Higher alveolar deposition of particulate matter in emphysematous lobes of COPD

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To the Editor:

Emphysema can be examined quantitatively on high-resolution computed tomography (HRCT) by measuring the low-attenuation areas of the lung and has been associated with decrease in lung function in patients with COPD [1]. Previous studies have associated levels of air pollution with emphysema severity of the total lung [2, 3]. However, the relationship between inhaled particulate matter (PM) deposition in the lungs and the degree of emphysema at the lung lobar level remains poorly understood. We examined the association of lung lobe-deposited doses of $PM_{2.5}$ (particles with a 50% cut-off aerodynamic diameter of 2.5 µm) with the extent of emphysema in different lung lobes of COPD subjects.

Between April 2010 and October 2019, we conducted a retrospective study in 86 COPD patients between 40 and 90 years of age who underwent HRCT of the lungs in the respiratory department of New Taipei City Hospital, Taipei, Taiwan. The inclusion criteria in this study were patients having been diagnosed with COPD by a post-bronchodilator forced expiratory volume in the first second/forced vital capacity ratio of <70% [4]. Patients with a known malignancy or a progressive inflammatory condition (*i.e.* bronchiectasis, asthma, or other non-COPD-related disease) were excluded. In order to recruit patients with stable COPD, we excluded patients with a history of exacerbations during the 3 months prior to the study. Smoking status of the patients were collected by oral questionnaire. The Ethics Committee of the Taipei Medical University-Joint Institutional Review Board approved this study (approval no. N202003075).

Deposition fractions of inhaled $PM_{2.5}$ in different lung lobes were estimated by $PM_{2.5}$ exposures. First, individual-level exposure to $PM_{2.5}$ were predicted by a hybrid kriging/land-use regression (hybrid kriging-LUR) approach, which has been previously demonstrated [5]. Briefly, mean air pollutant data were obtained from Taiwan Environmental Protection Administration air quality monitoring stations (https://airtw.epa.gov.tw/). Land-use predictors with a Spearman's correlation coefficient larger than 0.4 with an effect on air pollutants were entered into a stepwise linear regression. Furthermore, to improve the robustness of the LUR model, a set of pollutant levels was created through a leave-one-out kriging interpolation and added to the model. Next, the Multiple-Path Particle Dosimetry Model (MPPD, version 3.04 for Windows, Applied Research Associates, Albuquerque, NM, USA) computational algorithm was used to estimate the deposition fractions of inhaled $PM_{2.5}$ in different lung lobes [6]. Assuming symmetrical alveolar regions in both lungs, the deposition fractions were estimated for a functional residual capacity of 3300 mL, an upper respiratory tract volume of 50 mL, a tidal volume of 625 mL and a breathing frequency of 12 breaths per min, with an inspiratory fraction of 0.5 with no pause between inhalation and exhalation. Particles ranging from 0.01 to 1 µm in diameter were assumed to enter the lung *via* the nose. The deposition of $PM_{2.5}$ in each lung lobe was calculated by the deposition fraction of $PM_{2.5}$ in that lung lobe multiplied by that individual's exposure to $PM_{2.5}$.

Spirometry was performed according to the American Thoracic Society/European Respiratory Society guidelines [7]. HRCT scans were acquired at suspended full inspiration. APOLLO Version 1.2 software (VIDA Diagnostics, Coralville, IA, USA) was employed to assess image attenuation on full-lung scans at a single reading centre by trained readers without knowledge of the participants' information. The lung volume was calculated, and all voxels in the lung were identified. The percent emphysema (or percent low attenuation area (%LAA)) on HRCT scans was determined as the voxel numbers less than

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The novelty of this study is that it identified the associations between $PM_{2.5}$ deposition in the lung and the degree of emphysema in different lung lobes of COPD patients, especially in the right middle lobe and both upper lobes https://bit.ly/3k21ri0

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−950 Hounsfield units in a lung field divided by the total voxel numbers in that lung field based upon pathological comparisons [8]. Emphysema severity was categorised into three levels: level 1 if 1%⩽% LAA<5%, level 2 if 5% ⩽%LAA<25%, and level 3 if 25%⩽%LAA<50% as previously reported [9, 10].

A generalised linear model, adjusted for age, sex, body mass index (BMI) and smoking pack-years, was performed to identify the associations of $PM_{2.5}$ deposition in the total lung and alveolar region of five lung lobes with lung function and the percent emphysema in each lung lobe. The %LAA in each lung region was normally distributed in this study. In order to estimate the contribution of each of the individual variables, the beta coefficients were calculated.

The patients had a mean age of 70.4±7.9 years, and 91.9% were men. Their mean BMI was 23.3±4.4 $kg \cdot m^{-2}$. 40.7% of the subjects were current smokers, 51.2% were ex-smokers, and 8.1% were nonsmokers. Their mean smoking pack-years were 50.4±37.9 pack-years. The $PM_{2.5}$ deposition in the total lung, left upper lobe, left lower lobe, right upper lobe, right middle lobe, and right lower lobe were 27.99±3.36, 4.17±0.50, 8.14±0.98, 4.69±0.56, 2.50±0.30, and 8.49±1.02 $\mu g \cdot m^{-3}$, respectively. Next, we observed that $PM_{2.5}$ deposition in the alveolar region in five lung lobes decreased in the following order: right lower lobe>left lower lobe>right upper lobe>left upper lobe>right middle lobe (table 1). A previous study showed that $PM_{2.5}$ deposition in the tracheobronchial region were: left upper lobe (15%), left lower lobe (33%), right upper lobe (14%), right middle lobe (5%), and right lower lobe (30%) [11]. Although more particles are deposited in lower lobes, their associations with emphysema severity remain unclear.

