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Exposure to Ambient Particulate Matter Is Associated With Accelerated Functional Decline in Idiopathic Pulmonary Fibrosis

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BACKGROUND: Idiopathic pulmonary fibrosis (IPF), a progressive disease with an unknown pathogenesis, may be due in part to an abnormal response to injurious stimuli by alveolar epithelial cells. Air pollution and particulate inhalation of matter evoke a wide variety of pulmonary and systemic inflammatory diseases. We therefore hypothesized that increased average ambient particulate matter (PM) concentrations would be associated with an accelerated rate of decline in FVC in IPF.

METHODS: We identified a cohort of subjects seen at a single university referral center from 2007 to 2013. Average concentrations of particulate matter < 10 and < 2.5 $\mu g/m^3$ (PM_{10} and $PM_{2.5}$, respectively) were assigned to each patient based on geocoded residential addresses. A linear multivariable mixed-effects model determined the association between the rate of decline in FVC and average PM concentration, controlling for baseline FVC at first measurement and other covariates.

RESULTS: One hundred thirty-five subjects were included in the final analysis after exclusion of subjects missing repeated spirometry measurements and those for whom exposure data were not available. There was a significant association between PM_{10} levels and the rate of decline in FVC during the study period, with each $\mu g/m^3$ increase in PM_{10} corresponding with an additional 46 cc/y decline in FVC ($P = .008$).

CONCLUSIONS: Ambient air pollution, as measured by average PM_{10} concentration, is associated with an increase in the rate of decline of FVC in IPF, suggesting a potential mechanistic role for air pollution in the progression of disease. CHEST 2018; 153(5):1221-1228

KEY WORDS: air pollution; environmental pollution; idiopathic pulmonary fibrosis; interstitial lung disease; pulmonary fibrosis

ABBREVIATIONS: 6MWT = 6-min walk test; AQI = air quality index; ATS = American Thoracic Society; EMR = electronic medical record; EPA = Environmental Protection Agency; GIS = geographic information system; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; NAAQS = National Ambient Air Quality Standard; PFT = pulmonary function test; PM = particulate matter; $PM_{2.5}$ = particulate matter with diameter < 2.5 μm in diameter; PM_{10} = particulate matter with diameter < 10 μm in diameter; SSDI = Social Security Death Index

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Idiopathic pulmonary fibrosis (IPF) is a progressive fibroproliferative interstitial lung disease (ILD) of uncertain cause with a median survival of 3 years from diagnosis.[1] IPF is strongly associated with smoking, and case-control studies have demonstrated increased environmental and occupational exposure to a variety of industrial and organic inhalational agents in IPF.[2-5] Cellular and animal models have shown an alteration of the alveolar epithelial cell phenotype in IPF characterized by apoptosis, fibroblast proliferation, and collagen deposition.[6-8] These findings suggest a conceptual model of IPF in which genetically susceptible individuals mount an aberrant response to repetitive low-level toxic exposure over time that induces progressive loss of functional alveolar epithelium and macroscopic scarring.[9]

One potential source of repetitive toxic exposure is particulate air pollution. Ambient particles < 10 μm and < 2.5 μm in diameter (PM_{10} and $PM_{2.5}$, respectively) are composed of a complex mixture of organic chemicals, metals, and dusts, largely byproducts of hydrocarbon combustion, that are monitored and regulated by the Environmental Protection Agency (EPA). As the technology to measure daily atmospheric PM levels has improved, PM exposure has been implicated in a diverse range of systemic diseases, from atherosclerosis and diabetes to childhood autism.[10-13] Ambient PM has been implicated in a wide variety of pulmonary diseases, from decreases in functional pulmonary measures in healthy patients to increased frequency of hospitalizations and mortality in patients with COPD and asthma.[14,15]

Short-term fluctuations in two other components of air pollution (ozone and nitrogen dioxide) have been associated with an increased risk of acute exacerbations of IPF, but the effect of ambient PM on long-term functional measures of disease progression is unknown.[16] We hypothesized that increased exposure to air pollution in the form of ambient PM would be associated with an accelerated rate of decline in pulmonary function in IPF.

