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Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities

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ABSTRACT

BACKGROUND

Cigarette smoking is associated with emphysema and radiographic interstitial lung abnormalities. The degree to which interstitial lung abnormalities are associated with reduced total lung capacity and the extent of emphysema is not known.

METHODS

We looked for interstitial lung abnormalities in 2416 (96%) of 2508 high-resolution computed tomographic (HRCT) scans of the lung obtained from a cohort of smokers. We used linear and logistic regression to evaluate the associations between interstitial lung abnormalities and HRCT measurements of total lung capacity and emphysema.

RESULTS

Interstitial lung abnormalities were present in 194 (8%) of the 2416 HRCT scans evaluated. In statistical models adjusting for relevant covariates, interstitial lung abnormalities were associated with reduced total lung capacity (−0.444 liters; 95% confidence interval [CI], −0.596 to −0.292; P<0.001) and a lower percentage of emphysema defined by lung-attenuation thresholds of −950 Hounsfield units (−3%; 95% CI, −4 to −2; P<0.001) and −910 Hounsfield units (−10%; 95% CI, −12 to −8; P<0.001). As compared with participants without interstitial lung abnormalities, those with abnormalities were more likely to have a restrictive lung deficit (total lung capacity <80% of the predicted value; odds ratio, 2.3; 95% CI, 1.4 to 3.7; P<0.001) and were less likely to meet the diagnostic criteria for chronic obstructive pulmonary disease (COPD) (odds ratio, 0.53; 95% CI, 0.37 to 0.76; P<0.001). The effect of interstitial lung abnormalities on total lung capacity and emphysema was dependent on COPD status (P<0.02 for the interactions). Interstitial lung abnormalities were positively associated with both greater exposure to tobacco smoke and current smoking.

CONCLUSIONS

In smokers, interstitial lung abnormalities — which were present on about 1 of every 12 HRCT scans — were associated with reduced total lung capacity and a lesser amount of emphysema. (Funded by the National Institutes of Health and the Parker B. Francis Foundation; ClinicalTrials.gov number, NCT00608764.)

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The relationship between exposure to tobacco smoke and chronic obstructive pulmonary disease (COPD) is well described.[1] Two manifestations of COPD include emphysematous destruction of the lung parenchyma and elevated measures of total lung capacity.[2] However, there is increasing awareness that smoking may also result in areas of increased lung density — termed interstitial lung abnormalities — on high-resolution computed tomography (HRCT).[3,4] The extent to which interstitial lung abnormalities may be associated with a lesser amount of emphysema and lower measures of total lung capacity than anticipated on the basis of known smoking exposure is unclear.

We determined the relationship between radiographic interstitial lung abnormalities and HRCT measures of total lung capacity and emphysema in a cohort of non-Hispanic white and black smokers who had been recruited for the COPDGene Study on the basis of a self-reported history of more than 10 pack-years of smoking. Since we oversampled participants on the basis of COPD status,[5] we evaluated whether the associations between interstitial lung abnormalities and both total lung capacity and emphysema were modified by COPD status.

Methods

Study Design

From November 2007 through April 2010, a total of 2508 smokers (1867 [74%] non-Hispanic white and 641 [26%] black) between the ages of 45 and 80 years with a history of at least 10 pack-years were enrolled at 21 clinical centers under the auspices of the COPDGene Study, which is ongoing and has been described previously.[4,5] Participants with a history of any active lung disease other than asthma, emphysema, or COPD were excluded from the study. Spirometry was performed in accordance with the recommendations of the American Thoracic Society and the European Respiratory Society.[6] HRCT was performed at full inspiration and at relaxed exhalation. Quantitative measures of total lung capacity and emphysema were performed with the Airway Inspector (a free, open-source tool used for CT-based image analysis; available at www.airwayinspector.org). The COPDGene Study was approved by the institutional review boards of all participating centers, and all participants provided written informed consent. A detailed description of the study methods appears in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Visual HRCT Analysis

We divided the visual HRCT analysis into two stages. In stage 1, HRCT scans were evaluated by three readers (two chest radiologists and one pulmonologist) with the use of a sequential reading method, as previously described.[4] Interstitial lung abnormalities were defined as nondependent changes affecting more than 5% of any lung zone and included nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis (Fig. 1).[7,8] Focal or unilateral ground-glass attenuation, focal or unilateral reticulation, and patchy ground-glass abnormalities (present in <5% of the lung) were considered to be indeterminate findings. The fraction of the lung that met the criteria for radiographic emphysema was not included in the estimation of interstitial lung abnormalities.

