Interstitial Lung Abnormalities and Reduced Exercise Capacity

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Rationale: The relationship between interstitial lung abnormalities (ILA) and exercise capacity has not been comprehensively evaluated. **Objectives:** To assess the validity of the 6-minute walk test in subjects with ILA, and to examine the association between ILA and 6-minute walk distance (6MWD).

Methods: Spearman correlation coefficients were used to assess the strength of the relationships between 6MWD and relevant measures of dyspnea, health-related quality of life, and pulmonary function in a cohort of 2,416 people who smoke from the COPDGene study. Unadjusted and adjusted linear and logistic regression models were used to assess the strength of the association between ILA and 6MWD.

Measurements and Main Results: In all subjects, and in those with ILA, 6MWD in COPDGene was associated with relevant clinical and physiologic measures. The mean 6MWD in COPDGene subjects with ILA was 386 m (SD, 128 m), and 82% and 19% of subjects with ILA had 6MWDs less than or equal to 500 and 250 m, respectively. ILA was associated with a reduced 6MWD in univariate (-30 m; 95% confidence interval, -50 to -10 ; $P = 0.004$) and multivariate models (-19 m; 95% confidence interval, -33 to -5 ; $P = 0.008$). Compared with subjects without ILA, subjects with ILA had an 80% and 77% increase in their odds to have a walk distance limited to less than or equal to 500 and 250 m, respectively. Although these findings were dependent on ILA subtype, they were not limited to those with COPD. **Conclusions:** Our study demonstrates that ILA is associated with measurable decrements in the 6MWD of people who smoke.

Clinical trial registered with www.clinicaltrials.gov (NCT 00608764).

Keywords: six-minute walk distance; emphysema; interstitial lung disease; subclinical; idiopathic pulmonary fibrosis

Subjects with interstitial lung abnormalities (ILA) have high-resolution chest computed tomography (HRCT) features characteristic of patients with idiopathic interstitial pneumonia (IIP) (1)

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Although it has been shown that interstitial lung abnormalities are associated with reductions in total lung capacity, it is not known if these findings merely represent radiologic abnormalities or if they are associated with measurable decrements in exercise capacity.

What This Study Adds to the Field

Interstitial lung abnormalities are associated with reduced 6-minute walk distances. These findings, in conjunction with our prior work, suggest that a syndrome including reduced lung volumes, increased respiratory symptoms, and reduced exercise capacity can develop in people who smoke with interstitial lung abnormalities even when it has not been recognized by either the patient or a physician.

but have not been previously diagnosed with interstitial lung disease (ILD). Although our prior findings demonstrated that people who smoke with ILA have reduced total lung capacity and emphysema (2), it is not known if these findings merely represent radiologic abnormalities or if ILA results in measurable decrements in exercise capacity.

The 6-minute walk test (6MWT) is a well-described and reproducible (3) measure of exercise capacity, disease severity, and mortality in patients with cardiopulmonary disease in general (4, 5), and IIPs in particular (6–8). We hypothesized that subjects with ILA, comparable with those with clinically apparent ILD, would have reductions in the distance they could walk in 6 minutes (6MWD). To test this hypothesis, we first assessed the validity of 6MWT in all COPDGene subjects and in analyses limited to those with ILA. Next, we evaluated the association between ILA and 6MWD in 2,416 COPDGene subjects. Based on our results we evaluated the association between ILA and previously described clinically relevant 6MWD thresholds (3, 9), the role of ILA subtypes (2), and the result of ILA in analyses limited to those without chronic obstructive pulmonary disease (COPD) (based on the known association between COPD and reduced 6MWD) (10).

METHODS

For details, see the online supplement.

Study Design

Protocols for participant enrollment and phenotyping have been described previously (11). In brief, non-Hispanic white and African-American people who smoke (with ≥ 10 pack-years of smoking) aged 45–80 years were enrolled into COPDGene at 21 clinical centers;

subjects with active lung diseases other than asthma, emphysema, or COPD were excluded. Subjects completed a protocol that included an assessment of medical history, respiratory questionnaires, and spirometry (12–15). The COPDGene study was approved by the institutional review boards of all participating centers.

6MWTs

A standardized 6MWT was performed in accordance with American Thoracic Society guidelines (16). The 6MWT was performed on an unobstructed, flat, indoor course. Subjects were instructed and encouraged with standardized phrases to push themselves to achieve maximal distance. Subjects using oxygen with ambulation were instructed to use their oxygen for the test.

