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Prevalence and patterns of inhalational exposures in patients with interstitial lung diseases: a cross-sectional study

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Abstract

Given the etiologic importance of inhalational exposures in specific interstitial lung disease (ILD) subtypes like hypersensitivity pneumonitis (HP) and pneumoconiosis, this study systematically evaluates exposure patterns across all ILD subtypes and assesses the utility of a standardized questionnaire for improved exposure identification.

In this cross-sectional study, ILD patients were recruited between July 2023 and March 2024. Demographic, clinical, pulmonary function, radiological, and immunological parameters were recorded, and ILD subtypes were assigned by multidisciplinary discussion. Inhalational exposures were evaluated using a standardized questionnaire through in-person or telephonic interviews.

Out of 139 total ILD patients, 107 (77%) reported at least one inhalational exposure, and 67 (48.2%) reported multiple exposures. These exposures were prevalent across multiple ILD subtypes beyond HP. Biomass (39.6%) and hay/grain (25.9%) were the most common. Blue-collar occupations were linked with higher odds of having any (81.8%) and multiple exposures (55.6%). Significant associations with HP were observed for animal hair and avian exposures, while tobacco smoke was associated with idiopathic pulmonary fibrosis. Having multiple exposures was associated with a significant reduction in forced vital capacity % predicted. Use of the standardized exposure questionnaire revealed more exposures per patient vs. routine history [median 1 (interquartile range 1-3) vs. 0 (interquartile range 0-1)], with 77% of participants classified as exposed vs. 41.7% by routine history ($p < 0.001$).

Inhalational exposures are widely prevalent across ILD subtypes, including those not classically exposure-related, and standardized exposure assessment using questionnaires improves their detection.

Key words: interstitial lung disease, pulmonary fibrosis, questionnaire, inhalation exposure, occupational exposure.

Introduction

Interstitial lung diseases (ILDs) comprise a group of diverse pulmonary conditions marked by varying degrees of interstitial inflammation and fibrosis of the lung, leading to progressive respiratory impairment, impaired gas exchange, and dyspnea [1]. Collectively, ILDs impose a substantial global health burden [2], owing to their chronic course, diagnostic complexity [3], and limited therapeutic options [4]. In India, the estimated prevalence of ILD ranges from approximately 50 to 100 per 100,000 population, underscoring a significant and growing public health concern [5].

Although the etiology of several ILD subtypes remains incompletely understood, several contributing factors have been implicated, including genetic susceptibility, autoimmune disease, and environmental/occupational inhalational exposures [1]. Among these, inhalational exposures are increasingly recognized due to their high prevalence and potential influence on disease onset, subtype, progression, and treatment response [6]. Certain ILDs, such as hypersensitivity pneumonitis (HP) and pneumoconiosis, have well-established associations with inhaled antigens [7]. However, emerging evidence suggests that inhalational exposures are also common among patients with ILD subtypes not traditionally classified as exposure-related, where they may act as modifying factors rather than primary etiologic agents [8,9].

Given the largely irreversible nature of established pulmonary fibrosis and the limited availability of disease-modifying therapies [4], recognition and elimination of inciting agents may slow disease progression, reduce exacerbations [10-12], and in some cases, reduce the need for invasive diagnostic procedures [11].

Despite this, inhalational exposures remain insufficiently characterized in routine ILD care, particularly in high-volume outpatient settings [13,14]. Time constraints, heavy patient loads, and the absence of standardized exposure assessment tools often result in incomplete exposure histories [13,14], contributing to missed etiologic factors, diagnostic uncertainty, and delayed or inappropriate management. This gap is especially relevant in a setting where domestic, environmental, and occupational exposures are widespread and heterogeneous.

In this context, this study primarily aims to systematically characterize domestic and occupational inhalational exposures among patients with different ILD subtypes and to examine their associations with clinical, radiologic, and pulmonary function parameters.

In addition, we sought to evaluate the utility of a standardized exposure questionnaire in improving exposure identification compared with routine physician-led history taking.

