and used a frequency of 20 breaths·min^{-1} with an inspiratory fraction of 0.5. The deposition of particles ranging from 0.01 to 1 µm in size was computed for nasal inspiration. The individual exposure to $PM_{2.5}$ was multiplied by the deposition fraction to calculate the $PM_{2.5}$ deposition in each lung lobe.

Full-size posteroanterior CXRs in tuberculosis patients were measured at the time of tuberculosis diagnosis. The presence, distribution and extent of pulmonary abnormalities were evaluated on each CXR by two radiologists who were blinded to each other's interpretations, and the final diagnosis was determined by a pulmonary tuberculosis specialist [9]. The pulmonary parenchyma was evaluated for each lobe: left upper

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Inhaled $PM_{2.5}$ associated with pulmonary tuberculosis https://bit.ly/3VXAKfq

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TABLE 1 Associations of particulate matter of <2.5 μm in aerodynamic diameter ($PM_{2.5}$) deposition in the total lung and alveolar region of five lung lobes with per cent of chest radiograph abnormalities in 116 culture-positive tuberculosis patients

	Abnormalities of chest radiographs %, mean±SD	Multivariate, β coefficient (95% CI)						
		Ambient $PM_{2.5}$	$PM_{2.5}$ deposition in total lung region	$PM_{2.5}$ deposition in alveolar region				
				Left upper lobe	Left lower lobe	Right upper lobe	Right middle lobe	Right lower lobe
Total lung	11.3±16.2	1.05 (−0.07–2.18)	**2.46 (1.09–3.82)**					
Left upper lobe	14.7±24.5	0.71 (−1.05–2.47)	2.02 (−0.18–4.21)	**8.07 (1.34–14.80)**				
Left lower lobe	17.1±27.4	0.83 (−0.35–2.01)	**2.19 (0.75–3.63)**		2.69 (−1.53–6.90)			
Left lung	11.1±18.8	0.77 (−0.56–2.10)	**2.10 (0.46–3.74)**	**8.41 (3.43–13.40)**	3.20 (−1.55–7.95)			
Right upper lobe	16.6±24.2	**2.31 (0.67–3.95)**	**4.22 (2.23–6.21)**			**13.80 (7.64–19.95)**		
Right middle lobe	10.7±18.7	1.11 (−0.18–2.41)	**2.54 (0.95–4.13)**				**17.20 (7.64–26.76)**	
Right lower lobe	7.2±15.6	0.57 (−0.53–1.67)	**1.66 (0.33–3.05)**					4.98 (−1.82–11.77)
Right lung	11.5±17.0	**1.33 (0.16–2.50)**	**2.82 (1.40–4.23)**			**9.81 (5.47–14.14)**	**18.73 (10.23–27.24)**	**5.31 (3.12–7.49)**

Covariates adjusted for age, sex and smoking status. Values in bold are deemed statistically significant with p<0.05.

lobe, left lower lobe, right upper lobe, right middle lobe and right lower lobe. To determine the percentage of affected lung, the extent of opacification, cavitation or other pathology was visually estimated as a percentage of visible lung; dense opacification of a zone was graded as 100% of that zone, whereas patchy opacification within a zone attracted scores of 100% based on the extent of opacification [2]. Any discrepancies in radiographic interpretation were read, and if any disagreement, the results were finalised based on the interpretation of the more experienced pulmonary tuberculosis specialist.

Covariables of age, sex and smoking status were adjusted in a generalised linear model to estimate the associations of $PM_{2.5}$ deposition in different lung lobes with percent abnormalities in each lung lobe of the study subjects. The normality of distribution was determined using the Shapiro–Wilk test. To estimate the contribution of each individual variable, the β coefficients were calculated.

There were 116 cases of positive-culture pulmonary tuberculosis included in this study. About 54.3% of patients were male with a mean±SD age of 55.4±22.9 years, and 19% were current smokers. We observed that the 1-year mean±SD concentration of $PM_{2.5}$ was 17.5±2.6 $\mu g \cdot m^{-3}$. Furthermore, the $PM_{2.5}$ concentrations were 12.5±2.1 $\mu g \cdot m^{-3}$ in the total lung region, 9.9±7.6 $\mu g \cdot m^{-3}$ in the head and nasal region, 1.1±0.2 $\mu g \cdot m^{-3}$ in the tracheobronchial region, and 2.2±0.4 $\mu g \cdot m^{-3}$ in the alveolar region. The $PM_{2.5}$ deposition in left upper lobe, left lower lobe, right upper lobe, right middle lobe and right lower lobe was 0.3±0.1, 0.7±0.7, 0.4±0.1, 0.2±0.1 and 0.7±0.1 $\mu g \cdot m^{-3}$, respectively.

The associations of $PM_{2.5}$ deposition in the total lung and alveolar region of five lung lobes with the per cent abnormalities in each lung lobe are summarised in table 1. We observed significant associations of $PM_{2.5}$ deposition in the total lung with radiographic severity. Importantly, $PM_{2.5}$ deposition in the upper and middle lung lobes was associated with radiographic severity ($p<0.05$). Moreover, we observed that the $PM_{2.5}$ deposition after inhalation poses higher risk than the ambient $PM_{2.5}$ risk. Previous studies have reported the association between air pollution and pulmonary tuberculosis severity [3, 10]. $PM_{2.5}$ is able to penetrate into the lung, impairing macrophage function such as production of tumour necrosis factor-α in the granulomata formation, which is implicated in the more severe condition [11, 12]. Taken together, these results indicate that the more inhaled $PM_{2.5}$ deposited in the lungs, the greater the severity of pulmonary tuberculosis.

We found that a 1 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ deposition in the alveolar region was associated with an increase in abnormalities of 8.07% (95% CI: 1.34–14.80) in left upper lobe, 13.80% (95% CI: 7.64–19.95) in the right upper lobe and 17.20% (95% CI: 7.64–26.76) in the right middle lobe ($p<0.05$). However, we did not observe any statistical association of $PM_{2.5}$ deposition in the other lung lobes. A previous study has shown that the upper and middle lobes were the most affected lobes in pulmonary tuberculosis [13]. The anatomy of the middle lobe makes particle expulsion more difficult [14], which may lead to more inhaled $PM_{2.5}$ being deposited by gravitational settling and diffusion. Furthermore, increased tuberculosis severity was commonly observed in the upper lung lobes, developing in the apical or the posterior regions of the upper lobes, which are highly oxygenated [15]. Our data show that more particulate pollution deposition is associated with an increased radiographic severity of tuberculosis infection.

This is the first study to examine the association between lung-deposited PM dose and severity in patients with culture-positive pulmonary tuberculosis pleurisy, particularly in the right middle lobe and both upper lobes. There are some limitations to the current study. There was no information available for diabetes mellitus, malnutrition and alcohol consumption in this study. The chemical components of $PM_{2.5}$ and the contribution of indoor air pollution should be examined in future work. A case–control study should be conducted to understand the possible causal relationship. In conclusion, inhaled fine particulate pollution was associated with an increased radiographic severity of pulmonary tuberculosis in the upper and middle lung lobes.

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