BACKGROUND. Chronic obstructive pulmonary disease (COPD) is characterized by airway remodeling. Characterization of airway changes on computed tomography has been challenging due to the complexity of the recurring branching patterns, and this can be better measured using fractal dimensions.

METHODS. We analyzed segmented airway trees of 8135 participants enrolled in the COPDGene cohort. The fractal complexity of the segmented airway tree was measured by the Airway Fractal Dimension (AFD) using the Minkowski-Bouligand box-counting dimension. We examined associations between AFD and lung function and respiratory morbidity using multivariable regression analyses. We further estimated the extent of peribronchial emphysema (%) within 5mm of the airway tree as this is likely to affect AFD. We classified participants into 4 groups based on median AFD and %peribronchial emphysema, and estimated survival.

RESULTS. AFD was significantly associated with FEV$_1$ (p<0.001) and FEV$_1$/FVC (p<0.001) after adjusting for age, race, gender, smoking status, pack-years of smoking, body-mass-index, CT emphysema, air trapping, airway thickness, and CT scanner type. On multivariable analysis, AFD was also associated with respiratory-quality of life and six-minute walk distance, as well as exacerbations, lung function decline and mortality on longitudinal follow-up. We identified a […]
Airway Fractal Dimension Predicts Respiratory Morbidity and Mortality in COPD

Sandeep Bodduluri, Ph.D., 1,2,3 Abhilash S. Kizhakke Puliyakote, Ph.D., 4 Sarah E. Gerard, B.S., 5 Joseph M. Reinhardt, Ph.D., 5 Eric A. Hoffman, Ph.D., 5,6 John D. Newell Jr., M.D., 5,6 Hrudaya P. Nath, M.D., 5,7 MeiLan K. Han, M.D., 8 George R. Washko, M.D., 9 Raúl San José Estépar, Ph.D., 10 Mark T. Dransfield, M.D., 1,2,3 and *Surya P. Bhatt, M.D., 1,2,3 for the COPDGene Investigators

1Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL 35294; 2UAB Lung Imaging Core, University of Alabama at Birmingham, Birmingham, AL 35294; 3UAB Lung Health Center, University of Alabama at Birmingham, Birmingham, AL 35294; 4Department of Radiology, University of California, San Diego, CA 92093; 5Department of Biomedical Engineering, University of Iowa, Iowa City, IA 52242; 6Department of Radiology, University of Iowa Carver College of Medicine, Iowa City, IA 52242; 7Department of Radiology, University of Alabama at Birmingham, Birmingham, AL 35294; 8Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI 48109; 9Division of Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115; 10Division of Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115.

Conflict of Interest Statement:

Dr. Bhatt reports grants from NIH, and research funds to his institute from ProterixBio during the conduct of the study. Dr. Hoffman is a founder and shareholder of VIDA Diagnostics, a company commercializing lung image analysis software developed, in part, at the University of Iowa. Dr. Reinhardt reports owning stocks from VIDA Diagnostics, Inc., personal fees from Science24Seven, personal fees from Boehringer Ingelheim. Dr. San Jose Estepar reports grants from NIH, consulting fees from Boehringer Ingelheim, and is co-owner of Quantitative Imaging Solutions. Dr. Washko reports grants from NIH, grants and consulting for Boehringer Ingelheim, consulting for Genentech, co-owner of Quantitative Imaging Solutions, consulting for PulmonX, consulting for Regeneron, advisor for ModoSpira, grants from BTG Interventional Medicine, grants and consulting fees from Janssen Pharmaceuticals, consulting for Toshiba, and consulting for GlaxoSmithKline. Dr. Washko's spouse works for Biogen which is focused on developing therapies for fibrotic lung disease. Dr. Han reports grants from the NIH, personal fees from GSK, personal fees from BI, personal fees from AstraZeneca, non-financial support from Novartis, and non-financial support from Sunovion. Dr. Dransfield reports grants from NHLBI and the Department of Defense, personal fees and other from Boehringer Ingelheim, personal fees and other from GlaxoSmithKline, other from Novartis, personal fees and other from AstraZeneca, other from Yungjin, other from PneumRx/BTG, other from Pulmonx, personal fees from Genentech, personal fees and other from Boston Scientific. Dr. Newell reports grants from NIH, grants from Siemens Healthineers, personal fees from VIDA Diagnostics Inc, and grants from Hoffman La-Roche. In addition, Dr. Newell has a patent Software Patent issued. Drs. Bodduluri, Kizhakke Puliyakote, Gerard, and Nath have no disclosures.
*Corresponding author:* Surya P. Bhatt, MD, University of Alabama at Birmingham, Division of Pulmonary, Allergy and Critical Care Medicine, THT 422, 1720, 2nd Avenue South, Birmingham, AL 35294. Email: sbhatt@uabmc.edu. Phone: 205-934-5555. Fax: 205-934-6229