In stage 2 of the visual HRCT analysis, we divided the participants with interstitial lung abnormalities into four major radiographic subtypes: predominant centrilobular or peribronchial ground-glass opacities sparing the peripheral lung parenchyma (Fig. 1A); reticular, nodular, or ground-glass opacities in a predominantly subpleural distribution (Fig. 1B); mixed centrilobular and subpleural abnormalities (Fig. 1C); and extensive radiographic changes consistent with firm radiographic evidence of interstitial lung disease according to the guidelines of the American Thoracic and European Respiratory Societies[9] (Fig. 1D). Participants with interstitial lung abnormalities were divided into these four radiographic groups on the basis of the consensus opinion of the three readers, who were unaware of each participant's clinical characteristics.

Statistical Analysis

Total lung capacity was evaluated as both a continuous variable (in liters and as the percent of the predicted value[10]) and as a binary variable (<80% or 80% of the predicted value[11]). Lung volume at relaxed exhalation was evaluated as a continuous variable (in liters). The percentage of the lung that was emphysematous was evaluated as a continuous variable (defined by a threshold of both −950 Hounsfield units[12] and −910 Houns-

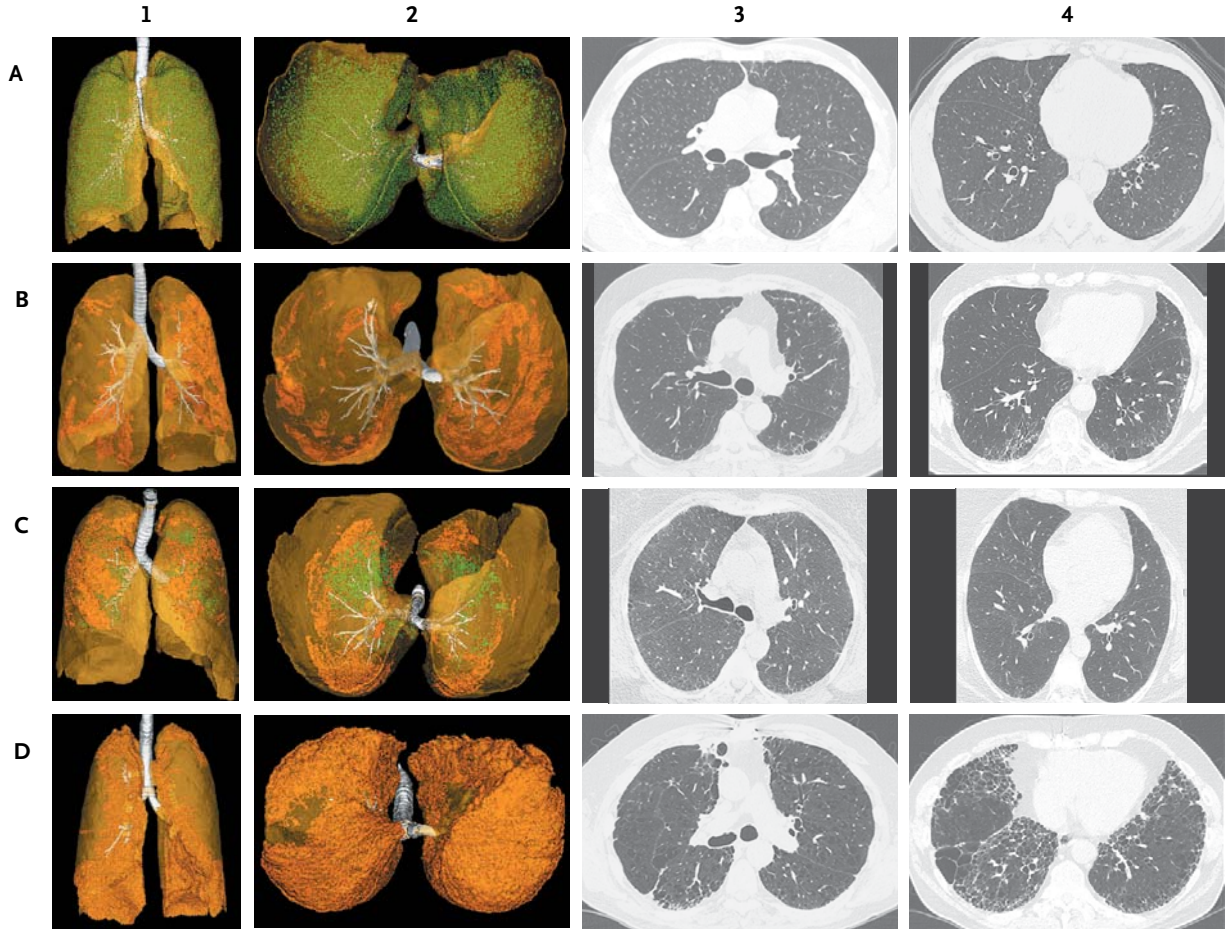

Figure 1. Four Major Radiographic Subtypes of Interstitial Lung Abnormalities.