Materials and Methods

This cross-sectional study was conducted at a tertiary care center in Southern India. Consecutive adult patients (≥ 18 years) with a confirmed diagnosis of ILD attending the pulmonary medicine outpatient department and ILD clinic were enrolled between July 2023 and March 2024. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Patients who were unable to provide a reliable exposure history due to communication difficulties or cognitive impairment were excluded. Demographic details, clinical characteristics, pulmonary function test results, radiological features and ILD-associated immunological markers were recorded. ILD subtype classification was established using standard diagnostic criteria [15,16], and, where appropriate, multidisciplinary discussion (MDD) [3], based on the routine physician obtained clinical history, imaging, immunological, and available histopathological findings, without the influence of findings from the structured, standardized exposure questionnaire.

Exposure assessment

Inhalational exposures were assessed using a structured, standardized questionnaire (*Supplementary Appendix S1*) adapted from a previously published, validated chronic hypersensitivity pneumonitis (CHP) exposure questionnaire [14], with permission from the original authors. The questionnaire was further modified to capture additional exposure items adapted from existing literature, particularly relevant to Indian occupational, environmental and domestic practices [8,9,13,14,17]. To address linguistic diversity and improve recall, visual aids depicting common exposures were used (*Supplementary Appendix S2*). Each reported exposure was further characterized by duration, frequency, recency, its temporal relationship to symptom onset (occurring within 5 years preceding symptom onset considered relevant), and use of protective equipment such as masks or ventilation. Routine clinical history-taking was completed by the consulting physician before administration of the structured exposure questionnaire. The questionnaire was administered independently by a different

physician or a research assistant, usually immediately after the consultation or by telephone within one week. The exposure history obtained by the consulting physician was extracted from the patient's medical records.

Statistical analysis

Data were collected and maintained in Microsoft Excel. Continuous variables were summarized as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), according to distribution, and categorical variables as counts and percentages.

The distribution of inhalational exposures across different ILD subtypes was compared using the Fisher's exact test. Associations of inhalational exposures with HP and high-resolution computed tomography (HRCT) features, were examined using separate multivariable logistic regression models, adjusting for age, sex, and smoking status, with adjusted odds ratios (OR) and 95% confidence intervals (CI) reported. Associations of inhalational exposures with pulmonary function parameters were assessed using multivariable linear regression models adjusted for age, sex, smoking status, occupation nature, ILD subtype and ILD duration, and reported as adjusted β coefficients with 95% CIs. Given their exploratory nature, these analyses evaluated individually specified exposure–outcome associations rather than test a single confirmatory hypothesis; therefore, each association was examined in a separate model without formal adjustment for multiple comparisons. The number of inhalational exposures identified by the standardized exposure questionnaire and routine clinical history-taking was compared using the Wilcoxon signed-rank test. Agreement between the two methods for identifying any exposure was assessed using McNemar's test. All tests were two-sided, and a p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 29.0.2).

Results

Baseline characteristics

Of the 155 participants who completed the structured exposure questionnaire, 16 were excluded because their ILD diagnosis remained uncertain, leaving 139 participants in the final study population. Participant enrollment, exclusions and reasons for exclusion, and inclusion in the final analyses are summarized in *Supplementary Figure 1*. The mean

age of the study population was 54.5 ± 13.1 years, and 66.2% were female. The most common ILD subtype was connective tissue disease-associated ILD (38.1%), followed by HP (15.1%), sarcoidosis (10.1%), and idiopathic pulmonary fibrosis (IPF) (10.1%). The median duration of illness was 20 months (IQR 6.5–42 months). HRCT demonstrated a high prevalence of fibrotic features, including traction bronchiectasis (56.1%) and honeycombing (38.9%). Mean FVC (% predicted) was $51.9 \pm 17\%$, indicating most patients presented with advanced disease. The characteristics of the study population are shown in Table 1.

Prevalence and patterns of inhalational exposures

Overall, 107 (77%) patients reported at least one inhalational exposure, and nearly half 67 (48.2%) reported multiple exposures. Environmental and domestic exposures were most common (53.2%), followed by occupational exposures (39.6%). Biomass fuel exposure (39.6%) was the most frequently reported, followed by hay/grain exposure (25.9%). Organic exposures were predominant (71.9%). Substantial overlap between exposure groups was observed (Figure 1), with many participants reporting multiple sources of exposures (Table 2, *Supplementary Figure 2*).

