

Quantitative CT Evaluation of Emphysema Progression over 10 Years in the COPDGene Study

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Conflicts of interest are listed at the end of this article.

See the editorial by Parraga and Kirby in this issue.

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Background: Long-term studies of chronic obstructive pulmonary disease (COPD) can evaluate emphysema progression. Adjustment for differences in equipment and scanning protocols of individual CT examinations have not been studied extensively.

Purpose: To evaluate emphysema progression in current and former smokers in the COPDGene cohort over three imaging points obtained at 5-year intervals accounting for individual CT parameters.

Materials and Methods: Current and former cigarette smokers enrolled between 2008 and 2011 from the COPDGene study were prospectively followed for 10 years between 2008 and 2020. Extent of emphysema as adjusted lung density (ALD) from quantitative CT was measured at baseline and at 5- and 10-year follow-up. Linear mixed models adjusted for CT technical characteristics were constructed to evaluate emphysema progression. Mean annual changes in ALD over consecutive 5-year study periods were estimated by smoking status and baseline emphysema.

Results: Of 8431 participants at baseline (mean age, 60 years \pm 9 [SD]; 3905 female participants), 4913 were at 5-year follow-up and 1544 participants were at 10-year follow-up. There were 4134 (49%) participants who were current smokers, and 4449 (53%) participants had more than trace emphysema at baseline. Current smokers with more than trace emphysema showed the largest decline in ALD, with mean annual decreases of 1.4 g/L (95% CI: 1.2, 1.5) in the first 5 years and 0.9 g/L (95% CI: 0.7, 1.2) in the second 5 years. Accounting for CT noise, field of view, and scanner model improved model fit for estimation of emphysema progression ($P < .001$ by likelihood ratio test).

Conclusion: Evaluation at CT of emphysema progression in the COPDGene study showed that, during the span of 10 years, participants with pre-existing emphysema who continued smoking had the largest decline in ALD. Adjusting for CT equipment and protocol factors improved these longitudinal estimates.

Clinical trial registration no. NCT00608764

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Supplemental material is available for this article.

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that causes progressive airflow obstruction. It is the fourth most common cause of death in the United States (1) with an almost threefold increase over the last few decades.

The following three distinct morphologic components of COPD can be quantified at CT: airway wall dimensions, small airway obstruction, and emphysema (2). The quantitative extent of emphysema is associated with increased frequency of COPD exacerbation, increased risk of lung cancer, and increased likelihood of progressive airflow obstruction over time (3,4). Additionally, a previous study (5) showed that emphysema progression measured by lung density is associated with higher risk of mortality. Quantitative metrics of emphysema at CT include

the percent of low attenuation areas with CT attenuation -950 HU or less, lung density at the 15th percentile of the CT histogram, and volume-adjusted lung density (ALD) at the 15th percentile. In longitudinal studies, ALD has provided the most robust metric of emphysema, and this is also supported by the Lung Density Biomarker Committee of the Quantitative Imaging Biomarkers Alliance (5–9). However, longitudinal assessment of lung density and ALD is challenging because of variation introduced by differences in CT technical characteristics and patient factors such as inconsistency in level of inspiration at scanning (6,10). These issues are challenging in long-term studies in which changes in imaging equipment and scanning protocol become inevitable. Previous longitudinal studies of emphysema have adjusted for lung volume,

Abbreviation

ALD = adjusted lung density, COPD = chronic obstructive pulmonary disease

Summary

Accounting for individual CT parameters, 10-year emphysema progression in the COPDGene study showed that participants with pre-existing emphysema who continued smoking had the largest decline in adjusted lung density.

Key Results

- A prospective study of 8431 current and former smokers who underwent quantitative CT evaluation for up to 10 years showed that baseline emphysema grade and smoking status were associated with emphysema progression.
- Current smokers with more than trace emphysema at baseline had an annual decrease in adjusted lung density of 1.4 g/L and 0.9 g/L in the first and second 5-year periods, respectively.
- Accounting for CT noise, field of view, and scanner model improved model fit for estimating emphysema progression.

scanner manufacturer, and scanner model (7,11). However, adjustment for characteristics of individual CT examinations such as noise magnitude and field of view (which controls pixel size) have not been studied extensively to mitigate variations in quantitative CT and improve the fit of statistical models for assessing progression. Moreover, to our knowledge, progression of emphysema for 10 years has not been studied.

Therefore, the purpose of our analysis was to evaluate emphysema progression in current and former smokers in the cohort at three imaging points obtained at 5-year intervals accounting for individual CT parameters.