HRCT Analysis

In brief, visual inspection of HRCTs was performed by three readers. ILA were defined as changes affecting more than 5% of any lobar region including nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis. Scans with focal or unilateral ground-glass attenuation, focal or unilateral reticulation, and patchy ground-glass abnormality (<5% of the lung) were considered indeterminate. Scans demonstrating ILA were additionally divided into subtypes as previously described (2). Quantitative measures of emphysema (evaluated as a continuous variable at –950 Hounsfield units) (17) were obtained with Airway Inspector (www.airwayinspector.org).

Statistical Analysis

To assess the validity of 6MWD in COPDGene, we evaluated the correlation between 6MWD and measures of physiologic status, dyspnea, and responses to respiratory symptom questionnaires. Spearman correlation coefficients (3) were used to assess the strength (using commonly described interpretations) (18) of these relationships.

To determine the association between ILA and 6MWD, measurements of 6MWD were assessed as continuous variables (in meters) and as commonly described binary thresholds used in trial enrollment (≤ 500 m) (9) and to predict death (≤ 250 m) (3) in patients with IPF. Univariate analyses were conducted with Fisher exact tests (for binary and categorical variables), and two-tailed *t* tests or Wilcoxon rank sum tests (for continuous variables) where appropriate.

For multivariate analyses, we used unbiased stepwise linear regression (allowing successive covariates to be included in the model starting

with the lowest *P* values and including all statistically significant covariates [*P* value < 0.05] in the final model). Additionally, we allowed covariates to be included in the final model that satisfied a change-in-estimate criterion ($\geq 10\%$ in β -estimate or the odds ratio) and assessed for interactions in unadjusted and adjusted models on a multiplicative scale. When covariates containing similar information were selected we included only the covariate with the lowest *P* value in the final model. In all models subjects indeterminate for ILA (*n* = 861) were excluded except when otherwise indicated. Based on our findings, subgroup analyses were performed to assess the role of ILA subtype (2) and to exclude those with COPD (10). All analyses were performed using Statistical Analysis Software version 9.2 (SAS Institute, Cary, NC). *P* values less than 0.05 were considered statistically significant.

RESULTS

Of the 2,416 COPDGene subjects characterized for ILA status (2), 2,404 (99.5%) were able to complete a 6MWT (Figure 1); 6MWD in the remaining 12 subjects was set to 0 m. Although there was significant evidence for interrater agreement in the identification of ILA by chest CT (*P* < 0.001) the strength of agreement was modest (kappa, 0.43; 95% confidence interval [CI], 0.39–0.47). Of note, and as reported previously (2), only 27% (361 of 1,361) of chest CTs initially scored as not having ILA were evaluated more than once, and 98% of all discordant reads (510 of 522) involved one indeterminate read. Characteristics of COPDGene subjects stratified by ILA status are included in Table 1 (*see* Table E1 in the online supplement for characteristics of COPDGene subjects stratified by 6MWD thresholds [3, 9]). As expected, reductions in 6MWD were correlated with expected changes in many demographic, cardiovascular, musculoskeletal, and spirometric parameters and alterations in baseline vital signs, respiratory symptom scores, and chest CT parameters (*see* Table E1). There was an increased prevalence of a reduced 6MWD among those with ILA compared with those without ILA (Table 1).

Validity of 6MWD in COPDGene

In COPDGene there were significant correlations between 6MWD and FVC (% predicted), resting arterial oxygen saturation, Modified Medical Research Council score, and St. George's Respiratory Questionnaire (SGRQ) score (Table 2). There was a high degree

Figure 1. A flow diagram of study enrollment divides participants into three groups according to 6-minute walk distance (6MWD). Each group is then broken down according to the subtype of interstitial lung abnormalities (ILA). HRCT = high-resolution chest computed tomography; ILD = interstitial lung disease.