Each row of radiographs and reconstructions represents data from a single study participant. The images in Panel A are characteristic of centrilobular interstitial lung abnormalities; Panel B, subpleural interstitial lung abnormalities; Panel C, mixed centrilobular and subpleural interstitial lung abnormalities; and Panel D, radiographic interstitial lung disease. The images in the first two columns are three-dimensional reconstructions of an anterior-to-posterior view of the lungs (column 1) and a caudal-to-cephalad view (column 2). The translucent yellow–green represents the lung parenchyma; white, the tracheobronchial tree; opaque green, centrilobular opacities; and opaque orange, subpleural abnormalities. Columns 3 and 4 present axial high-resolution computed tomographic images of the chest, with images in column 3 approximately at the level of the carina and those in column 4 approximately at the level of the right inferior pulmonary vein.

field units[13]). We defined COPD as a binary variable in accordance with the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for disease at stage 2 or higher.[14] Bivariate analyses were conducted with Fisher's exact test (for categorical variables) and two-tailed t-tests or the Wilcoxon rank-sum test (for continuous variables) as appropriate. Linear regression models were used for continuous variables and logistic-regression models for binary variables in multivariate analyses. All of the final multivariate models included the variables for age, sex, race, body-mass index (BMI), pack-years of smoking, smoking status (former vs. current smoker), diagnosis of COPD (defined as GOLD stage 2 or higher[14]), and additional covariates as described below. We oversampled participants on the basis of COPD status[5] and performed interaction tests to evaluate whether COPD status modified the associations between interstitial lung abnormalities and both total lung capacity and emphysema. P values of less than 0.05 were considered to in-

dicate statistical significance. All analyses were performed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE STUDY PARTICIPANTS

Of the 2508 participants originally recruited, 2416 (96%) had an HRCT scan available and were included in this analysis. Of these 2416 participants, 1171 (48%) were women, 613 (25%) were black, 1060 (44%) were active smokers, and 1002 (41%) met the GOLD criteria for COPD. Of the 2416 HRCT scans evaluated, 194 (8%) showed interstitial lung abnormalities, 861 (36%) were indeterminate, and 1361 (56%) did not show interstitial lung abnormalities (Table 1 and Fig. 2A). Of the 1421 HRCT scans scored by at least two readers (in stage 1 of the visual HRCT analysis), 899 (63%) had concordant scores. Among the 522 scans for which the evaluations were not concordant, a majority (510 [98%]) involved one indeterminate reading; discrepancies in the interpretation of HRCT scans with respect to the presence or absence of interstitial lung abnormalities were less common (12 scans [2%]).

Baseline characteristics of study participants in whom interstitial lung abnormalities were detected, those in whom interstitial lung abnormalities were not detected, and those for whom the diagnosis was indeterminate are shown in Table 1 and in Table E1 in the Supplementary Appendix. As compared with participants without interstitial lung abnormalities, those with interstitial lung abnormalities were significantly older, had a higher BMI, and had a greater amount of exposure to tobacco smoke. Both HRCT measurements of total lung capacity and lung volume at relaxed exhalation were lower in participants with interstitial lung abnormalities. In addition, participants with interstitial lung abnormalities were less likely to have COPD, were more likely to have spirometric measurements that could not be classified according to the GOLD criteria for

Table 1. Baseline Characteristics of the Study Participants.*

Variable	Participants without ILA	P Value	Participants with Indeterminate HRCT Scans	P Value	Participants with ILA	P Value
Total — no. (%)	1361 (56)		861 (36)		194 (8)	
Demographic characteristics						
Median age — yr	60 (52–67)	<0.001	63 (55–70)	0.12	64 (56–72)	<0.001
Female sex — no. (%)	648 (48)	0.54	422 (49)	0.47	101 (52)	0.25
Black race — no. (%)	328 (24)	0.19	229 (27)	0.53	56 (29)	0.15
Median body-mass index	27 (24–31)	<0.001	29 (25–33)	0.25	28 (25–33)	0.006
Median pack-yr of smoking	40 (29–54)	0.08	41 (28–60)	0.15	44 (31–63)	0.01
Current smoker — no. (%)	609 (45)	0.10	354 (41)	0.02	97 (50)	0.19
Respiratory symptoms						
Cough — no. (%)	473 (35)	0.01	344 (40)	0.87	79 (41)	0.11
Shortness of breath when hurrying on level ground or walking up slight hill — no. (%)	731 (54)	0.04	501 (58)	0.68	115 (60)	0.16
Spirometric measures						
GOLD stage — no. (%)†						
COPD (≥GOLD stage 2)	561 (41)	0.22	378 (44)	0.005	63 (32)	0.02
Unclassified	102 (7)	0.007	94 (11)	0.17	28 (14)	0.002
0	599 (44)		306 (36)		76 (39)	
1	99 (7)		83 (10)		26 (13)	
2	260 (19)		201 (23)		46 (24)	
3	186 (14)		121 (14)		12 (6)	
4	115 (8)		56 (7)		5 (3)	

Table 1. (Continued.)