Materials and Methods**The Study**

The Study is a prospective multicenter study focused on the investigation of the genetic epidemiologic structure of COPD (*ClinicalTrials.gov*: NCT00608764) (12). Between 2008 and 2011, 10 198 cigarette smokers with and without COPD were enrolled at 21 centers across the United States. Health Insurance Portability and Accountability Act–compliant institutional review board approval was obtained at all clinical centers, and written informed consent was obtained. The participants underwent baseline evaluation (phase 1), including chest CT (12), and 5697 participants returned for 5-year follow-up (phase 2) between 2013 and 2017 (11). A 10-year follow-up (phase 3) examination was performed in 2284 participants between 2018 and 2020.

Study Sample

Participants were excluded if they were in the never-smoker cohort, diagnosed with interstitial lung disease and/or bronchiectasis, or changed smoking status during follow-up. Participants with a change in smoking status were excluded from this analysis because smoking cessation is associated with decreased lung attenuation, which could be misinterpreted as increased emphysema (13,14). Observations following changes in the lungs that

would affect quantification (eg, lobectomy, transplant, and lung parenchymal opacities) were excluded. See Appendix S1 for details of follow-up patterns in selected participants.

CT Protocol

Inspiratory axial CT acquisition included a 0.5-mm section interval, 0.625–0.75-mm section thickness, and no intravenous contrast material. Complete scanner-specific (Siemens, Philips, and GE Healthcare) protocol details for phase 1 and phase 2 were published previously (3). The mean effective radiation dose for phase 1 and 2 was 6.5 mSv \pm 1 (SD), referred to as the full-dose protocol. For phase 3, the reduced radiation dose protocol was designed using dose modulation similar to the protocol recommended by Quantitative Imaging Biomarkers Alliance (8,15). Mean effective radiation dose for phase 3 was 1.5 mSv \pm 0.7. To assess the effects of the reduced-dose protocol on quantitative CT metrics, informed consent was obtained from 1508 participants from phase 2 to undergo scanning with the reduced-dose protocol in addition to the full-dose protocol (Appendix S2).

Quantitative CT

Lung and lobe segmentations on full-dose and reduced-dose CT scans were performed using software (LungQ v1.0.0; Thirona). Histogram analysis was used to compute the 15th percentile of lung voxel intensity and percentage of lung voxels with attenuation less than –950 HU. The ratio of observed lung volume from CT to expected lung volume was used to adjust for variable lung volume (15,16). Expected lung volume was calculated using the equation from the Multi-Ethnic Study of Atherosclerosis lung study (17). The primary outcome for this analysis was volume-ALD, computed as previously described (11). Participants were dichotomized by baseline emphysema grade (absent or trace vs more than trace emphysema), scored using a validated deep learning method (9,18,19).

Increased CT image noise can lead to an apparent reduction in lung density at quantitative CT (15). An estimate of CT noise magnitude was calculated using an image processing method based on subtraction of adjacent axial sections (20,21) (Appendix S3).

Statistical Analysis

Progression of emphysema was estimated by fitting ALD measures using linear mixed-effects models. All available data, including up to four observations per participant (phase 1, phase 2 full dose, phase 2 reduced dose, and phase 3), were used in model fitting. An unstructured covariance matrix was used to account for correlation between repeated measures within participants. Random intercepts were included for study center and scanner model and allowed for changes in both variables within participants over time. All models included terms for study phase, smoking status, baseline deep learning emphysema grade, ethnicity (self-reported), sex (self-reported), age (baseline or time-varying), visit height, body mass index, and an indicator for full versus reduced radiation dose. Ethnicity was included in models to adjust for potential genetic differences relating to emphysema progression. Interaction terms

were included to estimate change in mean ALD over time by smoking status and/or deep learning emphysema grade. CT noise, field of view (Appendix S4), section thickness, interaction terms between CT variables, and polynomial terms (up to cubic) for CT noise and body mass index were systematically entered into the model to find the best model fit. Models were compared by using the Akaike information criterion and likelihood ratio test.

An alternative modeling approach used phase 1 and 2 full-dose measurements and phase 3 reduced-dose measurements calibrated to the full-dose scale. Sensitivity analyses included fitting models with baseline visual emphysema (absent or trace vs more than trace) or baseline percentage of low attenuation area less than -950 HU ($<5\%$ vs $\geq 5\%$) instead of baseline deep learning emphysema. The impact of loss to follow-up and missing data on progression estimates was evaluated using multiple imputation and random slope models. Additional details regarding the models are in Appendices S5–S8. Comparisons in CT characteristics between full-dose and reduced-dose examinations were performed using paired t tests. Analysis was performed using software (SAS version 9.4; SAS Institute) and statistical significance was indicated by an α level of .05.