Gender and occupational differences

After adjusting for age, females had significantly higher odds of having biomass exposure and environmental/domestic exposure, whereas males had higher odds of tobacco smoke exposure. Inorganic and mixed composition exposures were more frequent among males (*Supplementary Table 1*). Blue-collar occupations were independently associated with higher odds of having any exposure, multiple concurrent exposures, suggesting a higher cumulative exposure burden among manual workers (*Supplementary Table 2*).

Association with ILD subtype, lung function and HRCT features

Biomass exposure differed significantly across ILD diagnostic groups (Fisher's exact $P = 0.005$), whereas no statistically significant differences were observed for the other inhalational exposures (*Supplementary Table 3*). In the unadjusted analysis, animal hair exposure was associated with higher odds of HP. This association remained consistently

significant after adjustment for age, sex, and smoking status. Avian exposure was also associated with higher odds of HP after adjustment (Table 3). In contrast, tobacco smoke exposure was associated with higher odds of IPF after adjustment for age and sex (adjusted OR 5.46; 95% CI (1.21 to 24.6); $P = 0.027$). Distribution of different ILD subtypes across different exposure composition types are shown in *Supplementary Figure 3*.

In adjusted linear regression analyses, hay/grain, avian, and mold exposures were each associated with lower FVC % predicted, whereas only hay/grain and avian exposures were associated with significant reductions in FEV1 % predicted. Multiple concurrent exposures were associated with both lower FVC% and FEV1% predicted, supporting a cumulative exposure effect on lung function (Table 4).

HRCT findings did not differ significantly between exposed and unexposed patients, nor between those with single and multiple exposures (*Supplementary Table 4*). There were no significant differences between HP and non-HP ILDs in the likelihood of reporting chronic exposure (>10 years) or daily exposure frequency for large parts of the day (*Supplementary Table 5*, *Supplementary Figures 4 and 5*). Time since last exposure (*Supplementary Table 6*) also did not differ across ILD subtypes.

Comparison of exposure assessment methods

The standardized exposure questionnaire identified a significantly higher number of exposures per patient compared with routine clinical history (median 1 [IQR 1–3] vs 0 [IQR 0–1]; $P < 0.001$). The questionnaire classified 107 (77%) participants as exposed, whereas routine clinical history identified only 58 (41.7%) as having any exposure ($P < 0.001$).

Discussion

Over three-quarters of ILD patients in this cross-sectional study reported at least one ILD-relevant inhalational exposure. This finding is consistent with prior studies reporting inhalational exposure prevalence rates exceeding 60% among patients with ILD, irrespective of subtype [8,9]. Beyond classic exposure-linked ILDs like HP, our findings demonstrate substantial proportions of inhalational exposures appeared in autoimmune-related ILD, IPF, and sarcoidosis cases. This indicates inhalational exposures are not

exclusive to HP, similar to the observations in prior studies [9,18,19], and reinforces the potential role of these exposures as disease modifiers even if they are not etiologic drivers.

While overall presence of exposures did not differ by sex, females were more likely to report biomass and domestic exposures, whereas tobacco smoke exposure was more common among males. These findings reflect well-established gender-based exposure patterns in low and middle-income countries [5,9,20]. Predominance of inorganic exposures among men is consistent with prior studies [8], likely due to the predominance of inorganic exposures such as silica and metals in male-dominated occupations.

Individuals working in blue-collar jobs were more likely to be exposed, often to multiple inhalational exposures, which is consistent with evidence from existing occupational epidemiology [21-24]. The predominance of biomass fuel use and agricultural exposures highlights the unique exposure ecosystem in India, where traditional cooking practices and farming remain very common. Prior studies have similarly shown that organic exposures from household and agricultural sources are associated with restrictive lung function abnormalities, supporting the relevance of these exposures in ILD [20,25,26].

Certain inhalational exposures appeared to align with specific ILD subtypes. Animal hair and avian exposures were associated with HP, consistent with the established role of these antigens in its pathogenesis [27,28]. This exposure pattern is biologically plausible and fits established models of chronic lung injury in HP from repeated antigen exposure [12,13,27,28]. Tobacco smoke exposure, in contrast, aligned more closely with IPF, consistent with prior evidence linking smoking history with increased IPF risk [29,30].