TABLE 1. BASELINE CHARACTERISTICS OF COPDGENE SUBJECTS STRATIFIED BY ILA STATUS

Variable*	Number (%) or Median (Interquartile Range) where Appropriate		
	No ILA (n = 1,361; 56%)	Indeterminate (n = 861; 36%)	ILA (n = 194; 8%)
Demographic parameters			
Age, yr	60 (52–67)	63 (55–70)	64 (56–72)
Sex, female	648 (48%)	422 (49%)	101 (52%)
Race, African-American	328 (24%)	229 (27%)	56 (29%)
Body mass index	27 (24–31)	29 (25–33)	28 (25–33)
Pack-years of smoking	40 (29–54)	41 (28–60)	44 (31–63)
Current smoker	609 (45%)	354 (41%)	97 (50%)
Baseline vital signs			
Systolic blood pressure	129 (117–140)	129 (118–140)	129 (118–139)
Diastolic blood pressure	77 (70–84)	76 (70–83)	75 (68–82)
Heart rate	76 (67–85)	75 (66–84)	74 (64–85)
Resting oxygen saturation	97 (95–98)	96 (95–98)	97 (94–98)
Cardiovascular parameters			
History of angina	53 (4%)	50 (6%)	9 (5%)
History of coronary artery disease	72 (5%)	61 (7%)	20 (10%)
History of congestive heart failure	37 (3%)	26 (3%)	12 (6%)
History of arrhythmia	117 (9%)	67 (8%)	18 (9%)
Musculoskeletal parameters			
History of osteoarthritis	244 (18%)	178 (21%)	41 (21%)
History of rheumatoid arthritis	79 (6%)	80 (9%)	20 (10%)
History of compression fracture	67 (5%)	43 (5%)	10 (5%)
History of chronic stiffness or back pain	328 (24%)	229 (27%)	59 (30%)
Spirometric parameters			
FEV ₁ , % of predicted†	80 (53–96)	77 (55–92)	81 (67–93)
FVC, % of predicted†	88 (75–100)	87 (74–99)	88 (77–98)
FEV ₁ /FVC %	0.7 (0.5–0.8)	0.7 (0.5–0.8)	0.7 (0.6–0.8)
Chronic obstructive pulmonary disease	561 (41%)	378 (44%)	63 (33%)
Respiratory parameters			
MMRC dyspnea score‡			
0	612 (45%)	353 (41%)	76 (40%)
1	190 (14%)	107 (12%)	34 (18%)
2	155 (11%)	126 (15%)	31 (16%)
3	240 (18%)	178 (21%)	36 (19%)
4	156 (12%)	93 (11%)	16 (8%)
SGRQ score	20.5 (5.7–44.2)	24.1 (8.1–43.6)	22.7 (7.6–39.6)
Chest computed tomography parameters			
Emphysema, % (–950 Hounsfield units)§	4.1 (1.3–12.4)	3.3 (0.9–9.7)	2.2 (0.7–6)
Exercise capacity			
Six-minute walk distance	426 (333–510)	399 (300–495)	403 (308–480)
Unable to walk 500 m in 6 min	970 (71%)	655 (76%)	160 (82%)
Unable to walk 250 m in 6 min	179 (13%)	144 (17%)	36 (19%)

Definition of abbreviations: ILA = interstitial lung abnormalities; MMRC = Modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.

*Data missing: systolic and diastolic blood pressure (n = 3); heart rate (n = 2); resting oxygen saturation (n = 1); history of osteoarthritis (n = 1); history of rheumatoid arthritis (n = 1); history of chronic stiffness or back pain (n = 1); FEV₁ and FVC (n = 1); COPD (n = 1); MMRC dyspnea score (n = 13); and emphysema % (n = 19).

†Postbronchodilator pulmonary function measurements presented.

‡Data missing (n = 9).

§Quantitative metrics of emphysema were performed using Airway Inspector (www.airwayinspector.org) for each inspiratory high-resolution chest computed tomography.

of correlation between 6MWD and Modified Medical Research Council and SGRQ scores, whereas weaker correlations were noted between 6MWD and FVC (% predicted) and resting arterial oxygen saturation. Similar correlations were noted in analyses limited to subjects with ILA (Table 2).

ILA and 6MWD in All Subjects

The mean 6MWD in all subjects with ILA was 386 m (SD, 128 m). ILA was associated with a reduced 6MWD in univariate analyses (Table 3). Compared with subjects without ILA, subjects with ILA had a 90% and 51% increase in their odds to have a walk distance limited to less than or equal to 500 and 250 m, respectively (Figures 2A and 2B and Table 3).