**Trial Registration:** ClinicalTrials.gov Identifier: NCT00608764

**Running Head:** Airway Fractal Dimension in COPD

**Word Count:** 3754
Abstract

Background

Chronic obstructive pulmonary disease (COPD) is characterized by airway remodeling.

Characterization of airway changes on computed tomography has been challenging due to the complexity of the recurring branching patterns, and this can be better measured using fractal dimensions.

Methods

We analyzed segmented airway trees of 8135 participants enrolled in the COPDGene cohort. The fractal complexity of the segmented airway tree was measured by the Airway Fractal Dimension (AFD) using the Minkowski-Bouligand box-counting dimension. We examined associations between AFD and lung function and respiratory morbidity using multivariable regression analyses. We further estimated the extent of peribronchial emphysema (%) within 5mm of the airway tree as this is likely to affect AFD. We classified participants into 4 groups based on median AFD and %peribronchial emphysema, and estimated survival.

Results

AFD was significantly associated with FEV₁ (p<0.001) and FEV₁/FVC (p<0.001) after adjusting for age, race, gender, smoking status, pack-years of smoking, body-mass-index, CT emphysema, air trapping, airway thickness, and CT scanner type. On multivariable analysis, AFD was also associated with respiratory-quality of life and six-minute walk distance, as well as exacerbations, lung function decline and mortality on longitudinal follow-up. We identified a subset of participants with AFD<median and peribronchial emphysema>median who had worse survival compared with participants with high AFD and low peribronchial emphysema (adjusted HR =
2.72, 95%CI 2.20 to 3.35; p<0.001), a substantial number of whom were not identified by traditional spirometry severity grades.

**Conclusions**

Airway fractal dimension as a measure of airway branching complexity and remodeling in smokers is associated with respiratory morbidity and lung function change, offers prognostic information additional to traditional CT measures of airway wall thickness, and can be used to estimate mortality risk.
Introduction

Airflow obstruction in chronic obstructive pulmonary disease (COPD) is a result of both emphysema and airway disease. (1, 2) Advances in computed tomographic (CT) imaging have enabled localization and quantification of structural changes in lung parenchyma, resulting in improved phenotyping of COPD. (3, 4) CT emphysema is associated with respiratory morbidity, change in lung function, as well as with mortality. (5-8) Although equally important, airway disease has, however, been harder to characterize, and the presence and severity of airway remodeling have been variously quantified using measurements from the segmental and sub-segmental airways. These include airway wall measurements such as bronchial diameter, airway wall area, airway wall thickness, and the tortuosity of airway branches. (9-11) These measurements describe the morphology of individual branches or specific generations and, in serving as surrogates of overall airway remodeling, assume that the airway tree geometry follows Euclidean relationships that can be represented in integer dimensions. However, the airway tree possesses a complex self-repeating geometry that is specific for each individual, and this branching pattern is represented better in fractional dimensions. (12, 13)

Fractal geometry is the study of structures that seem chaotic but exhibit a hierarchal self-similar pattern. (12) Using airway casts, Weibel demonstrated that fractal geometry is useful in characterizing the complex self-repeating airway branching patterns that are necessary for efficient gas exchange. (13) Fractal dimensions have been used previously in several applications to explain regional ventilation, (14) pulmonary vessel branching and blood flow patterns, (15, 16) pulmonary arterial hypertension, (17, 18) emphysema grouping in the lungs, (19) and to quantify airway remodeling in digitized airway casts in asthmatics. (20) It is likely that the same branching patterns that enhance efficient airflow and gas transfer in healthy individuals are associated with
increased turbulence, airflow obstruction and impaired airflow distribution in the setting of perturbations in the branching patterns. Using data from CT scans obtained from smokers with and without COPD, we hypothesized that the airway fractal dimension (AFD) provides a precise summative measurement of the morphological changes in the airways in COPD, and that airway fractals are associated with respiratory morbidity, lung function decline and all-cause mortality.

