Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

Visual Emphysema at Chest CT in GOLD Stage 0 Cigarette Smokers Predicts Disease Progression: Results from the COPDGene Study

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Conflicts of interest are listed at the end of this article

See also the editorial by Grenier in this issue..

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Background: The clinical significance of visually evident emphysema on CT images in individuals without spirometric evidence of chronic obstructive pulmonary disease (COPD) by current diagnostic criteria is, to the knowledge of the authors, unknown.

Purpose: To evaluate whether participants with visually evident emphysema at CT were more likely to have progressive disease and increased mortality at 5 years compared with those without visual emphysema.

Materials and Methods: This secondary analysis of the prospective Genetic Epidemiology of COPD study evaluated current or former smokers enrolled between 2008 and 2011 who did not meet current criteria for COPD (defined as Global Initiative for Obstructive Lung Disease stage 0). Statistical analysis was performed by using linear mixed models to estimate mean physiologic, imaging, and clinical outcomes for those with and without visual emphysema. Hazard ratios for mortality were calculated by using Cox regression models with emphysema as the main predictor.

Results: Of the 4095 participants, 48.3% (1979 participants; 1096 men and 883 women; mean age, 57 years ± 8 [standard deviation]) had trace or greater visual emphysema at CT and 51.7% (2116 participants; 1068 men and 1048 women; mean age, 56 years ± 8) had no emphysema at CT. At 5 years, participants with visual emphysema at CT demonstrated progressive airflow obstruction with lower values of ratio of forced expiratory volume in 1 second (FEV_1)-to–functional vital capacity (FVC) ratio (−1.7 vs −0.7) and greater progression in quantitative emphysema measured by 15th percentile lung density (−3.3 vs −0.3 HU), adjusted lung density (−3.1 vs −0.2 g/L), and percentage of lung voxels with CT attenuation less than −950 HU (0.17 vs −0.20) than participants without emphysema ($P < .001$ for each). The rate of quantitative emphysema progression increased with greater grades of emphysema severity within the emphysema group.

Conclusion: The presence of visual emphysema at CT in current and former Global Initiative for Obstructive Lung Disease stage 0 smokers predicted structural and physiologic disease progression.

Online supplemental material is available for this article.

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating respiratory condition that causes substantial morbidity and mortality worldwide and immense financial burden on the health care system (1,2). Cigarette smoking is the most important risk factor for developing COPD, although only one-third of people who smoke develop COPD during their lifetime (3). The diagnosis is made when a patient with symptoms is confirmed to have physiologic airflow obstruction (ie, postbronchodilator ratio of forced expiratory volume in 1 second [FEV_1]-to–functional vital capacity [FVC] ratio less than 0.70) in the absence of an alternative explanation for the symptoms or the airflow obstruction (4). Studies have shown, however, that current and former smokers without spirometric evidence of disease have respiratory symptoms and imaging abnormalities not captured by spirometry measurements, which limits the use of spirometry in early disease detection (5). As a result, smoking-related lung disease remains underdiagnosed in the general population, leading to increased disease burden, comorbidities, and costs (6).

CT can help detect presymptomatic abnormalities in cigarette smokers, before substantial end-organ damage occurs (5). A recent study showed that the visual presence and severity of emphysema at CT is associated with increased mortality risk, independent of the quantitative severity of emphysema (7). However, it remains unclear whether emphysema identified in smokers without spirometric impairment is clinically important. Thus, the purpose of this study was to evaluate differences in progression

Abbreviations

ALD = adjusted lung density, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, COPDGene = Genetic Epidemiology of COPD, GOLD = Global Initiative for Obstructive Lung Disease, Perc15 = CT attenuation at the 15th percentile of the lung CT histogram

Summary

The presence of visually evident emphysema on CT images in smokers with normal spirometry, labeled as GOLD stage 0, had progressive airflow obstruction and progression of emphysema over 5 years.

Key Results

- Compared with participants without visually evident emphysema at CT, participants with emphysema had lower baseline pulmonary function tests, worse quality of life, and greater dyspnea ($P <$ .01 for each).
- At 5 years, participants with visually evident emphysema at CT had progressive airflow obstruction (forced expiratory volume in 1 second–to–forced vital capacity ratio, $P <$ .001) and greater progression in quantitative emphysema measured by adjusted lung density, CT attenuation at the 15th percentile of the lung CT histogram, and percent low attenuation areas less than −950 HU ($P <$ .001 for each) than participants without emphysema.

of physiologic, imaging, and clinical parameters in smokers with and without visual emphysema at CT but without COPD. We chose to use the label Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0 for our cohort of nonobstructed smokers, despite that the stage is no longer included in the current GOLD classification system. We hypothesized that participants with visually evident emphysema at CT were more likely to have progressive disease and symptoms and increased mortality at 5 years, compared with those without visual emphysema.

Materials and Methods

This study is a secondary analysis from Genetic Epidemiology of COPD (COPDGene; *ClinicalTrials.gov*: NCT00608764), a prospective multicenter study focused on the genetic epidemiology of COPD (8). Between 2007 and 2011, 10 192 participants aged 45–80 years with at least a 10-pack-year smoking history were enrolled in this Health Insurance Portability and Accountability Act–compliant study at 21 clinical centers in the United States. Smokers were enrolled on the basis of smoking history and classified by using the GOLD spirometric criteria based on postbronchodilator spirometry. Participants self-identified as non-Hispanic African American or non-Hispanic white ethnicity. Those with respiratory conditions other than asthma and COPD were excluded from the study.