Results

Participant Characteristics

The study sample consisted of 8431 participants (mean age, 60 years \pm 9; 3905 female participants; 5726 White participants). Of the 10718 original participants enrolled, 1615 were excluded because they were never-smokers, they had a change in smoking status, or interstitial lung disease and/or bronchiectasis diagnoses. There were 672 participants who had missing baseline emphysema grades or missing complete CT data (Fig 1). Table 1 shows demographic and clinical characteristics at baseline (phase 1), 5-year follow-up (phase 2), and 10-year follow-up (phase 3). Phase 2 characteristics were stratified by all participants observed at phase 2 (full radiation dose) and participants who had an additional reduced radiation dose scan at phase 2. Approximately half of participants (4134 participants) were current smokers; the proportion of current smokers decreased at follow-up (40% at 5 years and 36% at 10 years). Table S1 shows longitudinal observation patterns by smoking status and emphysema grade. Participants with only one follow-up visit were mostly current smokers or had more than trace emphysema at baseline.

CT Metrics

The stochastic noise magnitude within each volumetric CT series was calculated for each participant at all observed phases. Figure 2 shows the distribution of CT noise (in Hounsfield units) by phase and radiation dose. Overall, the CT noise was highest on reduced-dose scans. Table S2 shows several CT metrics for the subset of participants who underwent both a full-dose and reduced-dose examination at 5-year follow-up. CT noise was significantly higher on reduced-dose scans compared with full-dose scans (mean difference, 14.6 HU \pm 3.9; $P = .004$).

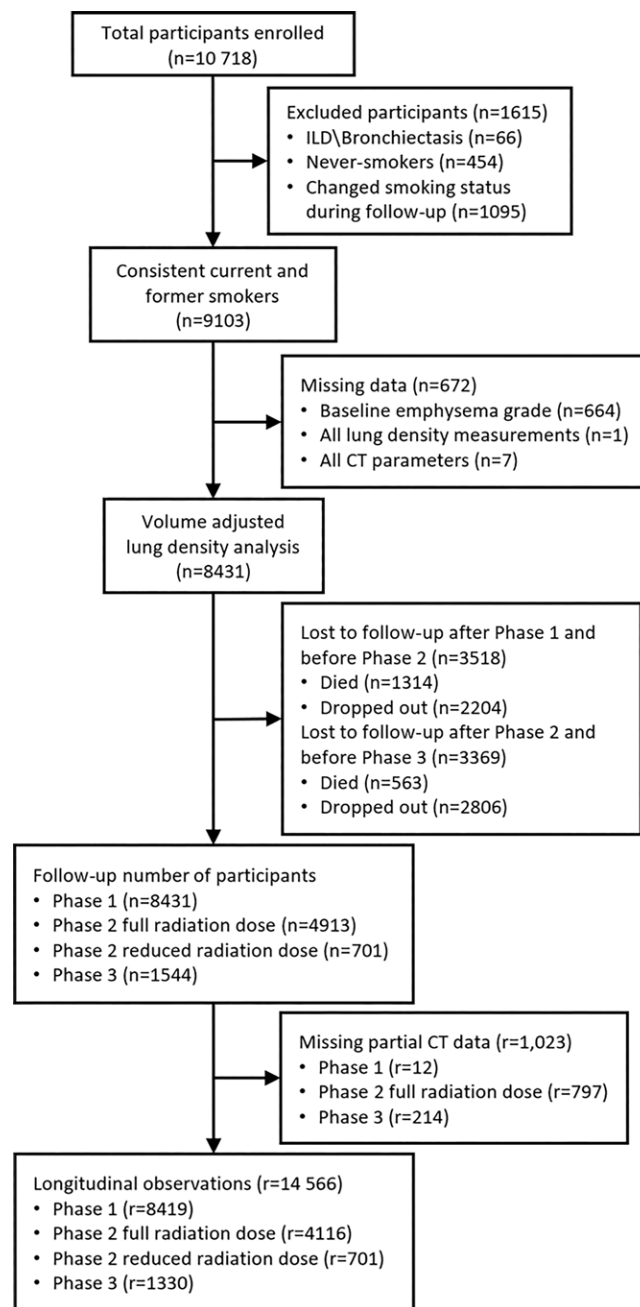


Figure 1: Flowchart shows participant selection. ILD = interstitial lung disease, r = number of longitudinal observations or records, n = number of unique participants.

