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Emphysema and Airflow Obstruction in Non-Smoking Coal Miners with Pneumoconiosis

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Statistical Analysis C
Data Interpretation D
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Literature Search F
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Background: Accumulating evidence shows that functional impairment in subjects with coal workers' pneumoconiosis (CWP) is principally due to emphysema and airflow obstruction, rather than underlying restrictive mechanisms. However, cigarette smoking has remained a major confounder. The aim of this study was to assess whether coal dust exposure was associated with emphysema and/or airflow obstruction in the absence of smoking history.

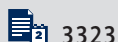
Material/Method: The subjects evaluated for possible pneumoconiosis between 2013 and 2015 were retrospectively enrolled into this study. After excluding those with history of smoking, tuberculosis, or lung cancer, the study population was a total of 57 subjects. The emphysema severity and airflow obstruction were quantified by computed tomographic densitometry analysis and spirometry, respectively. For comparability regarding emphysema, 9 age- and sex-matched nonsmoker (n=9) control subjects without known lung disease were randomly selected from a radiology database.

Results: Emphysema severity was significantly higher in the CWP group compared with the control group (15% vs. 4%, $p < 0.001$). The median percent emphysema and percentage of those with FEV1/FVC < 0.7 was 13% and 37% in subjects with simple CWP and 18% and 67% in subjects with complicated CWP, respectively. Percent emphysema and Perc15 (15th percentile of the attenuation curve) was correlated with FEV1/FVC ($r = -0.45$, $r = -0.47$) and FEF25-75 ($r = -0.36$, $r = -0.56$), respectively, but not with perfusion score. A linear regression analysis showed that factors associated with emphysema were FEV1/FVC ($\beta = -0.24$, $p = 0.009$) and large opacity ($\beta = -3.97$, $p = 0.079$), and factors associated with FEV1/FVC were percent emphysema ($\beta = -0.51$, $p = 0.018$) and tenure ($\beta = -0.63$, $p = 0.044$).

Conclusions: Our results support the observation that coal dust exposure is associated with emphysema and airflow obstruction, independent of smoking status.

MeSH Keywords: Coal • Emphysema • Pneumoconiosis • Pulmonary Disease, Chronic Obstructive • Smoking

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Background

Coal is a combustible mineral of organic origin, composed mainly of carbon and hydrocarbons. The ranking of coal (its hardness and age) increases from peat to lignite, sub-bituminous to bituminous, and then to anthracitic. As its rank increases, the ratio of carbon to other chemicals and mineral contaminants increases. Coal mine dust contains various minerals in small amounts, such as silica (quartz), iron, aluminum, pyrite, kaolin, and mica. Exposure to respirable mixed coal mine dust results in development of coal workers' pneumoconiosis (CWP), which is defined as the deposition of coal dust in the lungs, and the tissue's reaction to its presence [1]. The risk of CWP seems to depend on the concentration and duration of exposure to coal dust [1].

Pathologically, the defining lesion of CWP is the coal dust macule. These non-palpable lesions appear as 1–4 mm in diameter, black areas distributed diffusely throughout the lung, but more so in the upper zone. Microscopically, the macular lesion consists of focal collections of coal dust-laden macrophages at the division of respiratory bronchioles [2]. These cells extend into adjacent alveolar spaces as well as into the peribronchiolar interstitium. It is also seen along the lymphatics within the secondary lobular septa, and beneath the visceral pleura. Focal emphysema is a subtype of centriacinar emphysema, which is known to be a histopathologic sign of CWP [1,2]. It also shows similarities to centrilobular emphysema in terms of gross and histological features. This process is mediated by antiproteases, secreted by coal dust-activated macrophages [2–4], which, along with coal macules, forms the characteristic lesion of CWP. Earlier CWP studies have shown that patients with p opacities have a lower diffusing capacity than those patients with q or r opacities [5]. Authors have attributed this to the development of focal emphysema in patients with p opacities [6,7].

CWP is classified as a simple or complicated form, depending on the presence of progressive massive fibrosis (PMF). Clinically significant lung function impairment is believed to generally occur in complicated forms, predominantly in category B and C [2,8]. In contrast, the present data suggest that simple CWP can also be associated with lung function impairment [9]. Moreover, it seems that this impairment has been principally due to emphysema and airflow obstruction, rather than underlying restrictive mechanisms [10,11]. However, cigarette smoking has remained a major confounder in terms of causality.