**Results**

**Participants**

We measured AFD in the 8135 participants from the Genetic Epidemiology of COPD (COPDGene) cohort for whom we had complete airway segmentations, characteristics of subjects are shown in Table 1. This included 105 (1.2%) lifetime never smokers, 3961 (48.6%) without airflow obstruction (GOLD 0), and 721 (8.8%), 1755 (21.5%), 1052 (12.9%), and 541 (6.6%) with GOLD stages 1 to 4, respectively. 4121 (52.6%) were active smokers and 2503 (30.7%) were African-Americans. The mean AFD was 1.56 (SD 0.07) for non-smokers, and 1.52 (0.09), 1.50 (0.08), 1.46 (0.08), 1.45 (0.07), and 1.45 (0.07) for GOLD 0 through 4, respectively (trend-test p<0.0001).

**AFD and Lung Function**

AFD correlated significantly with FEV$_1$ (r=0.35; p<0.001) and FEV$_1$/FVC (r=0.26, p<0.001). After adjustment for age, race, gender, smoking status, pack-years of smoking, BMI, %emphysema on CT, % air trapping, Pi10, and CT scanner type, AFD remained significantly associated with FEV$_1$ (adjusted $\beta = 1.62$, 95%CI 1.48 to 1.76; p<0.001) as well as with FEV$_1$/FVC (adjusted $\beta = 0.23$, 95%CI 0.20 to 0.25; p<0.001) (Table 2).
**AFD and Respiratory Morbidity**

AFD was significantly associated with respiratory quality of life measured by SGRQ (adjusted β = -7.35, 95%CI = -12.49 to -2.21; p=0.005) after adjustment for age, race, gender, smoking status, pack years, BMI, FEV1 at baseline, CT emphysema (%), CT air trapping (%), Pi10, and CT scanner type. Similarly, AFD was also significantly associated with 6MWD (adjusted β = 266.92, 95%CI = 171.76 to 362.07; p<0.001), shown in Table 2.

**AFD and Exacerbations**

We had follow-up data for exacerbations on 5761 participants (median 6.6 years, range 0.2 to 9.5 years). After adjustment for age, sex, race, BMI, FEV1, pack-years of smoking, current smoking status, and emphysema, AFD was associated with the total number of exacerbations (Incidence risk ratio, IRR 0.17; 95% CI, 0.10 to 0.29; p<0.001) and with severe exacerbations (IRR 0.20; 95% CI, 0.10 to 0.41; p<0.001).

**AFD and FEV1 Change**

We had follow-up spirometry for 3948 participants for a median duration of 64 (interquartile range IQR=60 to 68) months. In models evaluating associations with change in FEV1 after 5-year follow-up with adjustment for age, race, sex, BMI, smoking status, pack-years of smoking, %CT Emphysema, FEV1 at baseline, CT scanner type, Pi10 was not associated with FEV1 change (adjusted β = -2.04, 95%CI: -17.76 to 13.66, p=0.798) but AFD was associated with FEV1 change (adjusted β = -31.55, 95%CI: -52.74 to -10.36, p=0.003). This relationship between AFD and FEV1 change held true in combined models that included adjustment for Pi10 (adjusted β = -33.41, 95%CI = -54.28 to -12.55; p=0.001).
**Mild Disease**

We assessed the value of AFD separately in subjects at risk for COPD but without airflow obstruction on spirometry (GOLD stage 0, n = 3961). We found AFD was similarly associated with FEV1, FEV1/FVC, SGRQ and 6MWD (all p<0.001) (**Table 3**). In addition, the inverse relationship between AFD and lung function decline was also seen in 2053 participants with GOLD 0 on follow-up (adjusted β = -38.81, 95%CI: -64.30 to -13.31, p=0.002) (**Table 3**).