Methods

Patient Population

The study population consisted of patients seen at a single university ILD referral center between 2007 and 2013 and who had at least two sets of pulmonary function test (PFT) results, including FVC. We considered the study entry point to be the first recorded FVC result in the medical record; therefore the study was composed of patients seen at follow-up and initial referral visits and included PFT results that preceded the implementation of the outpatient electronic medical record (EMR) in 2007. We initially identified subjects by EMR query for the standardized diagnostic code for IPF (International Classification of Disease, Ninth Revision code 516.31) and performed manual chart review to confirm that the subjects met 2011 American Thoracic Society (ATS) criteria for definite or probable IPF, as documented by a clinician with subspecialty expertise in the diagnosis and management of ILD, on the basis of clinical history and radiological and surgical pathologic examination (when available). In cases of diagnostic uncertainty, a comprehensive review of clinical history and radiological and surgical pathologic examination were presented to a multidisciplinary committee, including at least two ILD clinicians, a dedicated chest radiologist, and a pathologist, for adjudication based on 2011 ATS IPF criteria. The study was approved by the University of Pennsylvania Institutional Review Board (Protocol No. 817713).

Ascertainment of Exposure

Exposure to air pollution was characterized using a geospatial approach. The geographic catchment area of the referral center comprised urban, suburban, and rural areas within the greater Philadelphia metropolitan region. Subjects' home addresses were converted into latitude-longitude coordinates (geocoded) using ArcGIS, the industry standard professional geographic information system (GIS) software.[17]

The air quality monitoring station location and local daily air quality data were pulled from the Air Quality Index (AQI), an online tool developed by the EPA. Pollution exposure was measured using daily mean concentration levels for PM_{10} and $PM_{2.5}$ collected at the air quality monitoring station nearest the subjects' geocoded addresses. Local air quality monitoring site locations in the greater Philadelphia region varied during 2007 to 2013. This resulted in annual AQI data being unavailable for some subjects at certain times. To overcome these spatial and temporal limitations, all possible site locations were merged across time, enabling an assessment of the closest site reading to each subject's home address for each exposure variable. Local daily air quality data collected between 2007 and 2013 were used to generate an individual mean value for each subject for each PM exposure variable from the date of their study entry (January 1, 2007 for subjects that entered prior to this date) through their date of study exit.

In addition, we computed a geospatial measure of automobile-derived air pollution. We used GIS road network data to identify the location and features of every road segment in the study area. Each road was further classified by its primary feature. Using ArcGIS, we calculated the distance between each subject's geocoded home address and the

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nearest large road type: highway, state road (connect major cities), and large local roads (intrastate commerce and recreational travel).

Outcomes

The primary outcome was the rate of decline in FVC on serial PFTs, which is a reliable measure of disease status in IPF, a strong independent predictor of mortality, and the standard primary end point in clinical trials in IPF.[18-21] All PFTs available for review from time of initial referral through the end of the study period were included in the analysis. To evaluate potential inconsistencies in FVC measurement, we conducted a sensitivity analysis including only tests performed at our university center's pulmonary function laboratory, which were performed by trained personnel according to standardized protocols and met ATS criteria for acceptability and reproducibility.[22-25] To evaluate the possibility of a survivor effect or measurement error due to exposure preceding the study, we performed an additional sensitivity analysis excluding PFTs performed prior to January 1, 2007. Secondary end points included the rate of decline in the distance walked during the 6-min walk test (6MWT), number of liters of supplemental oxygen required to maintain oxygen saturation > 88% on the 6MWT, and all-cause mortality. All 6MWTs performed in our university's pulmonary function laboratory according to a standardized protocol were included in the analysis.[26] Mortality data were abstracted from the EMR, and vital status was additionally assessed using the Social Security Death Index (SSDI). If there was no documentation of mortality in the medical record or SSDI, all subjects with PFTs within 6 months of the study end point were assumed to be alive.