The primary goal of the present study was to test whether coal dust exposure is associated with emphysema and/or airflow obstruction in the absence of smoking history. We also investigated whether patients with P-type opacity have different traits regarding emphysema or airflow obstruction.

Material and Methods

Study design

This research was observational, as well as a hospital-based cross-sectional study. It was approved by the local Ethics Committee, although patient consent was not deemed necessary due to the study's retrospective nature. The paper was written according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) statement.

Participants and setting

All coal mine workers or ex-workers seeking compensation for possible pneumoconiosis were included in the study, and were evaluated by the Occupational Disease Diagnosis Council of Bulent Ecevit University, Zonguldak, Turkey from 1 January 2013 to 31 May 2015. These miners were from the Zonguldak coal basin, the major bituminous coal mine area in Turkey. All claimants were referred by the National Social Security Institution (NSSI).

The Occupational Diseases Diagnosis Council was composed of all faculty members working in the Department of Pulmonary Medicine of Bulent Ecevit University. The Turkish Institute for Occupational Health and Safety certified that each author was an expert on pneumoconiosis (on behalf of the International Labour Office, ILO). Having at least 3 members was necessary for the formation of the committee. Evaluation of pneumoconiosis was based on chest radiography, spirometry, and high-resolution computed tomography (HRCT), and is mandatory according to NSSI regulations. The committee evaluated and classified each chest radiograph for perfusion, size, and shape of small and large opacities, according to the 1980 ILO [12]. The perfusion evaluation was based on chest radiographs, as there are no validated standards for CT scans.

The presence of the opacity perfusion subcategory, 1/0 or greater, or large opacity (category A, B, or C) was considered as evidence of CWP. Large opacities were classified as follows: Category A: Sum of the greatest diameter of one or more opacities exceeding 1 cm but less than 5 cm. Category B: Sum of the greatest diameter of one or more opacities exceeding 5 cm, but their combined area not exceeding the equivalent of the right upper lung zone. Category C: One or more opacities with combined area exceeding the equivalent of the right upper lung zone. Agreement by 2 of the 3 readers was essential for a diagnosis of CWP. Five hundred thirty-two (n=532) subjects were evaluated for compensation for pneumoconiosis. We excluded smokers, former smokers, anyone with a history of tuberculosis or lung malignancy, as well as any pneumoconiosis. The remaining patients (n=57) formed the study sample (Figure 1).

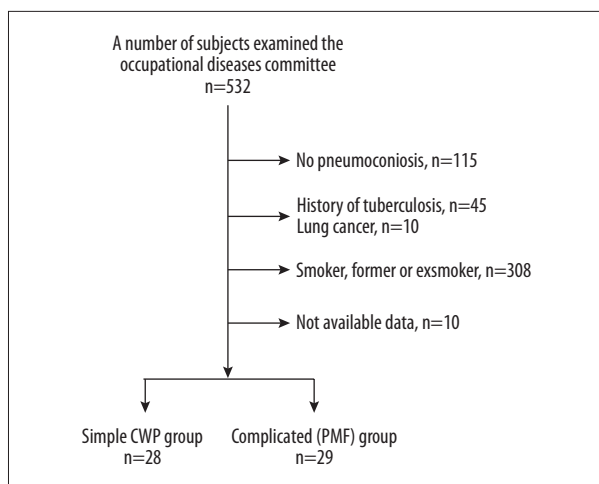


Figure 1. Flow diagram of subject enrollment. The exclusion categories are not mutually exclusive.

Data source and measurement

The electronic database was able to collect demographics, spirometric, and procedural data, including these variables for each subject: age, tenure, smoking history, body mass index, FEV1, FVC, FEF25-75, FEV1/FVC, shape of small opacity, perfusion category, and potential large opacity. The perfusion of small opacities was scored on a linear scale as follows: 1/0=2, 1/1=3, 1/2=4, 2/1=5, 2/2=6, 2/3=7, 3/2=8, and 3/3=9.

Spirometric measurements were performed with the MasterScreen pneumo-device (flow-based) at rest (i.e., while in a sitting position) by a trained technician, according to guidelines of the American Thoracic Society and European Respiratory Society. Spirometric predictive values were based on the European Community for Coal and Steel reference values [13]. All lung function data, except FEV1/FVC values, are expressed as percentages of the predicted values. The data for all variables were based on pre-bronchodilator spirometry.