Progression Models

Table 2 shows comparisons of model fit for candidate ALD models. Comparison of the base model and model 1 showed that inclusion of CT noise improved model fit (-327.7 reduction in Akaike information criterion; $P < .001$ by likelihood ratio test). Additionally, inclusion of field of view and a field of view by radiation dose interaction term improved model fit when comparing model 2 with model 1 (-65.4 reduction in Akaike information criterion; $P < .001$ by likelihood ratio test). Annualized rates of emphysema progression for successive 5-year intervals, stratified by smoking status and deep learning emphysema severity, are shown in Table 3 for model 2. We obtained annual

Table 1: Demographic Characteristics at Baseline, 5-year Follow-up, and 10-year Follow-up

Parameter	Phase 1	Phase 2 (Full Dose)	Phase 2 (Reduced Dose)	Phase 3
No. of participants	8431	4913	701	1544
Age (y)	59.8 ± 9.1	66.3 ± 8.9	65.5 ± 8.9	70 ± 8.7
Height (cm)	170.2 ± 9.5	169.4 ± 9.7	169.8 ± 9.7	168.9 ± 9.6
FEV ₁ (% predicted)	76.4 ± 25.6	78.3 ± 24.5	82.5 ± 22.1	78.9 ± 26.1
FEV ₁ -to-FVC ratio (%)	66.6 ± 16.2	67.4 ± 14.7	70.4 ± 12.5	66.3 ± 14.8
Sex				
Female	3905 (46)	2472 (50)	327 (47)	791 (51)
Male	4526 (54)	2441 (50)	374 (53)	753 (49)
Ethnicity				
Black or African American	2705 (32)	1282 (26)	214 (31)	401 (26)
White	5726 (68)	3631 (74)	487 (69)	1143 (74)
DL emphysema				
Absent or trace	3982 (47)	2445 (50)	423 (60)	795 (51)
More than trace	4449 (53)	2468 (50)	278 (40)	749 (49)
Smoking status				
Current	4134 (49)	1950 (40)	332 (47)	551 (36)
Former	4297 (51)	2963 (60)	369 (53)	993 (64)
No. of pack-years	44.3 ± 25	44.3 ± 24.1	41.8 ± 23.2	44.3 ± 23.4
GOLD stage				
GOLD 0	3629 (43)	1902 (43)	347 (50)	591 (41)
GOLD 1	665 (8)	426 (10)	70 (10)	187 (13)
GOLD 2	1614 (19)	887 (20)	116 (17)	281 (20)
GOLD 3	947 (11)	450 (10)	41 (6)	139 (10)
GOLD 4	509 (6)	180 (4)	19 (3)	76 (5)
PRISm	1016 (12)	536 (12)	96 (14)	162 (11)
TLC (L)	5.5 ± 1.4	5.5 ± 1.4	5.4 ± 1.4	5.4 ± 1.4
LAA ₋₉₅₀ (%)	6.5 ± 10	5.5 ± 9.1	4.1 ± 6.1	7.1 ± 9
Lung density (g/L)	83.5 ± 32.1	84.2 ± 30.1	87.9 ± 30	80.9 ± 30.8
ALD (g/L)	84.2 ± 26.9	84.9 ± 25.1	73.2 ± 21.6	69.6 ± 23.4

Note.—Baseline is phase 1, 5-year follow-up is phase 2, and 10-year follow-up is phase 3. Mean data are ± SD. Data in parentheses are percentages. ALD = adjusted lung density, DL = deep learning, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, LAA₋₉₅₀ = low attenuation area less than -950 HU, PRISm = Preserved Ratio Impaired Spirometry, TLC = total lung capacity.

progression estimates from three additional models (base model, model 1, and calibration model), which are shown in Table S3. The four modeling approaches yielded comparable mean emphysema progression estimates. Results in Tables 3 and S3 were based on models that used baseline age. Consequently, estimates of progression involved changes over time that included both aging and disease progression. Unless otherwise noted, results are presented for model 2 because it was assessed to have the best fit.

The largest change in ALD was observed in current smokers with more than a trace emphysema at baseline (Table 3). Within this group, average annual decreases of 1.4 g/L (95% CI: 1.2, 1.5) and 0.9 g/L (95% CI: 0.7, 1.2) were observed during the first and second 5-year follow-up periods, respectively. Among former smokers with more than trace emphysema at baseline, these respective declines were 0.8 g/L (95% CI: 0.7, 0.9) and 0.3 g/L (95% CI: 0.1, 0.5). For participants with absent or trace emphysema at baseline, the average annual decline in ALD was 0.5 g/L in the first 5 years (95% CI: 0.4, 0.6 [for both smoking groups]) and 0.4 g/L in the second 5 years for both current (95% CI: 0.2, 0.7) and former smokers (95% CI: 0.2, 0.6).