Reduced lung volumes were most evident with specific organic exposures, including agricultural dust, avian exposure, and mold. This is broadly consistent with earlier reports linking bird antigen, mold and fungal exposures to fibrotic lung disease [27,28,31], as well as occupational studies showing restrictive spirometry patterns among individuals exposed to agricultural dusts [32]. Reduced lung volumes were also observed when multiple exposures coexisted, a pattern supporting the concept of cumulative exposure burden contributing to functional impairment.

A key methodological finding of this study is the demonstration that a standardized exposure questionnaire identified substantially more inhalational exposures than routine clinical history-taking. This difference likely reflects constraints in high-volume

outpatient settings, where limited consultation time and competing priorities can restrict detailed exposure assessment, rather than limitations in clinician expertise. Similar findings have been reported previously, with structured exposure tools shown to improve exposure detection and diagnostic confidence, including studies in which a standardized questionnaire identified exposures missed during routine clinical evaluation in a substantial proportion of patients with ILD [9,13,14,33]. This approach is consistent with the National Institute for Occupational Safety and Health (NIOSH) Respiratory Health Agenda of 2019 [34], which emphasizes the use of validated exposure assessment tools to identify exposures related to ILD that may be overlooked in routine practice. In resource-limited settings such as India, integrating standardized questionnaires into routine ILD evaluation may offer a scalable and efficient strategy to improve exposure recognition without adding to clinician workload.

Clinically, our results support the routine incorporation of structured exposure assessment in all ILD patients, regardless of diagnostic subtype. Identification of specific inhalational exposures may aid in disease phenotyping and guide exposure avoidance strategies.

Limitations and future directions

The cross-sectional, single-center design limits causal inference and precludes assessment of longitudinal outcomes such as disease progression and survival. Additionally, the single-center setting may limit the generalizability of the findings to populations with different demographic, occupational, or environmental exposure patterns. Exposure assessment relied on patient recall and may be subject to recall bias, particularly for chronic, culturally normalized exposures such as biomass use. Several exposure-specific analyses were limited by small cell counts, resulting in less reliable estimates with wide confidence intervals. therefore, these findings are exploratory, do not establish causality and should be interpreted cautiously. Quantitative HRCT fibrosis scoring, diffusing capacity, and exercise capacity were not uniformly available and may have further clarified exposure–severity relationships. Future multicenter, longitudinal studies are needed to determine whether systematic exposure identification and avoidance translate into improved functional and radiologic outcomes.

Conclusions

Inhalational exposures are highly prevalent across ILD subtypes in this Indian population, including those not traditionally considered exposure-related. Standardized exposure questionnaires substantially improved exposure detection and represent a practical tool for improving ILD evaluation in high-burden healthcare systems. Systematic exposure assessment should be considered an essential component of ILD care and research.

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Online supplementary material

Supplementary Table 1. Association between gender and inhalational exposures among interstitial lung disease patients.

Supplementary Table 2. Association between the occupational nature and inhalational exposures.

Supplementary Table 3. Distribution of inhalational exposures across different interstitial lung disease subtypes.

Supplementary Table 4. Association of exposure burden with high-resolution computed tomography features.

Supplementary Table 5. Exposure characteristics in hypersensitivity pneumonitis (HP) vs. non-HP interstitial lung disease.

Supplementary Table 6. Time since last exposure among different interstitial lung disease subtypes.

Supplementary Figure 1. Flowchart of participant enrollment, and exclusions.

Supplementary Figure 2. Distribution of occupational and environmental/domestic inhalational exposures among interstitial lung disease patients.

Supplementary Figure 3. Proportion of interstitial lung disease subtypes among different exposure compositions.

Supplementary Figure 4. Distribution of duration and frequency of exposures across different interstitial lung disease subtypes.

Supplementary Figure 5. Distribution of duration and frequency of exposures in hypersensitivity pneumonitis (HP) vs. non-HP interstitial lung disease.

Supplementary Appendix 1. Inhalational exposure questionnaire.

Supplementary Appendix 2. Visual aids.