HRCT scans were obtained with the Activision 16-row CT scanner (Toshiba Medical Systems, Otawara, Japan; 1.5 mm slice thickness, tube voltage 140 kV, tube current 175 mA). The matrix size was 512×512 at a pixel size of 0.5 mm. The CT scans were performed during the same week as the spirometry. Airway Inspector Software (www.airwayinspector.org) was used for automated densitometric analysis. Emphysema was quantified by the percentage of low-attenuation areas, using a Hounsfield Unit (HU) threshold <-950 and Perc15 (HU point below which 15% of the voxels are distributed).

Data analysis

After determination of appropriate HRCT scan data (n=53 of n=57) for analysis in an electronic database, we decided to use

a control group for emphysema comparability because CT densitometric analysis is affected by multiple factors. Kumpel et al. found the emphysema index (%), (SD) to be 5.4 (66) and 30.2 (248) for non-smoking non-miners and never-smoking coal miners, respectively. The size effect (Hedges' g) of this study was 1.08. We used this value for sample size calculation along with an allocation ratio (n2/n1=5.7). We accepted a 0.05 level for type 1 error (α) and 0.2 for type 2 errors (β). Eight cases (n=8) were adequate to form a control group. Nine age- and sex-matched control cases (n=9) with no history of working in a mine or ever having smoked were chosen randomly from the radiology database.

Descriptive statistics of categorical variables are given as numbers or percentages; continuous variables are given as medians (interquartile range). A chi-square test was used to evaluate categorical variables. The Mann-Whitney U-test was used to compare the medians of variables when appropriate. The relationship between emphysema and spirometric variables was evaluated with a partial correlation analysis, controlling for age and body mass index (BMI). Multiple linear regression analysis (backward method) was used to determine independent factors associated with the percent of emphysema and FEV1/FVC, respectively. The following variables were included in the regression models: age, BMI, tenure, FEV1/FVC, perfusion score and large opacity for percent of emphysema (dependent variable) and age, BMI, tenure (underground working years), percent of emphysema, perfusion score and large opacity for FEV1/FVC (dependent variable), respectively. It was reported in previous studies that A-type large opacity shows similarity to simple CWP, rather than B- and C-opacities showing physiological impairment [14,15]. The presence of large opacity was defined as category B or C and was entered into the regression analysis as indicator variables.

Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS, IBM Inc., Chicago, IL) and MedCalc for Windows, version 12.2.1.0 (MedCalc Software, Ostend, Belgium). P values were two-sided, and values less than 0.05 were considered statistically significant. Sample size calculations were performed with G*Power software v.3.1.9.2.

Results

The study population consisted of 57 non-smoking men (n=57) with CWP. The control group included 9 (n=9) non-smoking men without any known pulmonary disease. The average age of subjects with CWP was 71 (IQR, 62–79) years. The average coal dust exposure duration was 24 years (range 10–35). Densitometric analysis was performed for 54 of 57 cases due to inappropriate HRCT scan data in 3 cases. Spirometric examination was used for evaluation in 51 of 57 cases. Subjects

Table 1. Demographics, spirometry, and radiologic characteristics in the cases with CWP and control.

	Pneumoconiosis			Control	p Value
	All	Simple	Complicated (PMF)		
Demographics*	n=57	n=28	n=29		
Age, years	71 (62–79)	63 (54–73)	75 (71–80)	70 (59–79)	0.786**
BMI	27 (24–31)	28 (26–33)	26 (22–29)	–	0.002
Tenure, years	24 (17–26)	19 (14–25)	25 (23–27)	–	0.01
Spirometry##					
FEV1, % predicted	73 (57–90)	81 (64–94)	66 (53–78)	–	0.012
FVC, % predicted	84 (69–95)	87 (69–99)	79 (70–89)	–	0.018
FEV1/FVC, %	70 (62–77)	72 (68–77)	64 (58–76)	–	0.015
FEV1/FVC<0.7, n (%)	26 (51)	10 (37)	16 (67)	–	0.035
FEF25–75, % predicted	39 (29–60)	49 (32–79)	34 (28–45)	–	0.024
Radiology					
Profusion, (n)		1/0 (2), 1/1 (13), 1/2 (5), 2/1 (1), 2/2 (5), 2/3 (2)	1/1 (2), 1/2 (5), 2/1 (1), 2/2 (6), 2/3 (12), 3/2 (1), 3/3 (2)		
Profusion score	5 (3–7)	3 (3–5.5)	7 (5–7)		<0.001
Small opacity, (n)		pp (6), ps (14), pq (1), qr (1), qt (2), rq (1), sp (2), tu (1)	pp (1), ps (5), pq (6), qr (3), qt (6), ru (2), sp (1)		
Large opacity, n (%)					
Category A			11 (38)		
Category B			11 (38)		
Category C			7 (24)		
Emphysema, % [#]	15 (11–22)	13 (10–17)	18 (13–25)	4 (3–6)	<0.001**
Perc15 [#]	948 (929–974)	940 (919–958)	959 (938–988)	897 (894–910)	<0.001**