Figure 3 shows estimated mean ALD at each visit by smoking and baseline emphysema status. Although current smokers with more than trace emphysema at baseline had the largest 5-year decreases in ALD, former smokers with more than trace emphysema at baseline had the lowest average ALD at all three phases (64.7 g/L at baseline; 95% CI: 60.9, 68.6). Figure 4A–4C shows nonprogression of emphysema during 10 years for a former smoker with trace emphysema. Figure 4D–4F shows progression of emphysema during 10 years for a current smoker with more than trace emphysema.

Table S4 shows progression estimates for models that include time-varying age rather than baseline age. These estimates are lower in magnitude because the use of time-varying age removes effects from between-subject age differences. The motivation for this approach was to separate aging effects from disease progression effects, although it is only approximate because the phase predictor is not a precise measurement of time since disease onset (Appendix S6). The yearly decline in estimates in Table S4 was, on average, about 0.3 g/L less than those shown in Table 3. Table S5 shows progression estimates stratified by baseline visual

emphysema grade and baseline percentage of low attenuation area less than -950 HU. Estimates were comparable across all three baseline emphysema groups; however, group numbers were more balanced when using deep learning or visual emphysema versus percentage of low attenuation area less than -950 HU.

Missing ALD, CT noise, field of view, baseline emphysema grade, height, and body mass index were imputed using multiple imputation techniques. Imputed data were then used to estimate emphysema progression by refitting the final linear mixed model (model 2). Additionally, emphysema progression was estimated with models by using continuous time and random slopes for time. Progression estimates from models derived from imputed data or models by using random slopes

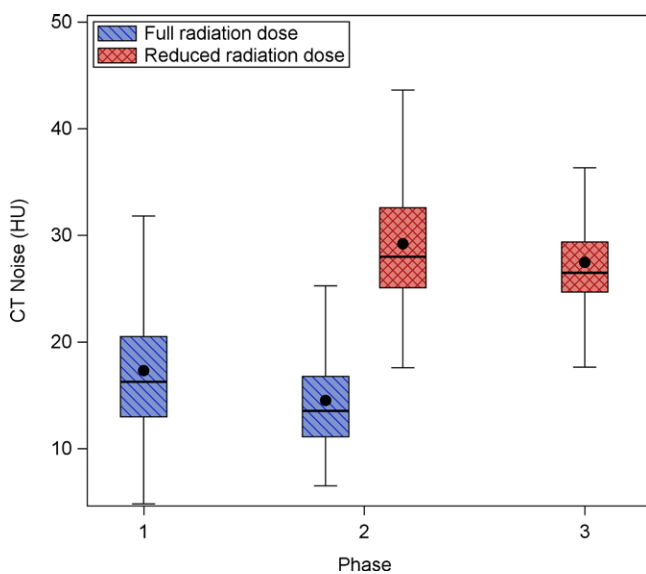


Figure 2: Box and whisker plot shows distribution of CT noise by phase and radiation dose. CT noise decreased slightly between baseline (phase 1) and 5-year follow-up (phase 2) but increased in the reduced-dose scans in phase 2 and 10-year follow-up (phase 3). Comparison of reduced-dose scans also shows that noise decreased from phase 2 to phase 3.

for time yielded more emphysema progression in the second 5-year study period (Table 4) relative to models that fit observed data. In particular, the multiple imputation approach yielded estimates that were fairly consistent between the two 5-year intervals (Appendix S8).

Discussion

In our investigation of emphysema progression within the smoking cohort, emphysema was modeled using volume-adjusted lung density (ALD) based on quantitative CT at three points spanning 10 years (baseline, or phase 1; 5-year follow-up, or phase 2; and 10-year follow-up, or phase 3). Including image-related parameters in the model improved longitudinal estimates of emphysema progression (Akaike information criterion difference, -393.1; $P < .001$ by likelihood ratio test). Change in CT scanning protocol at phase 3 was addressed with methods leveraging ALD measurements in participants who underwent a full-dose and a reduced-dose examination at phase 2. Former smokers with more than trace emphysema had the lowest baseline ALD (64.7 g/L; 95% CI: 60.9, 68.6), whereas current smokers with more than trace emphysema had the largest annual change in ALD (first 5 years, -1.4 g/L [95% CI: -1.5, -1.2]; second 5 years, -0.9 g/L [95% CI: -1.2, -0.7]).