In an unbiased multivariate model, ILA was significantly associated with reduced 6MWD (Table 3). The best fitting multivariate

model explained 57% of the variance of 6MWD ($r^2 = 0.57$; $P < 0.001$). Additional covariates selected included age; sex; race; body mass index (BMI); pack-years of smoking; current smoking status; clinical center; baseline heart rate; self reports of angina, arrhythmia, and osteoarthritis; SGRQ score; measurements of FVC; and the percentage of emphysema (see Table E2). No additional variables were identified as confounders. There was no major decrement in the association between ILA and reduced 6MWD in multivariate analyses excluding subjects unable to perform the 6MWT (–19 m; 95% CI, –33 to –5 m; $P = 0.007$), when either terms for FEV₁/FVC ratio (–19 m; 95% CI, –33 to –5 m; $P = 0.009$) or height were additionally included in the model (–19 m; 95% CI, –33 to –5; $P = 0.007$), and when terms were included grouping all cardiovascular and musculoskeletal covariates (–18 m; 95% CI, –32 to –4 m; $P = 0.01$). In multivariate analyses including ILA interpretation as an unordered categorical variable,

TABLE 2. CORRELATION BETWEEN 6-MINUTE WALK DISTANCE AND OTHER MEASURES IN COPDGENE

Variable	All Subjects (n = 2416)			Subjects with ILA (n = 194)		
	N	Coefficient*	P Value*	N	Coefficient*	P Value*
FVC, % predicted [†]	2,415	0.41	<0.001	193	0.38	<0.001
Resting SaO ₂ [‡]	2,415	0.19	<0.001	194	0.20	0.008
MMRC dyspnea score [§]	2,403	-0.51	<0.001	193	-0.48	<0.001
SGRQ score	2,416	-0.52	<0.001	194	-0.48	<0.001

Definition of abbreviations: ILA = interstitial lung abnormalities; MMRC = Modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.

*Spearman correlation coefficient and P value.

[†]Postbronchodilator pulmonary function measurements presented. Data missing all subjects and subjects with ILA (n = 1).

[‡]Data missing all subjects (n = 1).

[§]Data missing all subjects (n = 13) and subjects with ILA (n = 1).

compared with those without ILA, ILA was associated with a reduced 6MWD (-19 m; 95% CI, -33 to -5 m; $P = 0.009$), whereas indeterminate status was not (-4 m; 95% CI, -12 to 5 m; $P = 0.34$). To provide an estimate of the association between ILA and 6MWD that excludes potentially casual (e.g., metrics of tobacco smoke exposure) and intermediate (e.g., FVC and SGRQ score) variables, we provide a multivariate estimate excluding these covariates (-28 m; 95% CI, -43 to -13 m; $P = 3 \times 10^{-4}$). Comparable with univariate analyses, in multivariate models, subjects with ILA had an 80% and 77% increase in their odds to have a walk distance limited to less than or equal to 500 and 250 m, respectively (Table 3).

There was statistical evidence that the association between ILA and 6MWD was modified by BMI and the report of an arrhythmia (P values for the interactions 0.02 for both covariates). For example, although similar (but nonsignificant) correlations were noted for the association between ILA and 6MWD in those of normal weight (among those with a BMI ≤ 25 ILA was associated with a -22 m; 95% CI, -50 to 7 m; $P = 0.14$) and among those who were overweight to obese (among those with a BMI > 25 ILA was associated with a -19 m; 95% CI, -35 to -4 m; $P = 0.02$) the strength of the association between ILA and 6MWD was increased when obese subjects were evaluated alone (among those with a BMI ≥ 30 ILA was associated with a -37 m; 95% CI, -97 to -13 m; $P = 0.002$). Comparably, although there was evidence that ILA was associated with 6MWD among those without a report of an arrhythmia (-15 m; 95% CI, -30 to -0.4 m; $P = 0.04$) there was increased evidence for the association between

ILA and 6MWD in those with an arrhythmia (-76 m; 95% CI, -131 to -21 m; $P = 0.008$).