Statistical Analysis

All analyses were conducted in Stata, version 12.1 (StataCorp LLC). A longitudinal linear mixed-effects model with random intercept and random slope was chosen based on its assumptions regarding missing data (missing at random) and to account for individual variability in disease progression and severity at time of presentation. All outcome measures except mortality were continuous. Given the varied entry points and length of follow-up for individuals in this retrospective cohort, time was treated as linear and specified as the number of days since the first measurement of each outcome variable, with first measurement as day 1. The effect estimate and *P* values were drawn from the interaction between the exposure variable and time in a model, including main effects for exposure and time. Mortality analysis was conducted within a logistic regression model, using death at any point during the study period as the outcome. All outcomes were considered in independent models. Exposure variables were treated as continuous. Automobile-derived air pollution was measured by the log-transformed distance from the subject's residence to the nearest major road, as the distribution was skewed and automobile-derived air pollution decays exponentially as distance increases.[27]

After completion of initial analyses, potential confounders were added sequentially to the base model as covariates. Only variables that changed the point estimate of the ß-coefficient by > 15% were included in the final model.[28] Covariates assessed included study entry year; age; race; sex; baseline FVC; BMI; smoking status; the presence of comorbidities, including COPD, gastroesophageal reflux disease, pulmonary hypertension, and coronary artery disease; and use of medications, including systemic corticosteroids, N-acetylcysteine, and immunomodulatory agents, including azathioprine, mycophenolate, and methotrexate. The cohort predated the approval of pirfenidone and nintedanib. Age was continuous, and other variables were considered categorically. For longitudinal analyses, subjects were censored at time of death or lung transplantation. We estimated that a sample size of 130 subjects would provide > 80% power to detect a 5% difference in FVC change between dichotomous category of exposure (split at the median), assuming mean FVC of 50% predicted and SD of 10% in each group, at alpha = 0.05.

Results

The initial EMR data query returned 238 subjects from Pennsylvania and New Jersey seen in our referral center between 2007 and 2013, 175 of whom had sufficient longitudinal data for inclusion. Twenty-six subjects (15%) missing exposure data were excluded from the study, and 14 subjects (8%) were determined to be misclassified as having IPF based on manual chart review and adjudication, leaving 135 subjects in the final analysis. Characteristics of the study population are presented in Table 1. Excluded subjects had poorer baseline functional measures than did included subjects, but there were no significant differences in exposures between the groups (e-Table 1).

The median distance from the subjects' residences to the nearest EPA monitoring station was 15.0 km (interquartile range [IQR], 8.2-33.2 km) for PM_{10} and 11.2 km (IQR, 8.2-33.2 km) for $PM_{2.5}$. The median PM_{10} level during the study period was 18.5 $\mu g/m^3$ (IQR, 16-24 $\mu g/m^3$), and the median $PM_{2.5}$ level was 10.5 $\mu g/m^3$ (IQR, 9.5-12.5 $\mu g/m^3$). PM_{10} levels at all subjects' residences were less than the EPA National Ambient Air Quality Standards (NAAQS) throughout the study period, whereas $PM_{2.5}$ levels at some subjects' residences did not meet 2012 revised EPA NAAQS (although all levels were less than the 2006 NAAQS) (Fig 1). The median number of PFT measurements per subject was five (IQR, 3-10).

There was a significant relationship between increased exposure to PM_{10} and an accelerated FVC decline during the study period ($P = .019$). Each 5 $\mu g/m^3$ increase in average ambient PM_{10} concentration at subjects' residences corresponded with an additional 35 cc/y decline in FVC (95% CI, 6-65 cc/y) (Table 2). Figure 2 demonstrates this association graphically, comparing FVC decline in subjects with PM_{10} exposure greater than the median over the study period with those with less than median exposure. This relationship persisted in a model accounting for a wide variety of potential confounders. The main effect of PM_{10} on FVC was not significant ($P = .569$). Of potential confounders, only baseline FVC changed the point estimate for the