Previous studies (13,22,23) have shown that current smokers had higher ALD than former smokers, which is attributed to increased inflammatory cells in the lungs of current smokers. Former smokers with emphysema had the lowest average ALD at all three phases, probably because those with moderate or severe emphysema were more likely to quit smoking before follow-up began. However, the trajectory of lung density loss in former smokers was generally less than in current smokers. Wille et al (24) showed that emphysema progression during a 5-year span could be identified visually at chest CT in continued smokers but not in former smokers. This difference in the rate of emphysema progression provides

Table 2: Comparison of Candidate Models for Change in Adjusted Lung Density Over Time

Parameter	Base Model	Model 1	Model 2
Adjustment factors	Phase, smoking status, baseline DL emphysema grade, ethnicity, sex, age, visit height, visit BMI, visit BMI ² , indicator for radiation dose (full dose or reduced dose)	Same as base model with CT noise and CT noise squared	Same as base model with CT noise, CT noise squared, FOV, and interaction between FOV and dose indicator
Comparison metrics			
Change in AIC from base model	...	-327.7	-393.1
Change in BIC from base model	...	-325.5	-388.8
χ^2 P value			
Model 1 vs base model	...	<.001	...
Model 2 vs model 1	<.001

Note.— χ^2 P value based on likelihood ratio test. Akaike information criterion (AIC, where smaller is better) for the base model was 115 672.9, Bayesian information criterion (BIC, where smaller is better) for the base model was 115 705.2. All models included all interactions involving phase, smoking status, and baseline deep learning (DL) emphysema grade. BMI = body mass index, BMI² = BMI squared, FOV = field of view.

Table 3: Annual Changes in Adjusted Lung Density for Each Study Period

Follow-up Period	No. of Participants	Mean Change in ALD	P Value
Current smoker			
Absent or trace emphysema	2151		
First 5 years		-0.5 (-0.6, -0.4)	<.001
Second 5 years		-0.4 (-0.7, -0.2)	<.001
More than trace emphysema	1983		
First 5 years		-1.4 (-1.5, -1.2)	<.001
Second 5 years		-0.9 (-1.2, -0.7)	<.001
Former smoker			
Absent or trace emphysema	1831		
First 5 years		-0.5 (-0.6, -0.4)	<.001
Second 5 years		-0.4 (-0.6, -0.2)	<.001
More than trace emphysema	2466		
First 5 years		-0.8 (-0.9, -0.7)	<.001
Second 5 years		-0.3 (-0.5, -0.1)	.008

Note.—Data in parentheses are 95% CIs. Group-specific average follow-up time between baseline (phase 1) and 5-year follow-up (phase 2), and phase 2 and 10-year follow-up (phase 3) used to annualize rates were as follows: current smokers with absent/trace emphysema, 5.75 and 5.19 years; current smokers with more than trace emphysema, 5.62 and 4.92 years; former smokers with absent/trace emphysema, 5.64 and 4.71 years; and former smokers with more than trace emphysema, 5.59 and 4.74 years. ALD = adjusted lung density.

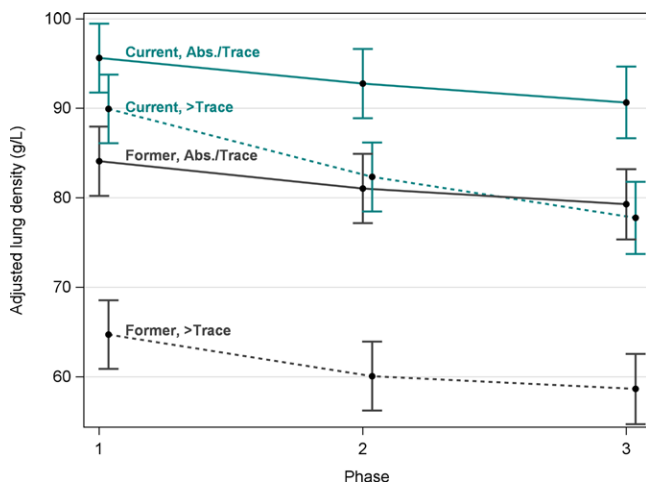


Figure 3: Graph shows mean and 95% CIs of volume-adjusted lung density (ALD) at each baseline (phase 1), 5-year follow-up (phase 2), and 10-year follow-up (phase 3) by smoking status and deep learning emphysema status at baseline. Means were estimated from a linear mixed model (model 2; see Statistical Analysis and Progression Models sections for details). Teal lines represent current smokers and dark gray lines represent former smokers. Solid lines represent absent (Abs.) or trace deep learning emphysema and dashed lines represent more than trace emphysema at baseline. Volume-ALD was higher in current smokers than in former smokers. Current and former smokers with absent or trace emphysema had only a slight decline in ALD during 10 years. Current smokers had the largest rate of decline in emphysema.

further support for smoking cessation even in individuals with established emphysema.