Written informed consent was obtained from all study participants. Our study evaluated the GOLD stage 0 group, defined as current and former smokers with a postbronchodilator ratio of FEV_1-to-FVC of at least 0.70 and an FEV_1 percentage of at least 80% predicted. Participants with baseline and 5-year follow-up inspiratory CT, visual emphysema scores, and mortality data were included (Fig 1). Clinical and radiologic evidence of lung disease in the GOLD 0 group was previously reported (5). The previous study focused on the GOLD 0 group at baseline, comparing them with never smokers and other COPD groups, whereas we focused solely on the GOLD 0 group and the significance of visually evident emphysema on disease progression at 5-year follow-up.

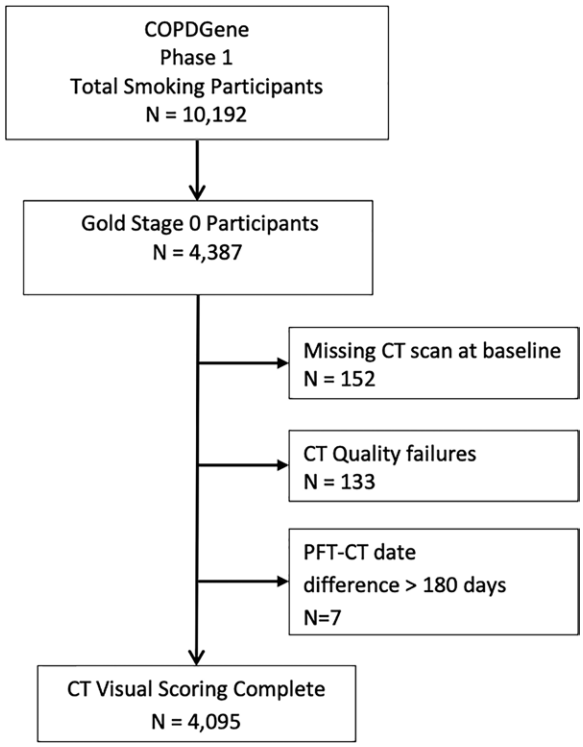

Figure 1: Study population consort diagram. COPDGene = Genetic Epidemiology of chronic obstructive pulmonary disease, PFT = pulmonary function testing.

Clinical Evaluation

All participants underwent pre- and postbronchodilator spirometry, evaluation of bronchodilator responsiveness, and 6-minute walk testing by using standard techniques at baseline and 5-year follow-up (8). Standardized questionnaires were used to assess disease-specific impact on quality of life by using the St George Respiratory Questionnaire total score (9), dyspnea by using the modified Medical Research Council dyspnea score cutoff of 2 or greater (10), health-related quality of life by the Medical Outcomes study 36-item short form survey (11), symptoms of chronic bronchitis defined as self-reported cough productive of phlegm for 3 months or more per year for at least 2 consecutive years (12), and history of severe respiratory exacerbations.

Visual Analysis

Visual analysis by trained research analysts was based on the Fleischner Society classification system (13) (Fig 2). The details of the methods and analysis were described previously (7).

Quantitative CT Analysis

All participants underwent volumetric noncontrast axial inspiratory and expiratory CT by using a standardized protocol (8,14). The scans were reconstructed with a section thickness of 0.625, 0.75, or 0.9 mm depending on the CT manufacturer; corresponding section intervals were 0.625, 0.5, or 0.45 mm, respectively, to achieve near-isotropic voxels (15).