* Data expressed as median (IQR), ** All group versus control group, PMF – progressive massive fibrosis; BMI – body mass index; Perc15 – 15th percentile of the attenuation curve; ## n=51; # n= 54.

were categorized into simple CWP (28 patients) and complicated CWP (PMF) (29 patients) groups. Table 1 shows demographics, spirometry, and radiologic measurements in CWP and control subjects.

Percent of emphysema and Perc15 values were significantly higher in the CWP group compared with the control group ($p<0.001$). There was also a significant difference in terms of emphysema and Perc15 between simple CWP and the control group ($p<0.001$, $p=0.001$), as well as between the PMF group and the control group ($p<0.001$, $p<0.001$), respectively. Spirometric evaluation revealed obstructive lung disease (FEV1/FVC<0.7) in the majority (n=26, 51%) of patients with CWP. We used the

Global Initiative for Chronic Obstructive Lung Disease, and defined 25/51 (49%) subjects at stage 0, 3 (6%) at stage I (mild), 16 (31%) at stage II (moderate), 6 (12%) at stage III (severe), and 1 (2%) at stage IV (very severe). The number and percent of subjects demonstrating the FEV1/FVC ratio was less than 0.7 and that the FEV1 was less than 80% of the predicted value was found to be 7 (26%) in simple CWP and 16 (67%) in the complicated CWP group. Restrictive impairment in lung function (FEV1/FVC ≥ 0.70 and FVC <80% as predicted) was seen in 9 patients (18%), all of which had complicated CWP.

Correlation between spirometric findings and densitometric emphysema values was investigated. In patients with CWP, partial

correlation analysis (controlling for age and BMI) revealed that the percent of emphysema and Perc15 were correlated with FEV1/FVC ($r=-0.45$, $p=0.002$, $r=-0.47$, and $p=0.001$), and FEF25-75 ($r=-0.36$, $p=0.015$ and $r=-0.56$, $p<0.001$), respectively. FEV1 was only significantly correlated with Perc15 ($r=-0.38$, $p=0.01$), but no correlation was found between FVC and percent of emphysema or Perc15. In partial correlation analysis, a significant correlation ($p<0.05$) was observed between tenure and percent of emphysema ($r=-0.36$), Perc15 ($r=-0.39$), FEV1/FVC ($r=-0.35$), FEF25-75 ($r=-0.38$), FEV1 ($r=-0.33$), but not with FVC ($r=-0.18$).

To evaluate factors associated with percent of emphysema and FEV1/FVC, we performed multiple linear regression analyses. In the first model, factors associated with percent of emphysema were FEV1/FVC and the presence of large opacity (B and C) ($\beta=-0.24$, $p=0.009$ and $\beta=-3.97$, $p=0.079$, respectively). Other factors not retained in the models were age, BMI, tenure, and the perfusion score. In the second model, emphysema ($\beta=-0.51$, $p=0.018$) and tenure ($\beta=-0.63$, $p=0.044$) remained independently associated with FEV1/FVC. Other factors (age, BMI, and perfusion score) did not reach statistical significance in this model.