Variable	Participants without ILA	P Value	Participants with Indeterminate HRCT Scans	P Value	Participants with ILA	P Value
Median FEV_1 — % of predicted‡	80 (52–97)	0.02	77 (55–92)	0.03	82 (67–93)	0.15
Median FVC — % of predicted‡	88 (75–100)	0.08	87 (74–99)	0.30	88 (77–98)	0.80
Median FEV_1:FVC %‡	70 (51–79)	0.04	68 (53–76)	0.01	71 (61–77)	0.32
Spirometric restriction — no. (%)§	414 (30)	0.82	266 (31)	0.004	81 (42)	0.002
Chest CT findings						
Median % emphysema¶						
–950 HU	4.1 (1.3–12.4)	<0.001	3.3 (0.9–9.7)	<0.001	2.2 (0.7–6.0)	<0.001
–910 HU	30 (15–47)	<0.001	23 (10–41)	<0.001	14 (7–29)	<0.001
Total lung capacity‖						
Median volume at full inspiration — liters	5.70 (4.80–6.78)	<0.001	5.21 (4.38–6.27)	0.08	5.02 (4.15–5.96)	<0.001
Median % of predicted value	107 (92–120)	<0.001	100 (84–112)	0.04	95 (81–109)	<0.001
<80% of predicted value — no. (%)	134 (10)	<0.001	169 (20)	0.77	40 (21)	<0.001
Median lung volume at relaxed exhalation — liters	3.13 (2.51–3.98)	0.06	3.04 (2.48–3.84)	<0.001	2.67 (2.23–3.44)	<0.001

* The body-mass index is the weight in kilograms divided by the square of the height in meters. Race was self-reported. Data with respect to chronic obstructive pulmonary disease (COPD) and pulmonary-function testing are missing for 1 participant, data on information about respiratory symptoms are missing for 13 participants, data on percentage of emphysema defined by lung-attenuation thresholds of –950 Hounsfield units (HU) are missing for 1 participant and data on percentage of emphysema defined by lung-attenuation thresholds of –910 HU are missing for 51 participants, data on total lung capacity are missing for 19 participants, and data on lung volume at relaxed exhalation are missing for 195 participants. The interquartile range is shown in parentheses for median values. The first column of P values is for the comparison between participants without interstitial lung abnormalities (ILA) and those with findings classified as indeterminate, the second column of P values is for the comparison between participants with findings classified as indeterminate and those with ILA, and the third column of P values is for the comparison between participants without ILA and those with ILA. P values were calculated with Fisher's exact test for binary variables and with paired t-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease, and HRCT high-resolution computed tomography.

† GOLD stages are defined as follows: unclassified (FEV_1:FVC ≥0.70, FEV_1 <80% of predicted value), GOLD stage 0 (FEV_1:FVC ≥0.70, FEV_1 ≥80% of predicted value), GOLD stage 1 (FEV_1:FVC <0.70, FEV_1 ≥80% of predicted value), GOLD stage 2 (FEV_1:FVC <0.70, FEV_1 <80% but ≥50% of predicted value), GOLD stage 3 (FEV_1:FVC <0.70, FEV_1 <50% but ≥30% of predicted value), and GOLD stage 4 (FEV_1:FVC <0.70, FEV_1 ≤30% of predicted value). P values represent the likelihood that participants are unclassified according to GOLD (an FEV_1 ≤80% of predicted value and an FEV_1:FVC >0.70) as compared with all other stages.

‡ Postbronchodilator measurements of pulmonary function are presented. The predicted values for FEV_1 and FVC are derived from Crapo et al.[15]

§ Spirometric restriction is defined as an FVC below the lower limit of normal and an FEV_1:FVC ratio above the lower limit of normal.[16]

¶ Quantitative metrics of emphysema, total lung capacity, and lung volume at relaxed exhalation were performed with Airway Inspector (www.airwayinspector.org) for each inspiratory (emphysema and total lung capacity) and expiratory (lung volume at relaxed exhalation) HRCT.