TABLE 1] Characteristics of the Study Population

Age, median, range, y	68 (46-92)
Sex, % male	75
Race, %	
White	74
African American	8
Other	17
BMI, kg/m^2, %	
< 25	27
25-30	44
30-35	20
≥ 35	9
Smoking status, %	
Current smoker	< 1
Former smoker	64
Never smoker	36
Pack-year history, %	
≥ 40	15
< 40	50
0	35
Comorbidities, %	
COPD	8
GERD	28
Pulmonary hypertension	11
Medications, %	
Corticosteroids	50
Steroid-sparing immunosuppressive agents	14
N-acetylcysteine	32
Deaths during study period, No. (%)	59 (44)
Transplantations during study period, No. (%)	17 (13)
Follow-up time, median, IQR, d	543 (244-1,128)
No. of pulmonary function tests, median, IQR	5 (3-9)
Baseline pulmonary function testing, median, IQR	
FVC, L	2.6 (2.0-3.1)
FEV_1, L	2.1 (1.7-2.7)
Total lung capacity, mL/min/mm Hg	4.0 (3.3-4.8)
Diffusion capacity of carbon monoxide	11.5 (8.9-14.3)
Baseline 6MWT-ft	1228 (935-1,538)
Supplemental oxygen required to maintain saturation > 88% on 6MWT, L	0 (0-4)

6MWT = 6-min walk test; GERD = gastroesophageal reflux disease; IQR = interquartile range.

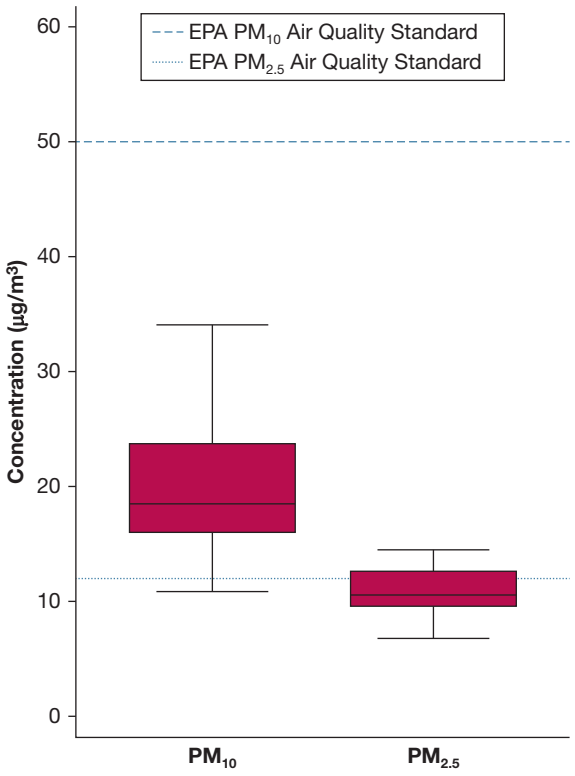

Figure 1 – *Distribution of average PM exposure during the study period for all subjects included in longitudinal analysis. Median (IQR) and maximum/minimum value for the average annual concentration of PM_{10} and $PM_{2.5}$ for each individual during the study period. EPA = Environmental Protection Agency; $PM_{2.5}$ = particulate matter with diameter < 2.5 µm in diameter; PM_{10} = particulate matter with diameter < 10 µm in diameter.*

relationship between PM_{10} and the rate of FVC decline by more than 15% and was retained in the final model. In the final model, each 5 µg/m^3 increase in PM_{10} corresponded to an additional 46 cc/y decline in FVC (95% CI, 12-81 cc/y) (Table 3; e-Table 2). In sensitivity analyses, this relationship did not significantly change when subjects whose PFTs were performed outside of our university health system or prior to 2007 were excluded (e-Table 3).

There was no significant relationship between ambient $PM_{2.5}$ and the rate of FVC decline or between any of our exposure variables and the rate of decline in 6MWT distance (Table 2) or the odds of mortality during the study period (Table 4). There was a significant relationship between increased exposure to $PM_{2.5}$ and an accelerated rate of increase in oxygen use on 6MWT (Table 2). Each 5 µg/m^3 increase in ambient $PM_{2.5}$ concentration at subjects' residences corresponded with an additional 1.15 L/y increase in oxygen use on the 6MWT (95% CI, 0.03-2.26 L/y). There were no

TABLE 2] Associations Between Average Particulate Matter Exposure and the Rate of Decline of Functional Measures of Disease Progression