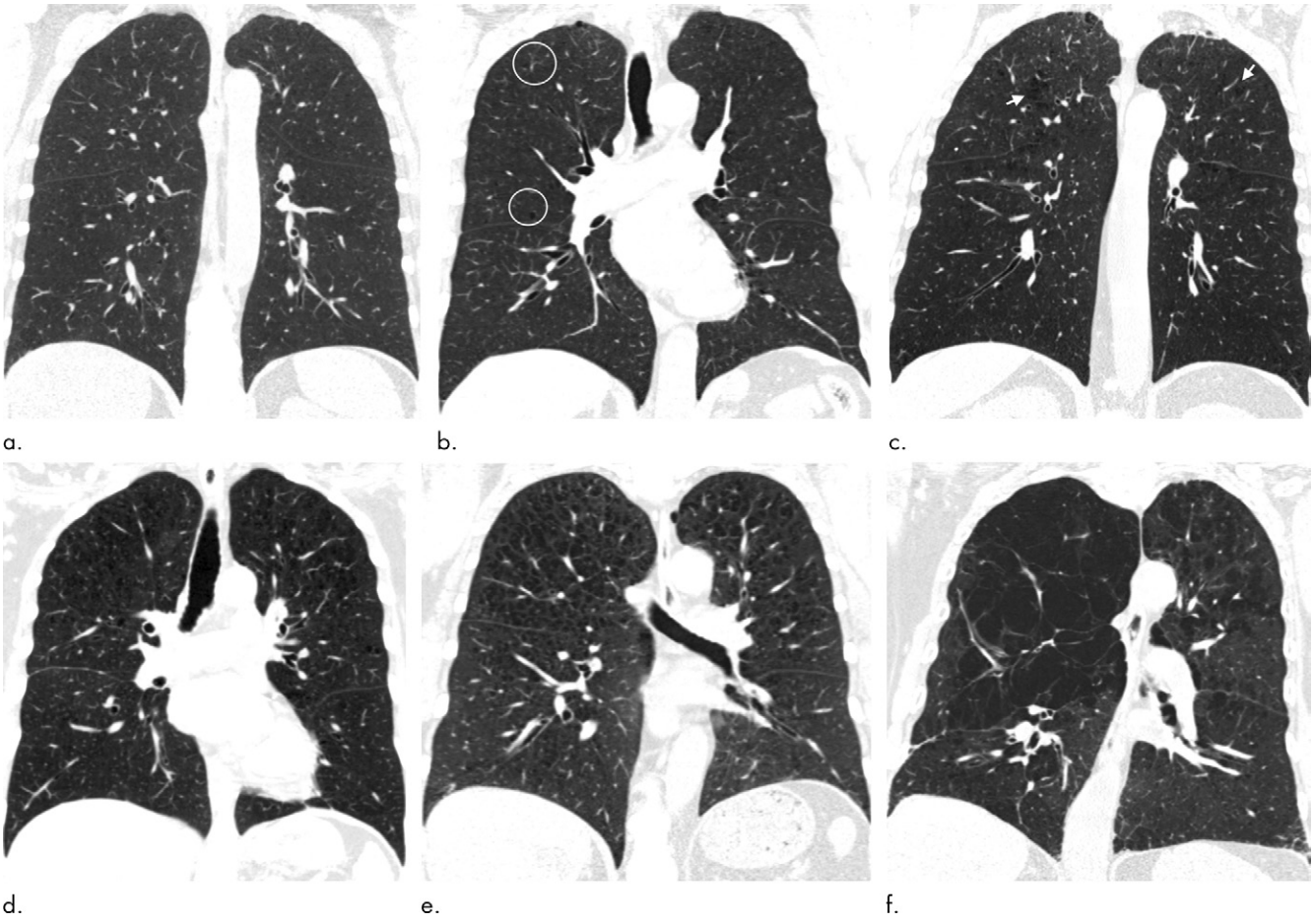

Figure 2: Coronal CT images show progressive grades of parenchymal emphysema on the basis of the Fleischner classification system. **(a)** Normal CT scan shows no emphysema. **(b)** Trace centrilobular emphysema (circles). **(c)** Mild centrilobular emphysema (arrows). **(d)** Moderate centrilobular emphysema involving more than 5% of the lung zone. **(e)** Confluent emphysema. **(f)** Advanced destructive emphysema.

Quantitative analysis of emphysema severity and air trapping was performed by using dedicated software programs (3DSlicer, *http://www.slicer.org*; Pulmonary Workstation 2, Vida Diagnostics, Coralville, Iowa) (15). Emphysema was quantified by using CT attenuation at the 15th percentile of the lung CT histogram (Perc15) (16) and percent low attenuation areas less than −950 HU on inspiratory CT (17,18) as previously described. Volume adjusted lung density (ALD) at the 15th percentile was also used to quantify emphysema by adjusting Perc15 for CT total lung volume. Gas trapping was measured by CT-derived functional residual capacity–to–total lung capacity ratio (19).

Evaluation of Survival Times

Deaths were reported to the central study from the clinical centers largely on the basis of the longitudinal follow-up program. Additional information from the U.S. Social Security Death Index and the COPDGene longitudinal follow-up program was used to determine a survival or censoring time for each participant, taking care to avoid ascertainment bias. Nine sites performed their own Social Security Death Index searches; all others used a centralized search performed by COPDGene staff. The median length of follow-up in this data set was 7.9 years (range, 25 days to 10.5 years).

Statistical Analysis

All analyses were performed by using statistical software (SAS version 9.4; SAS Institute, Cary, NC). A P value of less than .05 was considered to indicate statistical significance. Descriptive statistics of baseline characteristics were calculated and compared between participants with and without visual emphysema or in participants with emphysema between emphysema grades. Participant baseline characteristics were compared by using χ^2 tests for categorical data, analysis of variance for normally distributed continuous variables, and Wilcoxon rank sum tests (two groups) or Kruskal-Wallis test (multiple group comparison) for nonnormal continuous variables (6-minute walk distance and number of pack-years smoked, St George Respiratory Questionnaire, and percent low attenuation areas less than −950 HU at inspiratory CT).

Linear mixed models were used to estimate mean physiologic, imaging, and clinical outcomes for those with and without visual emphysema at CT at baseline by including time, visual emphysema status (present, absent), and time multiplied by emphysema status as predictors while adjusting for age, height, weight, sex, ethnicity, and current smoking status. A random intercept was included for study center. For CT outcomes, a fixed term for scanner make and a random intercept for scanner model were also included. For participants, either a

random intercept was included, or an unstructured error covariance matrix was used to account for repeated measures during the two visits depending on model convergence issues and goodness-of-fit statistics. Similar models were fit by using levels of emphysema severity (removing those with no presence) in place of presence or absence of visual emphysema severity. Further details of the models are provided in Appendices E1 and E2 (online).