‖ Percent of predicted total lung capacity was calculated in accordance with guidelines from the American Thoracic Society and European Respiratory Society.[10]

COPD (forced expiratory volume in 1 second [FEV_1], ≤80% of the predicted value; ratio of FEV_1 to forced vital capacity [FVC], >0.7), and were more likely to have a lower percentage of emphysema. Although there was an increased frequency of spirometric restriction in participants with interstitial lung abnormalities, the absence of an association with other baseline spirometric measures and the broad distribution of participants with interstitial lung abnormalities on a plot of FEV_1 (as a percentage of the predicted value) against the ratio of FEV_1 to FVC suggest that spirometry alone is not helpful in classifying interstitial lung abnormalities (Fig. 2B, and Fig. E1 and Table E2 in the Supplementary Appendix).

TOTAL LUNG CAPACITY AND RESTRICTIVE LUNG DEFICIT

In adjusted models, the HRCT scans for participants with interstitial lung abnormalities, as compared with the scans for participants without such abnormalities, revealed evidence of reduced total lung capacity (Table 2 and Fig. 2C). Similarly, participants with interstitial lung abnor-

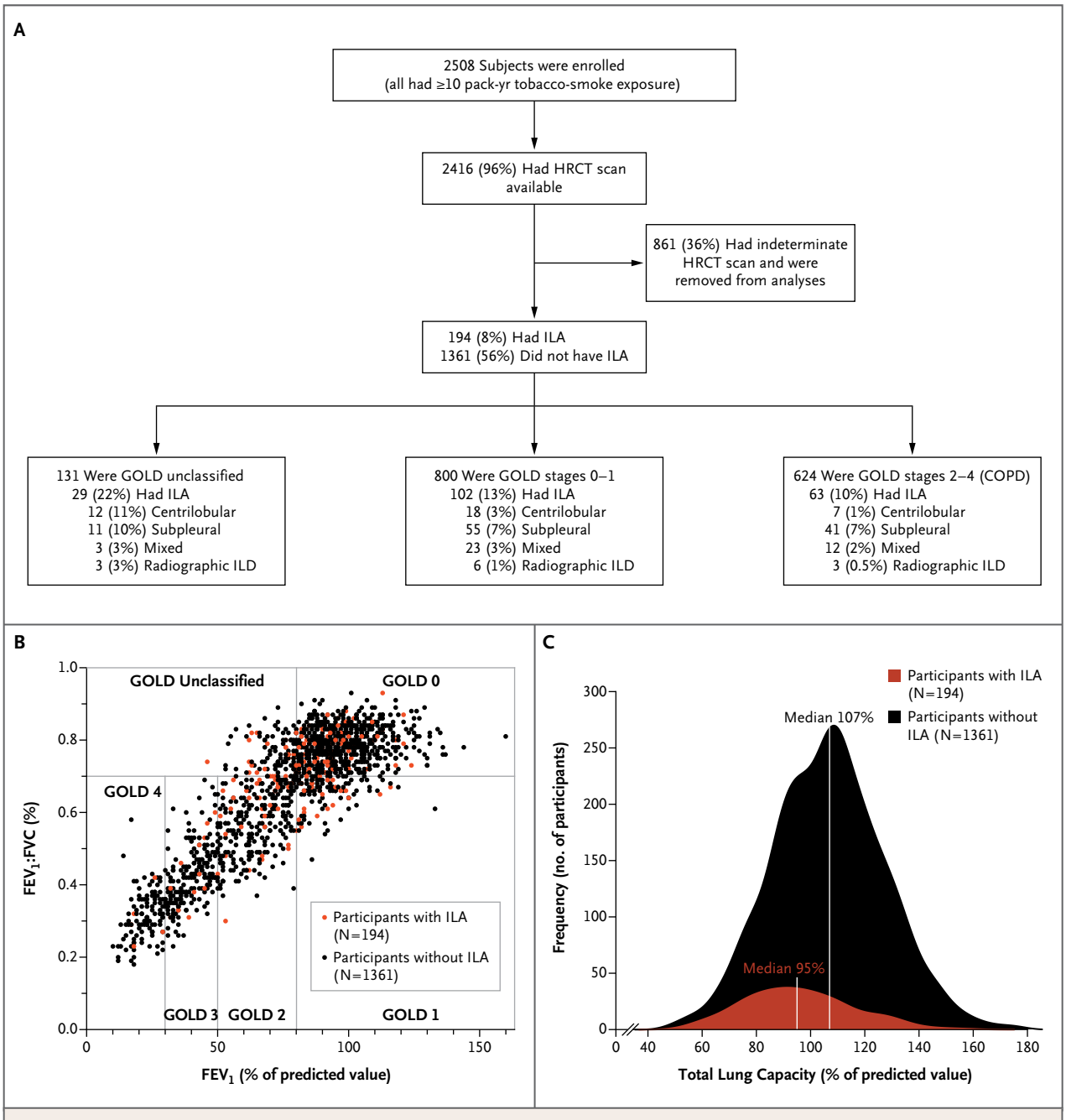

Figure 2. Study Enrollment and Findings.