The decline of ALD for current smokers with emphysema was comparable to the annual decline of 1.13 g/L found in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (known as ECLIPSE) study of former smokers with COPD, studied for 3 years (7). A previous study (11) evaluating 4268 smokers between phase 1 and phase 2 of showed the 5-year decline in ALD was 1.7 g/L in smokers without COPD and 5.3 g/L in smokers with COPD. A subsequent study (9) showed that ALD decline was minimal in participants without visible emphysema at baseline and the amount of decline increased with increasing severity of visual emphysema. Our 10-year follow-up study extends this finding. Therefore, it is important to stratify the long-term change in ALD by presence of emphysema at baseline. Moreover, because current smokers progressed faster than former smokers, stratification by smoking status is also important (7).

For emphysema progression because of aging versus because of disease, model estimates suggest that approximately 1–2 g/L in ALD was lost every 5 years because of aging whereas the excess decrease in ALD was because of disease. This result is supported by the work of Shaker et al (25), who reported declines of 0.33 g/L per year (1.65 g/L for 5 years) in a reference group of former-smoker male participants without airflow obstruction. Hoffman et al (17) reported similar changes for former smokers and never-smokers for another emphysema metric.

The strengths of our study include the large multicenter study sample, 10-year follow-up, deep learning to stratify on baseline emphysema, stratification for smoking status, and inclusion of image noise and field of view in models. Relative to previous work (11), our study extends progression estimates to 10 years and highlights the importance of adjusting for CT technical characteristics.

Our study had limitations. First, the absence of other studies with similar length of follow-up made validation difficult. However, a variety of modeling techniques was used yielding similar results, which increased confidence in the presented results. A second limitation, loss to follow-up, may have influenced progression estimates in the second 5 years, which may partially explain the decrease in progression rate during the second 5 years for some groups. Models built using imputed data or random slopes for time indicated more progression in the second 5 years relative to models using observed data. In particular, the models that were fit using imputed data showed relatively equal rates of progression in the first and second 5-year intervals, and the random slopes model showed a similar magnitude of progression.

Chronic obstructive pulmonary disease (COPD) is a complex disease; comprehensive quantitative CT evaluation requires consideration of metrics of airway wall thickening and air trapping. However, our study focused solely on progression of emphysema, a clinically important phenotype. Future work includes examination of other quantitative measures and ongoing changes in scanner technology that may require further adjustment in models. Additionally, future follow-up in this cohort may help to determine the effects of death and dropout on later emphysema progression estimates. Because of increased mortality

risk for participants with emphysema- and airway-predominant COPD, future work will examine emphysema progression in the context of varying COPD subtypes (26,27). In conclusion, within the smoker cohort, emphysema progression as adjusted lung density based on 10 years of quantitative CT data was greatest in current smokers who had more than trace emphysema at baseline. Furthermore, modeling techniques that include image-related parameters such as CT noise and field of view improved longitudinal estimates of emphysema progression.

Author contributions: Guarantors of integrity of entire study, D.B., D.A.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, D.B., S.M.H., D.A.L.; clinical studies, S.M.H., D.A.L.; experimental studies, S.M.H., R.S.J.E., J.P.C., R.L.; statistical analysis, D.B., M.S., S.M.H.; and manuscript editing, D.B., M.S., S.M.H., R.S.J.E., G.V.S.E., R.L., E.K.S., J.D.C., D.A.L.