Hazard ratios for mortality were calculated with Cox regression models by using emphysema severity class as the main predictor, with adjustment for age, height, sex, race, and current smoking status. The full model is presented in Appendix E3 (online).

Results

Participant Characteristics

We evaluated 4095 current and former smokers (2164 men and 1931 women) (Table 1). The mean age at enrollment was 57 years ± 8 (standard deviation), with mean ages of 56 years ± 8 for men and 57 years ± 8 for women. No emphysema was found in 2116 of the 4095 participants (51.7%). Trace or greater emphysema was manifest in 1979 of the 4095 participants (48.3%). Compared with participants without emphysema, those with emphysema were older, had a lower body mass index, were more likely to be African American, more likely to be men, had a higher tobacco exposure, and were more likely to be current smokers. The visual presence of emphysema was also associated with a lower baseline FEV_1, lower FEV_1-to-FVC, shorter 6-minute walk distance, more dyspnea, worse quality of life, and higher prevalence of chronic bronchitis symptoms. Radiologically, participants with emphysema had a higher ALD and higher CT-derived functional residual capacity–to–CT-derived total lung capacity ratio.

Within the emphysema cohort (Table 2), trace emphysema was present in 911 of the 1979 participants with emphysema (46%), mild in 784 (39.6%), moderate in 255 (12.9%), and confluent or advanced destructive in 29 (1.5%). Participants with greater emphysema severity were more likely to be older, have a lower body mass index, and more likely to be African American with greater tobacco exposure compared with those with less severe emphysema grade. Although emphysema was more common overall in men than in women (1096 men vs 883 women; 55% vs 45%), moderate emphysema was less common in men (117 men vs 138 women of 255 participants with moderate grade emphysema; 46% vs 54%). Further analysis comparing GOLD stage 0 men and women with moderate or greater emphysema did not show a difference between the two groups ($P = .26$). Additionally, as emphysema grade progressed, participants had lower baseline FEV_1-to-FVC, shorter 6-minute walk distance, more dyspnea, worse quality of life, more episodes of chronic bronchitis symptoms, lower ALD, and higher percent low attenuation areas less than −950 HU.

Multivariable Analysis

At the 5-year follow-up visit, multivariable analyses showed no difference in change in CT-derived functional residual capacity–to–CT-derived total lung capacity ratio (–0.57 vs −0.05, respectively; $P = .14$), distance walked in 6 minutes (−13.8 vs −16.8 m; $P = .54$), disease-specific impact on quality of life (St George Respiratory Questionnaire score, 0.22 vs −0.38, $P = .33$), or general health-related quality of life (Medical Outcomes study 36-item short form survey, −0.87 vs −0.76; $P = .80$) between the emphysema and no-emphysema groups (Table 3). Participants with visual emphysema did, however, demonstrate progressive airflow obstruction with lower FEV_1-to-FVC ratio compared with participants without visual emphysema (−1.7 vs −0.7%; $P < .001$) and greater progression in quantitative emphysema measured by Perc15 (−3.31 vs −0.30 HU; $P < .001$), ALD (−3.08 vs −0.22 g/L; $P < .001$), and natural log percent low attenuation areas less than −950 HU (0.17 vs −0.20; $P < .001$). An example of participants at GOLD stage 0 without and with emphysema progression and airflow obstruction at baseline and 5 years is shown in Figure 3.

A difference in longitudinal change in ALD, percent low attenuation areas less than −950 HU, and FEV_1-to-FVC ratio was present among the groups in the emphysema cohort stratified by emphysema grade (Table 4). Participants with mild or moderate emphysema had greater progression in quantitative emphysema measured by ALD (−4.13 [mild] vs −2.01 g/L [trace]; $P = .006$) and natural log percent low attenuation areas less than −950 HU (0.26 [mild] or 0.35 [moderate] vs 0.01 [trace]; $P < .001$) than those with trace emphysema, respectively. The group with moderate emphysema also had a greater decline in FEV_1-to-FVC ratio at 5 years compared with the group with trace emphysema (−3.2 vs −1.5%; $P = .005$).

There were 174 deaths in participants with emphysema. The Cox proportional hazards model results are shown in Table 5. The visual emphysema group had greater hazard of death than the group with no emphysema, but it was not statistically significant (hazard ratio, 1.19; 95% confidence interval: 0.94, 1.50; $P = .15$).

Discussion

We demonstrated that Global Initiative for Obstructive Lung Disease (GOLD) stage 0 smokers with visually evident emphysema on baseline CT images had significant and progressive respiratory disease compared with participants without emphysema. The presence of emphysema on CT images was associated with lower baseline pulmonary function tests, shorter 6-minute walk distance, greater dyspnea, and worse quality of life ($P < .01$ for each). At 5-year follow up, participants with emphysema had increased airflow obstruction (forced expiratory volume in 1 second [FEV_1]-to–functional vital capacity [FVC] ratio, $P < .001$) and greater progression in quantitative emphysema measured by CT attenuation at the 15th percentile of the lung CT histogram, adjusted lung density (ALD), and natural log percent low attenuation areas less than −950 HU than those without emphysema ($P < .001$ for each). Further stratification of the visually evident emphysema cohort on the basis of the Fleischner Society classification system showed progressive emphysema grade was associated with greater baseline airflow obstruction (FEV_1-to-FVC ratio),