Panel A divides the study participants into three groups according to the classifications established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Each group is then broken down according to the subtype of interstitial lung abnormalities (ILA). Patients who could not be classified according to the GOLD criteria had a forced expiratory volume in 1 second (FEV_1) that was less than or equal to 80% of the predicted value and a ratio of FEV_1 to forced vital capacity (FVC) that was greater than or equal to 0.7. Those patients meeting the criteria for GOLD stages 0 to 1 had an FEV_1 that was 80% or more of the predicted value, and those meeting the criteria for GOLD stages 2 through 4 had an FEV_1 of less than 80% and a ratio of FEV_1 to FVC of less than 0.7.[14] Panel B shows FEV_1 (percent of predicted value) plotted against the FEV_1:FVC (percent of predicted value) for participants with and those without ILA and classifies participants according to the GOLD criteria.[14] Panel C is a frequency plot of total lung capacity as a percent of the predicted value[10] in participants with and those without ILA. ILD denotes interstitial lung disease.

malities had reductions in lung volume at relaxed exhalation (−0.293 liters; 95% confidence interval [CI], −0.430 to −0.156; P<0.001). The odds of a restrictive deficit in participants with interstitial abnormalities were 2.3 times the odds in participants without such abnormalities (Table 2).

EMPHYSEMA AND COPD

Interstitial lung abnormalities were associated with a lower percentage of emphysema (at −950 and −910 Hounsfield units) in adjusted models (Table 2). Participants with interstitial lung abnormalities had a 47% decrease in their odds of having COPD (Table 2); the strength of this association was influenced by GOLD stage (P for the analysis of variance between GOLD stages 2 through 4 and interstitial lung abnormalities <0.001).

EFFECTS OF COPD

In analyses stratified according to COPD status, interstitial lung abnormalities were associated with reduced total lung capacity in participants with COPD (−12% of the predicted value; 95% CI, −17 to −8; P<0.001) and in those without COPD (−7% of the predicted value; 95% CI, −10 to −4; P<0.001); the magnitude of the reduction in total lung capacity was greater in participants with COPD (P=0.01 for the interaction between COPD and interstitial lung abnormalities). Findings were similar for emphysema — the magnitude of the reduction in emphysema was greater in participants with COPD (at −950 Hounsfield units, −7%; 95% CI, −10 to −4, P<0.001) than in those without COPD (defined by a threshold of −950 Hounsfield units, −0.6%; 95% CI, −1.3 to 0.1; P=0.08; P<0.001 for the interaction between COPD and interstitial lung abnormalities). After adjustment for the extent of emphysema, the reductions in total lung capacity were similar between participants with COPD (−7% of the predicted value; 95% CI, −11 to −4; P<0.001) and those without COPD (−6% of the predicted value; 95% CI, −9 to −3; P<0.001). This suggests that in participants with COPD, interstitial lung abnormalities are associated with a reduction in total lung capacity that can be explained by the contributions of both a restrictive lung deficit and an additional reduction in the physiological burden of emphysema (e.g., reduced gas trapping leading to lower lung volumes).

Table 2. Univariate and Multivariate Analyses of the Association between Interstitial Lung Abnormalities and Metrics of Restrictive and Obstructive Lung Disease.*

Analysis	Restrictive Lung Disease						Obstructive Lung Disease					
	TLC		% of Predicted TLC		<80% of Predicted TLC		% Emphysema, −950 HU†		% Emphysema, −910 HU†		COPD‡	
	CE (95% CI)	P value	CE (95% CI)	P value	OR (95% CI)	P value	CE (95% CI)	P value	CE (95% CI)	P value	OR (95% CI)	P value
	liters											
Unadjusted	−0.655 (−0.869 to −0.441)	<0.001	−11 (−14 to −8)	<0.001	2.38 (1.61 to 3.51)	<0.001	−4 (−6 to 3)	<0.001	−13 (−16 to −10)	<0.001	0.69 (0.50 to 0.95)	0.02
Adjusted§	−0.444 (−0.596 to −0.292)	<0.001	−9 (−11 to −6)	<0.001	2.29 (1.43 to 3.68)	<0.001	−3 (−4 to −2)	<0.001	−10 (−12 to −8)	<0.001	0.53 (0.37 to 0.76)	<0.001