Outcome Variable	Exposure	Attributable Change[a] (95% CI)	*P* Value
FVC, cc/y/5 μg/m^3	**PM_{10}**	**-35 (−65 to 6)**	**.019**
	$PM_{2.5}$	34 (−60 to 127)	.48
6MWT, ft/y/5 μg/m^3	PM_{10}	−1 (−18 to 16)	.90
	$PM_{2.5}$	−15 (−70 to 40)	.59
Supplemental oxygen use required to maintain saturation > 88% on 6MWT, L/y/5 μg/m^3)	PM_{10}	0.15 (−0.03 to 0.1)	.51
	$PM_{2.5}$	**1.15 (0.03-2.26)**	**.044**

Boldface indicates significant association. $PM_{2.5}$ = particulate matter with diameter < 2.5 μm in diameter; PM_{10} = particulate matter with diameter < 10 μm in diameter. See Table 1 legend for expansion of other abbreviations.
[a]Units in this column are based on the β-coefficient from the linear mixed-effects model converted into clinically meaningful units. For example, each 5 μg/m^3 unit increase in average PM_{10} exposure for each individual is associated with an additional 35-cc decline in FVC per year.

significant relationships between PM_{10} exposure and supplemental oxygen use or between road proximity and any of our outcome measures (e-Table 4).

Discussion

Our study demonstrates a significant relationship between exposure to ambient particulate matter (PM_{10}) and the rate of decline in FVC, a widely accepted indicator of disease progression in IPF. Higher PM_{10} exposure levels were associated with an accelerated rate of decline, even as all PM_{10} exposures met EPA NAAQS. The association between PM_{10} and FVC decline suggests that exposure to air pollution may be a contributing factor in a dysregulated response to alveolar epithelial injury leading to fibrosis.

It is intriguing that a significant relationship was seen between exposure to coarse (PM_{10}) but not fine PM ($PM_{2.5}$) and the rate of decline in FVC, as there is an inverse relationship between particle size and penetration into distal airways, and a higher concentration of fine particulates ($PM_{2.5}$) reach distal airways in experimental models of particulate exposure. It is likely that our findings were influenced by the greater variability in PM_{10} exposure seen in the geographic catchment area of the study, perhaps due to the more fully aerosolized nature of $PM_{2.5}$ (Fig 1). Nevertheless, in the context of studies demonstrating aberrant responses in bronchial epithelium in IPF, our findings may suggest a broader epithelial dysfunction in the pathogenesis of IPF than has previously been apparent.[29,30] The significant relationship between $PM_{2.5}$ exposure and increased use of supplemental oxygen in 6MWT over time lends strength to our primary finding and suggests that the cumulative burden of exposure to ambient PM, rather than a size-specific effect of PM_{10} exposure, leads to an accelerated functional decline in IPF.

No association was seen between the proximity of subjects' residences to major roads and highways and any of our outcome measures. Previous studies of traffic-related air pollution have demonstrated an exponential decline in the concentration of ambient particles as the distance from major roadways increases. Due in part to the size of the population included in the current study,

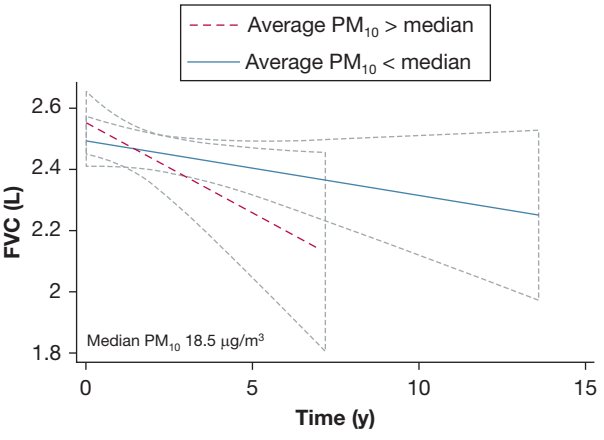

Figure 2 – *Average FVC trajectory over time compared between subjects with PM_{10} concentrations greater than or less than the median exposure level. Pooled trajectory of average FVC (mean and 95% CI) over time from study entry point and split dichotomously between individuals with PM_{10} exposure above and below the median level of exposure. The steeper trajectory in those with above the median exposure reflects the relationship between PM_{10} exposure and FVC decline, although the pooled analysis does not capture the statistical power of the mixed-effects model. PM = particulate matter. See Figure 1 legend for expansion of other abbreviations.*