Table 1: Baseline Characteristics according to Absence versus Presence of Visually Evident Emphysema on CT

Parameter	No Visually Evident Emphysema	Visually Evident Emphysema*	*P* Value†
No. of participants	2116 (51.7)	1979 (48.3)	
No. of deaths	127 (6.0)	166 (8.4)	.003
Demographics			
Age (y)	56 ± 8	57 ± 8	<.001
Height (cm)	170 ± 10	170 ± 9	.70
Weight (kg)	87 ± 19	81 ± 17	<.001
BMI (kg/m^2)	30 ± 6	28 ± 5	<.001
No. of men	1068 (50.5)	1096 (55.4)	.002
Ethnicity			
No. of non-Hispanic white participants	1347 (63.7)	1070 (54.1)	<.001
No. of African American participants	769 (36.3)	909 (45.9)	<.001
Smoking status			
No. of current smokers	1111 (52.5)	1313 (66.3)	<.001
No. of pack-years smoked‡	30 (21)	38 (23)	<.001
Comorbidities			
No. of exacerbations in past year	187 (8.8)	168 (8.5)	.69
No. with chronic bronchitis	155 (7.7)	189 (10)	<.01
Functional parameters			
Percentage predicted FEV_1	98 ± 12	97 ± 11	<.001
FEV_1-to-FVC ratio	0.8 ± 0.1	0.8 ± 0.0	<.001
6-minute walk distance (m)‡	461.1 (132.6)	445.5 (128.7)	<.001
No. of participants with mMRC dyspnea score answer of yes	736 (34.8)	776 (39.2)	.004
SGRQ‡	9 (21)	11 (26)	<.001
$\%LAA_{-950}$‡	0.90 (2.3)	0.98 (2.3)	<.03
Adjusted lung density (g/L)	94 ± 20	96 ± 21	<.001
FRC_{CT}-to-TLC_{CT} ratio	0.5 ± 0.1	0.5 ± 0.1	<.001

Note.—Unless otherwise indicated, data in parentheses are percentages. Mean data are ± standard deviation. BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, FRC_{CT} = functional residual capacity at CT, FVC = functional vital capacity, mMRC = modified Medical Research Council dyspnea score, $\%LAA_{-950}$ = percent low attenuation areas less than −950 HU at inspiratory CT, SGRQ = St George Respiratory Questionnaire total score, TLC_{CT} = total lung capacity at CT.

* Trace, mild, moderate, confluent, and advanced destructive emphysema.

† *P* values compare visual presence versus absence of emphysema at CT by using χ^2 tests for categorical data, analysis of variance for normally distributed continuous variables, and Wilcoxon rank sum tests for nonnormal continuous variables.

‡ Data are median; data in parentheses are interquartile range.

shorter 6-minute walk distance, more dyspnea, worse quality of life, and greater extent of quantitative emphysema ($P < .01$ for each). Similarly, at 5-year follow up, participants with more extensive grades of emphysema had a greater degree of airflow obstruction (FEV_1-to-FVC ratio, $P < .01$) and progression in quantitative emphysema (ALD and percent low attenuation areas less than −950 HU, $P < .01$) than did participants with trace emphysema. Our findings corroborate and extend the results of previous studies (5,20) that established the manifestation of clinical and physiologic disease in the GOLD stage 0 population.

Contrary to what was expected, the visual emphysema cohort had a higher ALD at baseline quantitative imaging (although progressive emphysema grade was associated with declining lung density). This is because participants with emphysema were more likely to be current smokers with higher tobacco exposure and more episodes of chronic bronchitis. Studies have shown that current smokers have denser lungs than never smokers and patients with COPD, which corresponds to measures of local inflammation in the bronchioles and/or airspaces (20–22). These findings, however, did not persist over time. At 5-year follow-up, the emphysema group had a greater decline in lung density and increased airflow obstruction compared with participants without emphysema. This confirms earlier studies of emphysema and airways disease identified on CT scans of ever smokers with normal spirometry and their association with greater rates of lung function decline (23,24). Moreover, we were able to show a gradient of progressive airflow obstruction and quantifiable emphysema with increasing emphysema grade, further validating the Fleischner emphysema classification system as a tool to assess emphysema severity (13). Our findings suggest that the presence of even trace emphysema at baseline CT predicts structural and physiologic progression at 5 years, highlighting the importance of imaging and its complemental role with spirometry in detecting early disease. Additionally, increasing radiologic severity of emphysema at baseline was associated with increased respiratory

Table 2: Baseline Characteristics of Participants with Emphysema on the Basis of Emphysema Grade