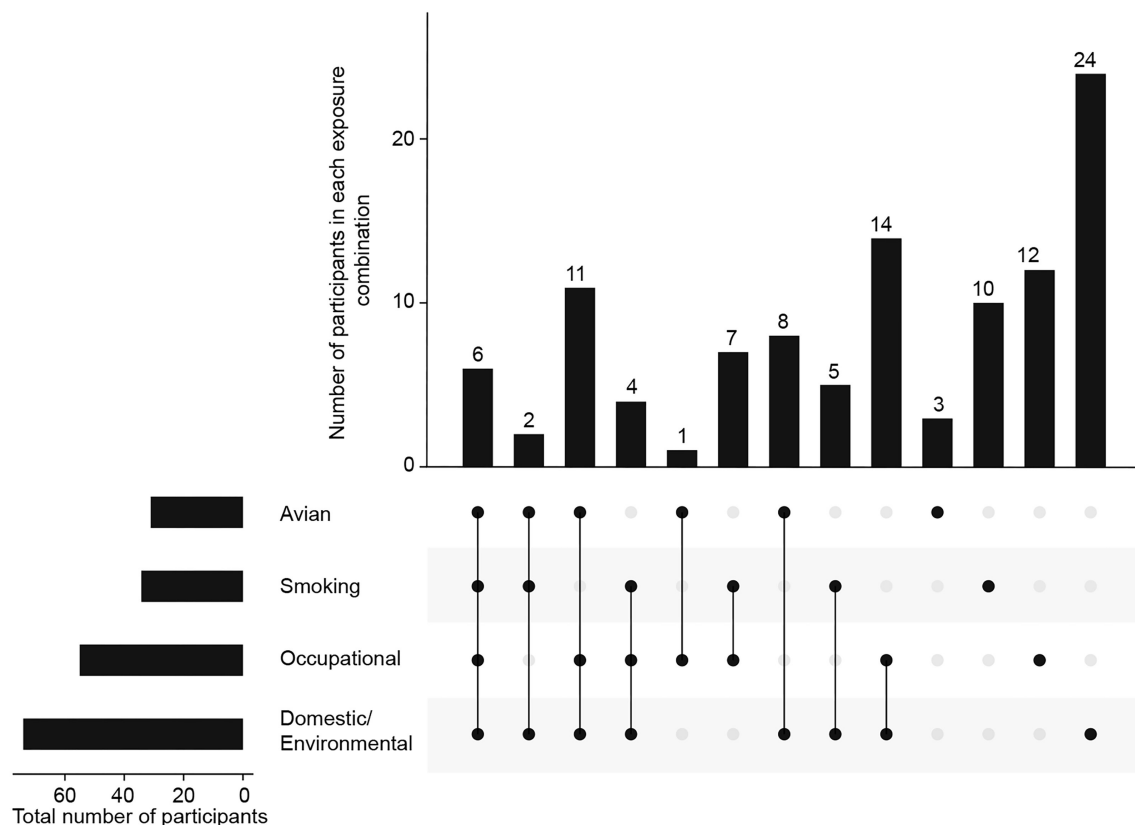


Figure 1. Overlap of different inhalational exposure groups among ILD patients. Connected filled dots denote the exposure groups included in each combination.

Table 1. Baseline characteristics of the study population (n=139).

Characteristic	Value
Age, years, mean $\pm$ SD	54.5 $\pm$ 13.1
Males, n (%)	47 (33.8)
Occupation nature, n (%)	
White-collar workers	40 (28.8)
Blue-collar workers	99 (71.2)
ILD subtype, n (%)	
HP	21 (15.1)
IPF	14 (10.1)
Autoimmune-related ILD	62 (44.6)
CTD-ILD	53 (38.1)
IPAF	9 (6.5)
Sarcoidosis	14 (10.1)
Other IIP	23 (16.5)
Others	5 (3.6)
Duration of illness, months, median (IQR)	20 (6.5-42)
HRCT Feature, n (%)	
Septal thickening	112 (80.6)
Traction bronchiectasis	78 (56.1)
Honeycombing	54 (38.9)
Ground glass opacity	80 (57.6)
Consolidation	19 (13.7)
Mosaic attenuation	28 (20.1)
Lymphadenopathy	21 (15.1)
Emphysema	8 (5.8)
Cysts	6 (4.3)
Baseline pulmonary function, mean $\pm$ SD (n = 135)	
FVC % predicted	51.9 $\pm$ 17
FEV1% predicted	56.6 $\pm$ 18.4
FEV1/FVC ratio	88.8 $\pm$ 8.5

Values are mean $\pm$ SD, median (IQR), or n (%). HP = hypersensitivity pneumonitis; CTD-ILD = connective tissue disease-associated interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; IPF = idiopathic pulmonary fibrosis; IIP = idiopathic interstitial pneumonia; HRCT = high-resolution computed tomography; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second.