Last, we evaluated whether the P-type ($n=18$) and other type of opacities (q, r, s, t, u) ($n=7$) have different traits in terms of emphysema or airway obstruction in cases with simple CWP. Regarding the topics of age, perfusion score (median), and tenure, there were no differences between groups. Percentage of emphysema and ratio of FEV1/FVC were compared between groups using the Mann-Whitney *U*-test. Although percentage of emphysema in subjects with P-type opacity was higher than it was in subjects with other type opacities, it was not statistically significant (Figure 2). In contrast, there was a statistically significant difference in FEV1/FVC between subjects with P-type opacities and other types (Figure 2).

Discussion

The present study shows that CWP is closely associated with both emphysema and airflow obstruction in non-smoking subjects. The average percent of emphysema and percent of subjects with a FEV1/FVC ratio was less than 0.7, and was 15% and 51%, respectively, in subjects with CWP. In a multivariate analysis, the percent of emphysema was associated with FEV1/FVC and the presence of large opacity (category B and C). Airflow obstruction (FEV1/FVC <0.7) was associated with percent of emphysema and tenure. We attempted to exclude effects of cigarette smoking and concomitant pulmonary pathology on the lungs, which is a major advantage of our study. We did not find a correlation between ILO perfusion score and impairment of lung function or emphysema, which was

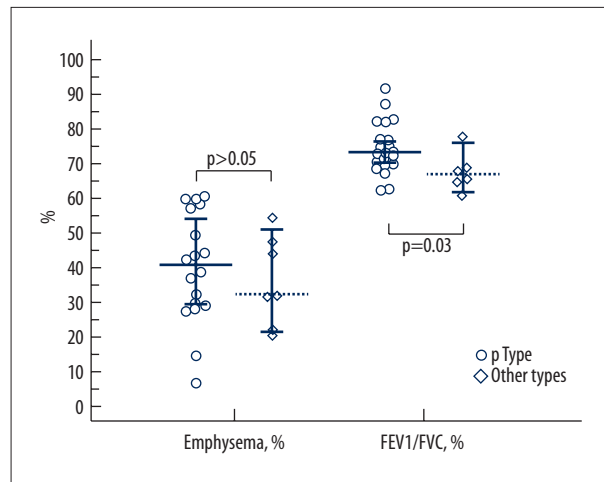


Figure 2. Comparison of small opacities (p-type vs. other type) for emphysema and FEV1/FVC. The percent values for emphysema is multiplied by 3 for better comparison.

similar to previous studies [16]. Additionally, in subjects with simple CWP, P-type opacities showed a higher percent of emphysema, although not significant, but a higher FEV1/FVC value than other opacities.

Airflow obstruction, spirometrically, is diagnosed by decreased FEV1/FVC, which is the result of decreased elastic recoil (i.e., emphysema) of the lungs, promoting airflow and increased resistance (airway wall thickening and bronchiolar obliteration) of the airways, which limits airflow. Concerning the relationship between CWP and emphysema, the majority of reported studies are based on chest radiograph or autopsy. Chest radiograph is insensitive for quantification of emphysema and determination of concomitant pulmonary pathology [17]. Autopsy studies also have some limitations, such as the possibility of subjects with severe disease (selection bias) and a long interval between spirometry and death [18,19].

Additionally, the effect of smoking on the development of emphysema or airflow obstruction cannot be eliminated, which is the most important problem in these studies [20-22]. Despite this, autopsy studies have strongly demonstrated that coal mine dust exposure is associated with emphysema, and its severity increases with increasing lung dust retention. The best evidence was reported by Kumpel et al. [18], who found that coal mine dust exposure and cigarette smoking presented similar problems in the prediction of emphysema severity. Furthermore, this study showed that the largest difference in emphysema severity was between non-smoking miners and non-smoking non-miners (about 6-fold). They found that the average percent of emphysema in non-smoking miners was 30%. We found the percent of emphysema in non-smoking subjects with CWP to be 15% (median, about 4-fold compared with the control group). Our study showed that large opacities

(category B and C) were associated with emphysema in the regression model. This suggests that paracicatricial emphysema in areas adjacent to PMF contribute to emphysema severity [2].

Coal dust inhalation can initiate toxic and inflammatory processes in the airways and alveolar tissue [23,24]. Increased airway resistance in CWP was shown in a series of physiological studies [25,26]. Moreover, it is well-documented that the prevalence of chronic bronchitis is higher in coal miners [27]. Available evidence indicates that functional impairment is associated with small airways, rather than central or large airways [28]. However, the underlying mechanism in obstructive ventilatory defect is largely unknown [20]. We found that the prevalence of airway obstruction (FEV1/FVC <0.7) in subjects with simple CWP was 37%. Similarly, Kibelstis et al. reported that the prevalence of airway obstruction in non-smoking coal miners was 37.6% (10).