Parameter	Trace	Mild	Moderate	Confluent and Advanced Destructive*	*P* Value†
No. of participants	911 (46.0)	784 (39.6)	255 (12.9)	29 (1.5)	
Demographics					
Age (y)	56 ± 8	58 ± 8	59 ± 8	62 ± 9	<.001
Height (cm)	171 ± 9	170 ± 9	169 ± 9	165 ± 10	.001
Weight (kg)	83 ± 18	79 ± 16	78 ± 15	78 ± 20	<.001
BMI (kg/m^2)	29 ± 5	27 ± 5	27 ± 5	28 ± 7	<.001
No. of men	533 (58.5)	436 (55.6)	117 (45.9)	10 (34.5)	.001
Ethnicity					
No. of non-Hispanic white participants	496 (54.4)	427 (54.5)	124 (48.6)	23 (79.3)	.01
No. of African American participants	415 (45.6)	357 (45.5)	131 (51.4)	6 (20.7)	.01
Smoking status					
No. of current smokers	599 (65.8)	538 (68.6)	167 (65.5)	9 (31)	<.001
No. of pack-years smoked‡	35 (23)	39 (24)	38 (21)	53 (23)	<.001
Comorbidities					
No. of exacerbations in past year N (%)	70 (7.7)	62 (7.9)	34 (13.3)	2 (6.9)	.03
No. of participants with chronic bronchitis	69 (7.9)	76 (10.2)	41 (17.1)	3 (11.5)	<.001
Functional parameters					
Percentage predicted FEV_1	97 ± 12	96 ± 11	96 ± 11	98 ± 11	.56
FEV_1-to-FVC ratio	0.79 ± 0.05	0.77 ± 0.05	0.75 ± 0.04	0.75 ± 0.03	<.001
6-minute walk distance (m)‡	451.5 (131.4)	445.8 (122.7)	426.0 (127.5)	405.0 (508)	<.001
No. of participants with mMRC dyspnea score answer of yes	329 (36.1)	309 (39.4)	123 (48.2)	15 (51.7)	.003
SGRQ‡	10 (26)	11 (24)	16 (30)	15 (24)	<.001
Adjusted lung density (g/L)	97 ± 21	96 ± 20	93 ± 20	81 ± 28	<.001
$\%LAA_{-950}$‡	0.7 (1.6)	1.1 (2.0)	2.3 (3.5)	5.6 (9.6)	<.001
FRC_{CT}-to-TLC_{CT} ratio	0.54 ± 0.08	0.54 ± 0.09	0.55 ± 0.08	0.51 ± 0.07	.09

Note.—Unless otherwise indicated, data in parentheses are percentages. Mean data are ± standard deviation. BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, FRC_{CT} = functional residual capacity at CT, FVC = functional vital capacity, $\%LAA_{-950}$ = percent low attenuation areas less than −950 HU at inspiratory CT, mMRC = modified Medical Research Council dyspnea score, SGRQ = St George Respiratory Questionnaire total score, TLC_{CT} = total lung capacity ratio at CT.

* Confluent (n = 31) and advanced destructive (n = 1).

† *P* values for differences across emphysema grade, calculated with χ^2 tests for categorical data, analysis of variance for normally distributed continuous variables and Kruskal-Wallis tests for nonnormal continuous variables.

‡ Data are median; data in parentheses are interquartile range.

Table 3: Presence or Absence of Visually Evident Emphysema at Baseline CT in Relationship to Change in CT Parameters, Lung Function, and Clinical Status over 5 years

Parameter	No Visually Evident Emphysema		Visually Evident Emphysema		Comparison of Groups *P* Value
	Mean Change	*P* Value	Mean change	*P* Value	
ALD (g/L)	−0.22 (−0.92, 0.48)	.54	−3.08 (−3.84, −2.33)	<.001	<.001
Perc15 (HU)	−0.30 (−1.40, 0.81)	.60	−3.31 (−4.50, −2.11)	<.001	<.001
Natural log $\%LAA_{-950}$	−0.20 (−0.27, −0.13)	<.001	0.17 (0.10, 0.24)	<.001	<.001
FRC_{CT}-to-TLC_{CT} ratio	−0.05 (−0.59, 0.48)	.84	−0.57 (−1.16, 0.02)	.06	.14
(FEV_1-to-FVC ratio) · 100 ratio	−0.7 (−1.0, −0.4)	<.001	−1.7 (−2.0, −1.3)	<.001	<.001
FEV_1 (mL)	−55 (−72, −38)	<.001	−81 (−100, −63)	<.001	.02
6MWD (M)	−16.8 (−22.8, −10.5)	<.001	−13.8 (−20.7, −7.2)	<.001	.54
SGRQ total	−0.38 (−1.27, 0.51)	.40	0.22 (−0.75, 1.18)	.66	.33
SF36 general	−0.76 (−1.41, −0.10)	.02	−0.87 (−1.54, −0.19)	.01	.80

Note.—Data in parentheses are 95% confidence intervals. All point estimates are adjusted for sex, ethnicity, smoking status, current age, weight, and height. The full model is in Appendix E1 (online). ALD = volume-adjusted lung density, FEV_1 = forced expiratory volume in 1 second, FRC_{CT} = functional residual capacity at CT, FVC = functional vital capacity, $\%LAA_{-950}$ = percent low attenuation less than −950 HU, Perc15 = 15th percentile of the attenuation histogram, SF36 = Medical Outcomes study 36-item short form survey, SGRQ = St George Respiratory Questionnaire total score, TLC_{CT} = total lung capacity at CT, 6MWD = 6-minute walk distance.