* Percent of predicted total lung capacity was calculated in accordance with guidelines from the American Thoracic and European Respiratory Societies.[10] CE denotes coefficient estimate, HU Hounsfield units, OR odds ratio, and TLC total lung capacity.
† Percentage of emphysema is defined by lung-attenuation thresholds of −950 or −910 HU.
‡ COPD was defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 or higher.
§ All multivariate models were adjusted for age, sex, race, body-mass index, pack-years of smoking, current smoking status, and status with respect to COPD (except in the model for COPD status). Analyses for TLC, TLC as a percent of predicted value, and emphysema (at both −950 and −910 HU) are the result of multivariate linear regression models. Analyses for TLC at less than 80% of predicted value and COPD are the result of multivariate logistic-regression models.

Table 3. Multivariate Analyses of the Association between Subtypes of Interstitial Lung Abnormalities and Metrics of Restrictive and Obstructive Lung Disease.*

Subtype of Abnormality	No. of Participants†	Restrictive Lung Disease			
		TLC		% of Predicted TLC	
		CE (95% CI)	P value	CE (95% CI)	P value
		liters			
Centrilobular	37	−0.133 (−0.456 to 0.190)	0.42	−4 (−9 to 1)	0.14
Subpleural	107	−0.481 (−0.681 to −0.281)	<0.001	−10 (−13 to −7)	<0.001
Centrilobular and subpleural	38	−0.416 (−0.734 to 0.98)	0.01	−6 (−11 to −1)	0.02
Radiographic interstitial lung disease	12	−1.053 (−1.639 to −0.466)	<0.001	−19 (−29 to −10)	<0.001

* All multivariate models were adjusted for age, sex, race, body-mass index, pack-years of smoking, current smoking status, and status with respect to COPD (except in the model for COPD status). Analyses for total lung capacity (TLC), TLC as a % of predicted value, and emphysema (defined by lung-attenuation thresholds of −950 and −910 HU) are the result of multivariate linear regression models. Analyses for TLC <80% of predicted and COPD are the result of multivariate logistic-regression models. Percent of predicted total lung capacity was calculated in accordance with guidelines from the American Thoracic Society and European Respiratory Society.[10] CE denotes coefficient estimate, HU Hounsfield units, and OR odds ratio.

† For each subtype, participants with abnormalities were compared with 1361 participants without abnormalities.

‡ COPD was defined as Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) stage 2 or higher.

MAJOR SUBTYPES OF INTERSTITIAL LUNG ABNORMALITIES

Of the 194 participants with interstitial lung abnormalities, 37 (19%) could be classified as having centrilobular abnormalities (Fig. 1A), 107 (55%) as having subpleural abnormalities (Fig. 1B), 38 (20%) as having centrilobular and subpleural (or mixed) abnormalities (Fig. 1C), and 12 (6%) as having radiographic interstitial lung disease (Fig. 1D) (see also Tables E3 and E4 of the Supplementary Appendix). Table 3 shows the association between the subtypes of interstitial lung abnormalities and the measures of restrictive and obstructive lung disease. As compared with participants who did not have interstitial lung abnormalities, those with radiographic interstitial lung disease had the greatest reduction in lung volumes, followed by intermediate reductions in the subpleural and mixed subtypes, with the centrilobular subtype having the smallest reduction in lung volumes (P=0.02 for analysis of variance between subtypes) (Table 3). Emphysema was reduced by a similar magnitude in all subtypes of interstitial lung abnormalities (Table 3).

EXPOSURE TO TOBACCO SMOKE

As reported previously,[3] both the extent of exposure to tobacco smoke and smoking status were associated with the odds of having interstitial lung abnormalities, in adjusted models (see the Supplementary Appendix). The specific interstitial abnormality most strongly associated with current smoking status was the presence of centrilobular nodules (odds ratio, 4.82; 95% CI, 2.47 to 9.44; P<0.001). For findings on the association between interstitial lung abnormalities and variables other than smoking, see Table E5 and elsewhere in the Supplementary Appendix.

DISCUSSION

Our analysis of HRCT scans from this large cohort shows that interstitial lung abnormalities are present in approximately 8% of smokers. The findings also show that interstitial lung abnormalities are associated with both reduced total lung capacity and a lesser amount of emphysema in smokers, and the magnitude of these reductions is greatest among those with COPD. We found that smokers with interstitial lung abnormalities have reduced total lung capacity (the extent of which varies according to the subtype of interstitial lung abnormality) and are at an increased risk for a restrictive lung deficit. Although reductions in total lung capacity are expected in established clinical interstitial lung disease,[17] our data provide a quantitative estimate of the degree to which interstitial lung abnormalities are associated with reductions in total lung capacity.