TABLE 1 Associations of $PM_{2.5}$ deposition in the total lung and alveolar region of five lung lobes with lung function and percent emphysema in 86 COPD patients

	Mean±SD	Multivariate, beta coefficient (95% CI)					
		Total lung	Alveolar region				
			Left upper lobe	Left lower lobe	Right upper lobe	Right middle lobe	Right lower lobe
Mean±SD $PM_{2.5}$ deposition in lung regions, $\mu g \cdot m^{-3}$		27.99±3.36	4.17±0.50	8.14±0.98	4.69±0.56	2.50±0.30	8.49±1.02
Lung function							
FEV_1, %	56.6±19.8	−0.710 (−1.960–0.541)					
FEV_1, L	1.3±0.5	−0.022 (−0.053–0.009)					
FEV_1/FVC, %	52.3±10.0	−0.356 (−0.991–0.279)					
Percent emphysema							
Emphysema severity, point	2.1±0.5	**0.059 (0.029–0.090)***					
Total lung LAA, %	15.6±9.4	**1.296 (0.782–1.811)***					
Left upper lobe LAA, %	17.0±11.7		**9.962 (5.523–14.402)***				
Left lower lobe LAA, %	14.0±11.1			**4.492 (2.314–6.671)***			
Left lung LAA, %	15.8±10.8		**9.561 (5.518–13.603)***	**4.897 (2.824–6.970)***			
Right upper lobe LAA, %	16.5±11.2				**7.795 (4.039–11.552)***		
Right middle lobe LAA, %	17.3±10.4					**13.658 (6.964–20.353)***	
Right lower lobe LAA, %	13.1±9.1						**3.294 (1.646–4.942)***
Right lung LAA, %	15.4±9.0				**6.888 (3.914–9.863)***	**12.952 (7.366–18.537)***	**3.804 (2.157–5.450)***

Adjusted for age, sex, body mass index, and smoking pack-years. Values in bold characters are deemed statistically significant. FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; LAA: low attenuation area; $PM_{2.5}$: particles with a 50% cut-off aerodynamic diameter of 2.5 μm. *: p<0.05.

The associations of $PM_{2.5}$ deposition in the total lung and alveolar region of five lung lobes with the lung function and the percent emphysema in each lung lobe are summarised in table 1. We observed significant associations of $PM_{2.5}$ deposition in the total lung with the severity of emphysema. Importantly, $PM_{2.5}$ deposition in each lung lobe was associated with the degree of emphysema in the same lung lobe ($p<0.05$). Air pollution has been reported to be associated with emphysema severity [2, 3]. Previous studies showed that $PM_{2.5}$ may penetrate deeply into the lung and destroy the alveolar septa through the generation of excessive reactive oxygen species (ROS) [12]. ROS can cause endothelial cell apoptosis, thus causing emphysema [13, 14]. Taken together, our data suggest that $PM_{2.5}$ deposition in each lung lobe is positively associated with the degree of emphysema.

We observed that a 1 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ deposition in each lung lobe was significantly associated with increases in %LAA (beta coefficient) of that lung lobe ($p<0.05$). Furthermore, the beta coefficients decreased in the following order: right middle lobe >left upper lobe>right upper lobe>left lower lobe>right lower lobe ($p<0.05$). Previous findings also showed that the right middle lobe has the highest percent emphysema compared with other lobes in spite of its small size [15]. Although $PM_{2.5}$ deposition is the least in the right middle lobe, it is also likely that particle clearance would also be more difficult due to the anatomy of the right middle lobe [6, 11, 15]. Furthermore, smoking-induced emphysema was also commonly observed in upper lung lobes. It was reported that higher mechanical stress and more negative intrapleural pressures during inhalation in the upper lung lobes may result in the high distribution of emphysema in the upper lung lobes [16, 17]. Nevertheless, further studies should be performed to clarify this association.

The limitation of this study included its small sample size. The chemical components of $PM_{2.5}$ (*i.e.* water soluble ions, heavy metals, and polycyclic aromatic hydrocarbons) were not examined in our study. The effects of indoor pollution should also be clarified in future studies. We observed the associations between $PM_{2.5}$ deposition and percent emphysema, but the inflammatory responses and underlying mechanisms need to be investigated in the future. Finally, because our study was retrospective in design, causal inferences of association could be a limitation.

This is the first study identifying the associations between deposited particles in the lungs and the degree of emphysema in different lung lobes of COPD patients, especially in the right middle lobe and both upper lobes. Our results suggest that inhaled particulate pollution may be a risk for the development of emphysema in different lung lobes.

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