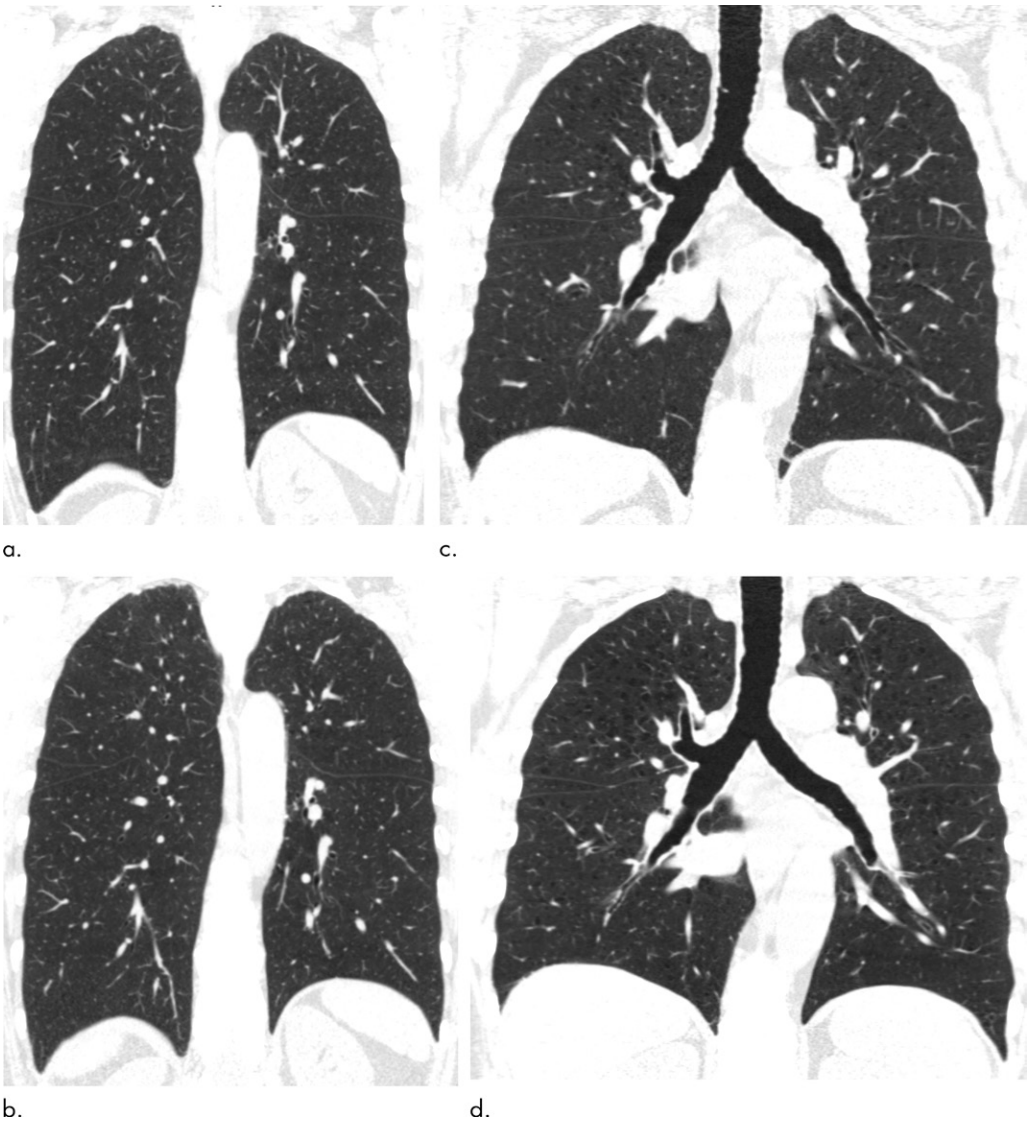

Figure 3: Baseline and 5-year follow up inspiratory CT scans in two Global Initiative for Chronic Obstructive Lung Disease stage 0 participants showing no progression and progression. **(a)** Baseline and **(b)** 5-year follow-up scans in a 55-year-old female participant without visually evident emphysema and no interval progression at follow-up. Forced expiratory volume in 1 second (FEV_1) decreased by 62 mL. **(c)** Baseline and **(d)** 5-year follow-up scans in a 49-year-old male participant with trace emphysema at baseline but progression to moderate emphysema at follow-up. FEV_1 decreased by 780 mL between visits.

symptoms, severity of clinical and physiologic impairment, and progression of quantitative emphysema and airflow obstruction. This highlights the importance for the radiologist to routinely record and characterize emphysema at CT (including in patients undergoing lung cancer screening). Given that 67% of the participants with emphysema in our study were current smokers, the identification of emphysema in such individuals might provide an important incentive for smoking cessation.

There was no significant difference in mortality between the two cohorts. In the overall COPDGene population, Lynch et al (7) showed that the visual presence and severity of emphysema was associated with increased mortality risk, though these findings were not found to be significant in the subgroup with trace emphysema. Because almost 50% of our participants with visual emphysema fell into the trace category, the lack of significant mortality difference was not unexpected. Because the rate of progression of COPD is relatively slow, it is conceivable that with a longer follow-up time, the emphysema grade in our studied population could progress and potentially lead to increased mortality risk.