A major finding of our analyses is the inverse association between interstitial lung abnormalities and the severity of COPD or of emphysema (particularly among participants with COPD). We considered the possibility that interstitial lung abnormalities would result in an erroneous underestimation of the amount of emphysema by

				Obstructive Lung Disease			
<80% of Predicted TLC		% Emphysema, −950 HU		% Emphysema, −910 HU		COPD‡	
OR (95% CI)	P value	CE (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
2.02 (0.76 to 5.37)	0.16	−3 (−6 to 0.2)	0.06	−12 (−16 to −7)	<0.001	0.33 (0.14 to 0.81)	0.02
2.86 (1.53 to 5.35)	0.001	−3 (−5 to −2)	<0.001	−9 (−12 to −6)	<0.001	0.60 (0.39 to 0.94)	0.03
1.10 (0.42 to 2.92)	0.85	−3 (−6 to −0.5)	0.02	−10 (−14 to −5)	<0.001	0.67 (0.31 to 1.46)	0.32
9.55 (1.90 to 48.01)	0.006	−2 (−7 to 3)	0.39	−9 (−11 to −7)		0.21 (0.05 to 0.93)	0.04

increasing the overall lung density defined by Hounsfield-unit thresholds. Several lines of evidence suggest that a density shift in the distribution of Hounsfield units is unlikely to explain our findings. First, the associations we found between emphysema and interstitial lung abnormalities were not most prominent in the lower lobes, where more interstitial abnormalities are expected (see the Supplementary Appendix). Second, the reductions in emphysema noted in participants with interstitial lung abnormalities were paired with the physiological consequences of reduced emphysema (e.g., additional reductions in total lung capacity). Third, we noted inverse associations between the presence of interstitial lung abnormalities and clinically diagnosable COPD, a variable that is independent of the measurement of emphysema with the use of HRCT.

Our findings are consistent with, and add weight to, previous studies showing that cigarette smoking is associated with both spirometric restriction[18] and areas of high attenuation on HRCT.[3] Since emphysema and interstitial lung abnormalities have opposing effects on lung volume, our findings suggest that HRCT may provide important diagnostic information in smokers whose total lung capacity is unexpectedly "normal." We speculate that this could be clinically important to physicians who may think that a patient who does not have symptoms or characteristic abnormalities on lung-function tests is disease-free, when in fact the patient could be affected by two of the consequences of smoking — emphysema and interstitial lung abnormalities.

It is possible that a number of smokers with interstitial lung abnormalities have clinically diagnosable respiratory bronchiolitis, a well-described interstitial lung disease that is related to smoking and associated with ground-glass opacities and centrilobular nodules,[19,20] or smoking-related interstitial fibrosis,[21] a less well-defined entity with features overlapping those of usual interstitial pneumonia and emphysema.[22] However, among the participants in the COPDGene Study with interstitial lung abnormalities, 81% (157) had specific radiographic features and reductions in lung volumes that are not typical of respiratory bronchiolitis.[9] As mentioned previously, expected reductions in lung volumes among patients with smoking-related interstitial lung abnormalities could be masked by concomitant emphysema.

Our study has several limitations. First, we recognize that congestive heart failure, compression artifacts from bullous emphysema, and atelectasis could mimic the changes on chest HRCT that we have defined as interstitial lung abnormalities. However, in a prior study that excluded participants with heart failure (defined by a physician's diagnosis), a similar association between interstitial lung abnormalities and cigarette smoking was noted.[3] In addition, a strong inverse association between emphysema and interstitial lung abnormalities suggests that compression artifacts associated with bullous emphysema are an unlikely explanation for our findings. Moreover, our study shows similar associations with total lung capacity and lung volume at relaxed exhalation, which suggests that our findings are probably not the result of differences in inspiratory effort (or atelectasis). Second, although our measurements of total lung capacity were obtained by means of HRCT, not body plethysmography, previous studies have consistently reported very high degrees of correlation between these measurements (r^2 approximately 0.9),[23,24] and recent data suggest that plethysmography may be a

less accurate measurement of total lung capacity than radiographic measurement in patients with COPD.[25] Third, since our population includes smokers with an oversampling of participants with COPD, caution should be exercised in extrapolating our findings to general population samples.

We have found that as compared with smokers without interstitial lung abnormalities, smokers with interstitial abnormalities on HRCT, particularly smokers with COPD, have a reduced total lung capacity and a lesser amount of emphysema. Longitudinal follow-up studies of persons with interstitial lung abnormalities will be required to determine whether these radiographic abnormalities, and the associated reductions in lung volumes, are transient or stable, or whether they will progress to clinically significant disease.

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