TABLE 3] Change in the Association Between Average PM_{10} Concentration and the Rate of FVC Decline With Adjustment for Potential Confounders

Adjustment for Potential Confounders	Effect Estimate for PM_{10}-Attributable Change[a]	% Change from Unadjusted Model[b]	*P* Value[c]
None	−35	Reference	.019
Age	−36	1.0	.018
Sex	−36	1.0	.019
Race	−40	14.0	.008
Job-based SES	−38	7.3	.024
BMI	−35	0.0	.019
Comorbid COPD	−35	0.0	.019
Comorbid GERD	−35	0.5	.019
Comorbid PHTN	−35	0.0	.019
Use of steroids	−35	0.5	.018
Use of steroid-sparing agents	−35	0.0	.019
Smoking status (never/former/current)	−35	0.0	.019
Pack-year history	−35	−0.5	.019
Year of study entry	−34	−2.6	.021
Baseline FVC[d]	−46	30	.008

PHTN = pulmonary hypertension; SEC = socioeconomic status. See Table 1 legend for expansion of other abbreviations.
[a]Units in this column are based on the β-coefficient from the linear mixed-effects model for the association between PM_{10} and the rate of FVC decline in the model adjusting for the covariate of interest converted into clinically meaningful units (cc/y/5 μg/m^3 increase in average PM_{10} exposure). For example, in a model adjusting for age, each 5 μg/m^3 unit increase in average PM_{10} exposure for each individual is associated with an additional 36-cc decline in FVC per year.
[b]Percent change in the point estimate for the primary association between PM_{10} and the rate of decline in FVC in the model adjusting for the covariate of interest. No covariates changed the point estimate for this association > 15%.
[c]*P* value for the primary association between PM_{10} and rate of decline in FVC in model adjusted for covariate of interest.
[d]Covariate included in final model.

there were very few subjects who lived within a short distance of a major road. This small sample size may have resulted in a failure to capture an association if one did exist.

This study included a wide geographic catchment area spanning urban and rural areas, which resulted in high variability in subject exposure to particulate pollution. The inclusion of subjects captured at varying time points in their disease progression decreases the possibility of systematic geographic bias in referral and lead time. Adjustment for calendar time and the use of potentially harmful medications reduces the risk of confounding by temporal trends in care delivery. The mixed-effect longitudinal model also makes relatively modest assumptions with respect to missing data. The diagnosis of IPF was made by clinicians with subspecialty expertise in the diagnosis and management of ILD, with multidisciplinary adjudication in cases of diagnostic uncertainty, leading to a precise IPF case definition. Nearly all PFTs were performed and recorded by trained technicians at a central laboratory according to established criteria, leading to reliable and reproducible outcome measures.

TABLE 4] ORs for Mortality in Unadjusted Analysis

OR	PM_{10}[a]	$PM_{2.5}$[a]	Road Distance[b]
OR for death[c]	0.95 (95% CI, 0.69-1.29; *P* = .70)	0.91 (95% CI, 0.38-2.20; *P* = .85)	1.00 (95% CI, 0.97-1.03; *P* = .79)

See Table 1 legend for expansion of abbreviations.
[a]PM concentrations in these columns are converted to clinically meaningful units (5 μg/m^3). OR represents the odds of documented death during the study period for each 5 μg/m^3 increase in average PM concentration.
[b]Road distance in this column is converted to clinically meaningful units (100 m). OR represents the odds of documented death during the study period for each 100-m increase in distance from nearest major road.
[c]OR for documented death at any time during the study period for each unit increase in the variable of interest.

This study has several important limitations. It is a single-center study of patients from a single, albeit diverse, geographic area, which limits the variability of exposure to PM, particularly $PM_{2.5}$. In addition, an approach to exposure relying on listed residence in the EMR and data from regional monitoring stations limits the precision with which true PM exposure can be ascertained. Furthermore, confounding by environmental or subject-specific factors not captured in the medical record or selection bias due to differential loss to follow-up based on geographic factors unrelated to ambient air pollution may obscure the nature of the association.