In our study, the percent of subjects with FEV1/FVC ratio was less than 0.7, and FEV1 was less than 80% of the predicted value, or 26% in the simple CWP group and 67% in the PMF group, respectively. It is known that clinically significant COPD develops in approximately 25% of smokers [29]. The percentage with simple CWP was almost identical.

The relationship between the ILO perfusion score and lung function (or emphysema) is not clear. We did not find a significant relationship between the perfusion score and pulmonary function parameters, or the percent of emphysema. Similar results have been reported in several previous studies [16,19,30,31]. Gevenois et al. suggest that the presence of micronodules in coal miners has no effect on lung function, and that it should only be considered as a marker of exposure [19]. Bauer et al. did not find an association between perfusion score and pulmonary function or blood gas parameters [16]. On the other hand, there are studies showing that the perfusion score is associated with airway limitation [32,33]. It is also known that the presence of emphysema may reduce accuracy of reading of perfusion on chest radiographs [4,7]. In our study, subjects with lower perfusion scores had higher emphysema scores (data not reported). Furthermore, morphologic changes at the level of respiratory bronchioles are not detected by conventional spirometry [19].

Previous reports noted that the shape of small opacities is associated with impairment of pulmonary function. It was shown that individuals with p opacities have a lower diffusing capacity than patients with q and r opacities [5]. There is additional evidence that P-type opacity is associated with increased air space size, which is a result of development of focal emphysema [6,7,34]. In our study, emphysema more common in individuals with P-type opacity than with other types, although this difference was not statistically significant. In contrast,

other opacities were associated with airway obstruction; obstructive disease of the small airways (less than 1 mm in diameter) are often not detected by conventional spirometry or measurements of airway resistance, and are ultimately responsible for less than 15% of total airway resistance [35,36]. This may be a reason for normal spirometric findings in individuals with P-type opacity. Pathologically, q and r opacities (formerly micronodular and nodular, respectively) were pathological palpable lesions. They are classified as anthracosilicotic nodules due to the similar histology to silicotic nodules [37]. It was similarly demonstrated in previous reports that these lesions were associated with increased airway resistance [14]. Furthermore, in some studies, irregular opacities, which are considered to be related to tissue reaction to inhaled coal dust, were reported to be more strongly associated with impaired pulmonary function than were round opacities [38]. In the group classified as "other type opacities," the reason for impaired pulmonary function may be the combined effects of these opacities mentioned above. However, the limited number of cases in this group makes interpretation difficult.

Limitations

There are several limitations in our study, including a recall bias due to the retrospective design and small sample size, affected by strict inclusion criteria. A large proportion of the study population was composed of retired coal miners who had already applied for compensation, so selection bias was possible. Underlying pulmonary disease (e.g., alpha 1-antitrypsin deficiency, asthma, or bronchial hyperreactivity) may similarly change study outcomes. However, pre-recruitment medical examination should have largely eliminate this possibility. Another limiting factor was that the pre-bronchodilator spirometric assessment was performed, which can influence prevalence of airway obstruction. The quantification of emphysema using CT densitometry can be influenced by multiple factors, including scanning protocol, scanner calibration, and variation in inspiratory level. Exposure to dust varies widely from mine to mine, and, in certain places, within a given mine. Multiple etiologic factors other than coal may be involved in individual cases, which makes causal interpretation difficult.

Conclusions

Some authors have expressed doubt as to whether coal mine dust can cause clinically significant loss of lung function in the absence of complicated pneumoconiosis [2,8,21]. However, available evidence indicates that the presence of simple CWP contributes significantly to the impairment of lung function in coal miners, which also seems to be related to obstructive lung disease [9,11,26]. Smoking is a major confounder in this relationship as well. Lifelong non-smokers offer a unique

opportunity to evaluate the association between coal dust exposure and obstructive lung disease. Despite all of these limitations, this study highlights the association of obstructive lung disease with coal dust exposure in non-smoking coal miners with pneumoconiosis.

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Conflicts of interest

The authors report no declaration of conflict of interest. The authors alone are responsible for the content and writing of the paper.