ILA Subtype and 6MWD

Differences were noted in the magnitude of the association between ILA subtypes and reduced 6MWD (P for the analysis of variance between subtypes = 0.006). Although centrilobular ILA was not associated with a reduced 6MWD (-6 m; 95% CI, -51 to 38; $P = 0.78$), subpleural ILA (-32 m; CI, -58 to -5; $P = 0.02$; a similar but nonsignificant association was noted with the mixed ILA) and radiologic ILD (-116 m; 95% CI, -193 to -38; $P = 0.004$) were significantly associated with a reduced 6MWD. Despite the magnitude of association between radiologic ILD and reduced 6MWD, in multivariate analyses, ILA remained associated with reduced 6MWD even when subjects with radiologic ILD were excluded (-17 m; 95% CI, -32 to -3; $P = 0.02$). Similar evidence of association was noted when centrilobular ILA was excluded from analyses (-21 m; 95% CI, -36 to -5; $P = 0.01$). Although many ILA subtypes were more prevalent among those with walk distances limited to less than or equal to 500 m compared with those without ILA (Figure 2A), subpleural and radiologic ILD had the greatest contribution to the association between ILA and having a walk distance limited to less than or equal to 250 m (Figure 2B).

ILA and 6MWD in Subjects without COPD

The mean 6MWD in those with ILA but without COPD was 406 m (SD, 130 m). Although the evidence for COPD status as an effect modifier of ILA on reduced 6MWD was marginal (P for COPD-by-ILA interaction = 0.07), based on the known association between COPD and reduced 6MWD (10) we present our findings in subjects without COPD to remove this potential confounder. Among subjects without COPD, ILA was associated with a reduced 6MWD in univariate and multivariate models (Table 3, Figure 3). In addition, among subjects without COPD, subjects with ILA had a more than 2.5-fold increase in their odds to have a walk distance limited to less than or equal to 250 m (Figure 2B, Table 3). Comparable, but attenuated, associations were noted between ILA and the odds to have a walk distance limited to less than or equal to 500 m (Figure 2A, Table 3).

Among those with COPD, nonstatistically significant trends of similar magnitude were noted in the associations between ILA and reduced 6MWD (see Table E3), despite substantial reductions in emphysema among those with ILA compared with

TABLE 3. UNIVARIATE AND MULTIVARIATE ANALYSES OF ASSOCIATION BETWEEN INTERSTITIAL LUNG ABNORMALITIES AND SIX-MINUTE WALK DISTANCE

	All Subjects (n = 1555)			Subjects without COPD (n = 930)		
	6MWD $\leq$ 500 m	6MWD $\leq$ 250 m	6MWD (m)	6MWD $\leq$ 500 m	6MWD $\leq$ 250 m	6MWD (m)
	OR (95% CI) P Value	OR (95% CI) P Value	CE (95% CI) P Value	OR (95% CI) P Value	OR (95% CI) P Value	CE (95% CI) P Value
Unadjusted	1.90 (1.30 to 2.80) 0.001	1.51 (1.01 to 2.23) 0.04	-30 (-50 to -10) 0.004	2.19 (1.42 to 3.39) <0.001	2.56 (1.49 to 4.39) <0.001	-50 (-72 to -27) <0.001
Adjusted*	1.80 (1.12 to 2.89) 0.02	1.77 (1.04 to 3.03) 0.04	-19 (-33 to -5) 0.008	1.48 (0.86 to 2.55) 0.16	2.67 (1.23 to 5.80) 0.01	-18 (-35 to -1) 0.04

Definition of abbreviations: 6MWD = 6-minute walk distance; CE = coefficient estimate; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio.

*Multivariate models were additionally adjusted for age, sex, race, body mass index, pack-years of smoking, FVC (% of predicted), emphysema %, baseline heart rate, current smoking, history of osteoarthritis, St. George's Respiratory Questionnaire Score, history of arrhythmia, history of angina, and clinical center.

Figure 2. Bar graphs represent the percentage of all subjects and subjects without chronic obstructive pulmonary disease (COPD) who had a 6-minute walk distance (6MWD) (A) less than or equal to 500 m and (B) less than or equal to 250 m. It is further subdivided into subjects without interstitial lung abnormalities (ILA) (gray), with ILA (red), with centrilobular ILA (light green), with subpleural ILA (light orange), with mixed ILA (light green and light orange), and with radiologic ILD (orange). *P* values for comparisons between those with ILA (or in analyses limited to a subtype of ILA) and those without ILA (**P* < 0.05, ***P* < 0.005, and ****P* < 0.0005). ILD = interstitial lung disease.

those without ILA (Figure 3). Findings of association for binary outcomes are additionally presented risk ratios (see Table E4).