Despite these limitations, this study demonstrated an association between exposure to ambient PM and important clinical indicators of disease progression in IPF. The identification of a potentially modifiable contributing factor to progression of disease through environmental exposure to particulate air pollution may have implications for the clinical management of the disease.

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Author contributions: C. J. W. and J. D. C. are the guarantors of the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C. J. W. and J. D. C. drafted the manuscript. C. J. W. performed the data analysis under the supervision of J. D. C. and A. R. L. C. J. W., J. D. C., R. J. S., K. C. P., M. E. K., T. M. P., R. A. P., K. H., and T. J. contributed to study design. C. J. W., R. J. S., K. C. P., M. E. K., L. A. L., and W. T. M. contributed to case adjudication. C. J. W., K. H., T. J., and B. R-L. contributed to data collection. All authors contributed to the interpretation of the data, critical revision of the final manuscript, and approval of the final version of the manuscript.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788-824.
2. Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *Lancet*. 1996;347(8997):284-289.
3. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proc Am Thorac Soc*. 2006;3(4):293-298.
4. Miyake Y, Sasaki S, Yokoyama T, et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. *Ann Occup Hyg*. 2005;49(3):259-265.
5. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1997;155(1):242-248.
6. Jin HL, Dong JC. Pathogenesis of idiopathic pulmonary fibrosis: from initial apoptosis of epithelial cells to lung remodeling? *Chin Med J (Engl)*. 2011;124(24):4330-4338.
7. Uhal BD, Joshi I, Hughes WF, Ramos C, Pardo A, Selman M. Alveolar epithelial cell death adjacent to underlying myofibroblasts in advanced fibrotic human lung. *Am J Physiol*. 1998;275(6 Pt 1):L1192-L1199.
8. Plataki M, Koutsopoulos AV, Darivianaki K, Delides G, Siafakas NM, Bouros D. Expression of apoptotic and antiapoptotic markers in epithelial cells in idiopathic pulmonary fibrosis. *Chest*. 2005;127(1):266-274.
9. Gunther A, Korfei M, Mahavadi P, von der Beck D, Ruppert C, Markart P. Unravelling the progressive pathophysiology of idiopathic pulmonary fibrosis. *Eur Respir Rev*. 2012;21(124):152-160.
10. Hoffmann B, Moebus S, Mohlenkamp S, et al. Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation*. 2007;116(5):489-496.
11. Hoffmann B, Moebus S, Dragano N, et al. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. *Environ Health Perspect*. 2009;117(8):1302-1308.
12. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry*. 2013;70(1):71-77.
13. Chen H, Burnett RT, Kwong JC, et al. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. *Environ Health Perspect*. 2013;121(7):804-810.
14. Kesavachandran C, Pangtey BS, Bihari V, et al. Particulate matter concentration in ambient air and its effects on lung functions among residents in the National Capital Region, India. *Environ Monit Assess*. 2013;185(2):1265-1272.
15. Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. *Am J Respir Crit Care Med*. 2013;187(7):721-727.
16. Johannson KA, Vittinghoff E, Lee K, et al. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J*. 2014;43(4):1124-1131.
17. ArcGIS Desktop [computer program]. ESRI, Redlands, CA; 2013.
18. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2083-2092.
19. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-2082.
20. Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J*. 2010;35(4):830-836.
21. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med*. 2003;168(5):531-537.
22. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26(4):720-735.
23. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of

lung volumes. *Eur Respir J*. 2005;26(3):511-522.

24. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
25. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J*. 2005;26(1):153-161.
26. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
27. Zhu Y, Hinds WC, Kim S, Sioutas C. Concentration and size distribution of ultrafine particles near a major highway. *J Air Waste Manag Assoc*. 2002;52(9):1032-1042.
28. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol*. 1993;138(11):923-936.
29. Baughman RP, Lower EE, Miller MA, Bejarano PA, Heffelfinger SC. Overexpression of transforming growth factor-alpha and epidermal growth factor-receptor in idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 1999;16(1):57-61.
30. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med*. 2011;364(16):1503-1512.