Sato and colleagues have applied the concept of fractal geometry to CT imaging of COPD in mouse and human emphysema studies, demonstrating that the size distribution of clusters of emphysematous regions follow a power law characterized by the fractal dimension, *D* (25,26). By showing that low attenuation areas on CT images display fractal properties, they determined that *D* is more sensitive to changes in emphysema progression than percentage low attenuation area (27). By using two Japanese COPD cohorts, they established that a lower *D* (representing an increase in terminal airspace enlargement) predicts future exacerbations, whereas percent low attenuation volume was associated with a decline in FEV_1 and higher 10-year mortality

Table 4: Estimated 5-year Mean Change in CT Parameters, Lung Function, and Clinical Status for Participants Stratified by Emphysema Grade according to the Fleischner Society Classification System

Parameter	Trace	Mild	Moderate	Confluent and Advanced Destructive	*P* Value
ALD (g/L)	−2.01 (−3.11, −0.91)	−4.13 (−5.28, −2.98)	−3.79 (−5.52, −2.05)	−5.63 (−10.09, −1.17)	.006
Perc15 (HU)	−2.68 (−4.37, −1.00)	−4.05 (−5.82, −2.28)	−2.71 (−5.45, 0.03)	−5.77 (−12.97, 1.42)	.50
Natural log $\%LAA_{-950}$	0.01 (−0.09, 0.10)	0.26 (0.17, 0.36)	0.35 (0.20, 0.50)	0.37 (−0.02, 0.77)	<.001
FRC_{CT}-to-TLC_{CT} ratio	−0.50 (−1.37, 0.38)	0.13 (−0.80, 1.06)	−1.14 (−2.63, 0.34)	−4.12 (−8.04, −0.21)	.10
(FEV_1-to-FVC ratio) · 100	−1.5 (−2.0, −1.0)	−1.9 (−2.4, −1.4)	−3.2 (−4.0, −2.3)	−1.1 (−3.4, 1.1)	.005
FEV_1 (mL)	−85 (−112, −58)	−97 (−126, −68)	−81 (−128, −34)	−98 (−221, 24)	.90
6MWD (m)	−10.8 (−20.4, −1.5)	−15.0 (−25.5, −4.8)	−15.0 (−31.8, 1.8)	−9.0 (−54.6, 36.6)	.92
SGRQ total	0.67 (−0.83, 2.16)	1.39 (−0.23, 3.00)	−0.04 (−2.63, 2.55)	−0.78 (−7.75, 6.20)	.74
SF36 general	−1.51 (−2.56, −0.47)	−0.73 (−1.85, 0.39)	−1.71 (−3.51, 0.09)	0.66 (−4.28, 5.61)	.56

Note.—Data are mean change; data in parentheses are 95% confidence intervals. All point estimates are adjusted for sex, ethnicity, smoking status, current age, weight, and height. Participants with no visually evident emphysema were removed. *P* values are for comparisons of groups. The full model is in Appendix E2 (online). ALD = volume-adjusted lung density, FEV_1 = forced expiratory volume in 1 second, FRC_{CT} = functional residual capacity at CT, FVC = functional vital capacity, $\%LAA_{-950}$ = percent low attenuation less than −950 HU, Perc15 = 15th percentile of the attenuation histogram, SF36 = Medical Outcomes study 36-item short form survey, SGRQ = St George Respiratory Questionnaire total score, TLC_{CT} = total lung capacity at CT, 6MWD = 6-minute walk distance.

Table 5: Cox Multivariable Model for Predicting Mortality

Parameter	Reference Group	Hazard Ratio	*P* Value
Visually evident emphysema	No visually evident emphysema	1.2 (0.94, 1.5)	.15
Age per year		1.05 (1.04, 1.07)	<.001
Height, per cm		0.99 (0.98, 1.01)	.34
Ethnicity, white	African American or Black	2.4 (1.7, 3.3)	<.001
Sex, male	Female	0.79 (0.61, 1.04)	.09
Current smoker	Former smoker	2.7 (2.0, 3.6)	<.001

Note.—Data in parentheses are 95% confidence intervals. Model adjusted for age, height, sex, ethnicity, and smoking status at enrollment. The full model is in Appendix E3 (online).

(25). Morphologic assessment of emphysema by using fractal *D* and percent low attenuation volume in future work may help elucidate different subtypes of emphysema and progression in individuals with GOLD stage 0 who have predominantly trace and mild grades of disease severity.

There were several limitations to our study. The large sample size and number of clinical centers resulted in CT scanner heterogeneity with varying models and manufacturers. Whereas the protocols were designed to minimize this variability, it is possible that this may have led to slight discrepancies in the quantitative imaging measurements. Additionally, whereas COPDGene is more inclusive than many COPD studies, it is not a population-based study, which may impact the generalizability of our findings.

Our study confirmed the limitations in current diagnostic criteria in capturing smoking-related lung injury in GOLD stage 0 participants. As of 2017, there are an estimated 34 million current smokers in the United States (28), of which only half are diagnosed with COPD (29). Many of the remaining 17 million smokers have smoking-related lung disease undiagnosed with the current COPD spirometric criteria (5,30). We have shown that the breadth of symptomatic, structural, and physiologic smoking-related lung disease in these individuals is not adequately captured by the present diagnostic criteria and that participants with emphysema on CT images may require more diligent monitoring for disease progression.

In conclusion, the presence of emphysema in Global Initiative for Obstructive Lung Disease stage 0 participants is an important predictor in determining structural and physiologic progression. Emphysema should be routinely recorded by using an ordinal scale (ie, Fleischner guidelines) or with quantitative CT metrics in radiology reports because CT can play a role in early detection of smoking-related lung disease.

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