Table 2. Characteristics of inhalational exposures (n=139).

Characteristic	Value
Any exposure	107 (77)
Multiple exposures (>1)	67 (48.2)
Exposure by source	
Occupational	55 (39.6)
Hay/Grain	36 (25.9)
Pesticide	9 (6.5)
Environmental/Domestic	74 (53.2)
Biomass	55 (39.6)
Mold ^a	26 (18.7)
Animal hair	14 (10.1)
Tobacco Smoke	34 (24.5)
Active smoking	20 (14.4)
Passive smoking	14 (10.1)
Avian particles	31 (22.3)
Exposure by composition	
Organic	100 (71.9)
Inorganic	57 (41)
Mixed	50 (36)
Location of exposure (n = 107)	
Home	87 (81.3)
Work	58 (54.2)
Both	38 (35.5)
Improvement after exposure-withdrawal (n = 37)	
Yes	24 (64.9)
No	13 (35.1)

Values are n (%). ^aMold exposure category includes visible mold and other potential sources of mold, including indoor air-regulating devices and musical wind instruments. Exposures are not mutually exclusive; participants can report more than one exposure type, composition, and location.

Table 3. Association of inhalational exposures with HP

Exposure	HP (n=21)	Non-HP (n=118)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P ^a
Any exposure	18(85.7)	89(75.4)	2.0(0.6 to 8.8)	0.309	2.4(0.6 to 9.2)	0.193
Hay/Grain	4(19)	32(27.1)	0.6(0.2 to 1.9)	0.44	0.7(0.2 to 2.2)	0.495
Mold	6(28.6)	20(17)	2.0(0.6 to 5.5)	0.214	2.1(0.7 to 6.1)	0.191
Animal hair	5(23.8)	9(7.6)	3.8(1.1 to 12.5)	0.031	4.4(1.2 to 16.6)	0.027
Biomass	10(47.6)	45(38.1)	1.5(0.6 to 3.8)	0.415	1.2(0.4 to 3.4)	0.759
Avian particles	8(38.1)	23(19.5)	2.5(0.9 to 6.8)	0.065	2.8(1 to 8.1)	0.05
Multiple exposure	10(47.6)	57(48.3)	1.0(0.4 to 2.5)	0.954	1.1 (0.4 to 2.9)	0.842

Values are n (%). ^aAdjusted for age, sex, and smoking status. HP, hypersensitivity pneumonitis.

Table 4. Association of inhalational exposures with pulmonary function parameters (n=135).

Exposure	FVC% predicted			FEV1% predicted		
	mean ± SD	β (95% CI)	P ^a	mean ± SD	β (95% CI)	P ^a
Any exposure	51±18	-2.88(-11.07 to 5.31)	0.488	56±19	-1.48(-9.08 to 6.13)	0.701
Hay/Grain	47±18	-8.41(-15.91 to -0.91)	0.028	52±20	-7.51(-14.47 to -0.55)	0.035
Mold	47±15	-9.52(-17.5 to -1.53)	0.020	49±17	-6.11(-13.61 to 1.38)	0.109
Biomass	51±19	-1.37(-8.71 to 5.97)	0.712	55±20	-1.16(-7.96 to 5.65)	0.737
Avian	45±14	-8.67(-16.34 to -1)	0.027	48±15	-7.42(-14.56 to -0.29)	0.041
Multiple exposure	49±16	-7.69(-14.28 to -1.09)	0.023	54±18	-7.05(-13.17 to -0.94)	0.024

^aAdjusted for age, sex, smoking status, occupation nature, ILD subtype and ILD duration. FVC, forced vital capacity; FEV₁ = forced expiratory volume in 1 second.