DISCUSSION

Our study demonstrates that ILA is associated with measurable decrements in the 6MWD of people who smoke. After adjusting for important covariates, subjects with ILA in COPDGene had an 80% and 77% increase in their odds to be unable to walk greater than 500 and 250 m in 6 minutes, respectively. Although findings on multivariate analysis can be critically dependant on model design, our findings demonstrate that the association between ILA and decreased 6MWD is robust to many alternative modeling strategies. Although the effect of ILA on reduced 6MWD is influenced by BMI, a report of an arrhythmia, and radiologic subtype, reductions in 6MWD noted in those with ILA were less evident in those with coincident COPD. The latter

finding may be, in part, explained by substantial reductions in emphysema among those with ILA and COPD (2). These findings suggest that a syndrome including reduced lung volumes (2, 19), increased respiratory symptoms (2), and reduced exercise capacity can develop in people who smoke with ILA even when this syndrome has not been recognized by either the subject or a physician.

Comparable with previous analyses of IPF (3) and COPD (20), measurements of 6MWD in COPDGene demonstrated robust correlations with measures of health-related quality of life and breathlessness, whereas more modest correlations were noted with measures of physiologic function. Similar degrees of correlation were noted in analyses limited to those with ILA. Our findings demonstrate that even among people who smoke without a known diagnosis, substantial decrements in 6MWD can exist.

To put our findings in context, it is helpful to compare the degree of exercise impairment experienced by those with ILA with those with pulmonary fibrosis. The mean 6MWD among

Figure 3. Box plots comparing subjects without chronic obstructive pulmonary disease (COPD) or interstitial lung abnormalities (ILA) (column 1) with ILA but without COPD (column 2), with COPD but without ILA (column 3), and with both ILA and COPD (column 4) versus measurements of 6-minute walk distance and % emphysema are presented (*** $P < 0.0005$).

those with ILA (386 m) is comparable with the 6MWD of patients with idiopathic pulmonary fibrosis (IPF) in recent clinical trials (373–392 m) (3, 21) and more than that of patients with IPF recruited on the basis of advanced disease (246–268 m) (22). Although most subjects with ILA were unable to walk greater than or equal to 500 m in 6 minutes, it is somewhat of a surprise that 19% (17% when subjects with COPD are excluded) of subjects with ILA were unable to walk greater than or equal to 250 m in 6 minutes. In a recent analysis of patients with IPF from the Phase 3 clinical trial of interferon γ -1 β , a 6MWD of less than 250 m occurring at any visit ($\sim 11\%$ of subjects) was associated with a 2.65-fold increase in the risk of death over 1 year (3). It is not known if substantially reduced walk distances would predict similarly poor outcomes among those with ILA.

It is important to note that ILA among people who smoke has been associated with reduced lung volumes (2, 19), less emphysema (2), reduced diffusion capacity of carbon monoxide (23), and now reduced exercise capacity. Taken together, these findings suggest that in addition to emphysema and COPD, an unrecognized, clinicoradiologic syndrome resembling ILD may be occurring in a substantial number of people who smoke. Although the histopathologic correlates of ILA in people who smoke are not well described, biopsies on similarly ascertained asymptomatic members of families with familial pulmonary fibrosis (24, 25) and rheumatoid arthritis (26) have demonstrated pathologies consistent with IIP.

Our study has several additional limitations. First, our study differs from one prior study that was not able to demonstrate a statistically significant reduction in 6MWD among those with ILA (23); however, small sample size and different methods of detection may have influenced this outcome. Second, the generalizability of our findings may be limited to populations of people who smoke and may be affected by the exclusion of indeterminate subjects. Third, although 6MWD can be affected by a variety of factors related and unrelated to cardiopulmonary status (27), our analysis demonstrates that the association between ILA and reduced 6MWD is robust to adjustments for many potential confounders. The validity of our findings is additionally supported by our multivariate model, which includes many well-recognized factors associated with reduced 6MWD (e.g., obesity [28], resting heart rate [29], osteoarthritis [30], and atrial fibrillation [31]). Finally, ambulatory oxygen saturation was not measured during the 6MWT in COPDGene. Because exercise-induced desaturation in patients with IPF has been

associated with increased mortality (8), these data could have provided additional supportive information.

Conclusions

ILA is associated with decreases in 6MWD in all subjects and in subjects without COPD. Longitudinal follow-up studies are important to evaluate if these alterations in 6MWD in patients with ILA are paired with increases in morbidity and mortality.

Author disclosures are available with the text of this article at www.atsjournals.org.

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