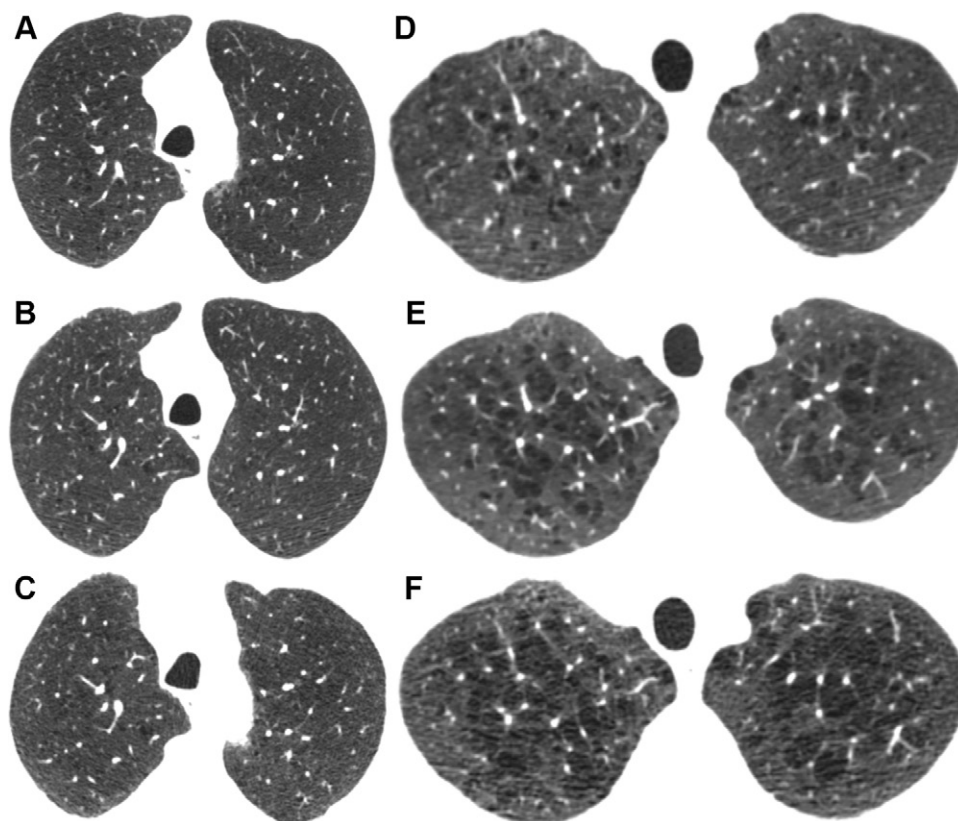


Figure 4: Axial CT sections at each follow-up visit show (A–C) nonprogression for a former smoker with trace emphysema and (D–F) progression for a current smoker with more than trace emphysema. (A–C) Images in a male former smoker who was 62 years old at baseline. (A) Baseline CT scan shows trace emphysema. CT scans obtained at (B) 5 and (C) 10 years show no significant change. (D–F) Images in a male current smoker who was 48 years old at baseline. (D) Baseline CT scan shows mild centrilobular emphysema. CT scans obtained at (E) 5 and (F) 10 years show increasing size and number of emphysematous spaces.

Table 4: Annual Changes in Adjusted Lung Density for Each Study Period Using Missing Data Method

Follow-up Period	Multiple Imputation			Random Slope Model		
	No. of Patients	Mean Change in ALD	P Value	No. of Patients	Mean Change in ALD	P Value
Current smoker						
Absent or trace emphysema	2360			2151		
First 5 years		-0.7 (-1, -0.3)	.005		-0.6 (-0.7, -0.5)	<.001
Second 5 years		-0.8 (-2, 0.3)	.12		-0.6 (-0.7, -0.5)	<.001
More than trace emphysema	2149			1983		
First 5 years		-1.3 (-1.6, -1)	<.001		-1.4 (-1.5, -1.3)	<.001
Second 5 years		-1.1 (-2.7, 0.4)	.12		-1.4 (-1.5, -1.3)	<.001
Former smoker						
Absent or trace emphysema	1954			1831		
First 5 years		-0.6 (-0.8, -0.3)	.001		-0.6 (-0.7, -0.5)	<.001
Second 5 years		-0.95 (-2.2, 0.3)	.10		-0.6 (-0.7, -0.5)	<.001
More than trace emphysema	2640			2466		
First 5 years		-0.7 (-1, -0.3)	.003		-0.8 (-0.9, -0.7)	<.001
Second 5 years		-0.7 (-2.3, 0.9)	.31		-0.8 (-0.9, -0.7)	<.001

Note.—Data in parentheses are 95% CIs. Group-specific average follow-up time between baseline (phase 1) and 5-year follow-up (phase 2), and phase 2 and 10-year follow-up (phase 3) was used to annualize rates. Model 2 architecture was used for estimating emphysema progression with imputed data. Five imputed data sets were generated, and progression estimates were averaged across these five data sets. ALD = adjusted lung density.

Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

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