**Survival**

Survival data was available in 7154 participants for a median duration of 80 (interquartile range IQR=71 to 88) months. In the entire cohort, 980 (13.7%) patients died over the period of follow-up, 188 (2.6%), 52 (0.7%), 236 (3.2%), 242 (3.3%) and 262 (3.6%) in GOLD stages 0 through 4 respectively. After adjusting for age, race, sex, BMI, and pack-years of smoking, both Pi10 (adjusted HR=15.74, 10.37 to 23.91, p<0.001, AIC=15913.24) and AFD (adjusted HR=0.04, 0.02 to 0.10, p<0.001, AIC=16512.2) were both significantly associated with mortality in subjects with COPD. In combined models with addition of Pi10 to the AFD model, AFD was still independently associated with mortality in COPD (adjusted HR=0.14, 0.06 to 0.29, p<0.001, AIC=15888.36).

**Table 4** shows baseline data for the 4 groups based on AFD and %peribronchial emphysema. **Figure 1A** shows the 4 groups, and **Figure 1B** shows the distribution of participants by GOLD stage across the groups. **Figure 1C** shows survival curves for these groups. 122 (6.8%), 150 (8.6%), 309 (16.2%) and 399 (23.1%) participants died in groups I through IV respectively. Of note, a substantial proportion of participants in group IV had GOLD 0 and 1 disease, 247 (14.3%), and 135 (7.8%), respectively. After adjustment for age, race, sex, and pack-years of smoking, the hazards ratio for participants in groups II, III, and IV was 1.36
(95%CI 1.07 to 1.73; p=0.011), 1.69 (95%CI  1.36 to 2.10; p<0.001), and 2.72 (95%CI 2.20 to 3.35; p<0.001), respectively, compared with participants in group I.

**AFD: Influence of airway narrowing and airway loss**

AFD is likely affected by multiple pathologic processes including airway narrowing and airway loss, in addition to changes in branching angles and airway tortuosity, with major contributions from airway narrowing and airway loss. Total airway count is progressively reduced in subjects with increasing disease severity, and is seen early in the disease process.(21, 22) We ran simulation analyses where we progressively decreased the total intraluminal volume of the airways in a representative subject (Figure 2). As loss of airway branches cannot follow strict percentage volume loss to parallel the simulation of airway narrowing, a trend in loss of volume that parallels airway narrowing is shown in the Figure. We found that for a given decrease in intraluminal volume, AFD is more significantly affected by loss of airways than by narrowing of airways. This influence of loss of airways is unlikely to be captured by Pi10 which relies on measurements of existing airways.

**Discussion**

In a cohort of smokers, we demonstrated that the fractal dimension of the airway tree, a measure of airway branching complexity, is significantly associated with airflow obstruction and respiratory morbidity as well as with lung function decline after adjustment for traditional measures of airway narrowing. We also showed that a significant number of smokers without airflow obstruction, who would be considered to have mild or no disease by traditional
classification schema, can be identified to have high mortality risk based on grouping using fractal dimensions and peribronchial emphysema.

Airway remodeling in cigarette smokers involves a complex combination of airway wall changes, luminal narrowing, and eventual attrition of airways.\(^{(21, 23, 24)}\) A number of imaging metrics are used to quantify these changes, including airway wall thickness, wall area percent (WA%), or the summary measures of the square roots of the wall areas of hypothetical airways with internal perimeters 10 mm and 15 mm (Pi10 and Pi15).\(^{(9, 25)}\) Although these airway metrics have strong associations with lung function and respiratory morbidity,\(^{(10, 26, 27)}\) these classic geometrical measurements are limited to dimensions averaged over a few generations of segmental and subsegmental bronchi. They assume that changes in some generations of airways are reflective of changes throughout the airway tree, and do not capture the complex morphological changes in the airway tree which is highly irregular with rough surfaces and self-similar bifurcations at each generation. As fractals show self-similarity, they may better reflect the stochastic airway luminal narrowing and branching changes throughout the airways.

Airway fractal dimensions have considerable clinical implications. The branching angles and tortuosity impact airflow dynamics, as well as smoke and drug deposition.\(^{(28-30)}\) Weibel et al. theorized that the fractal nature of airway branching enables the large central airways with a cross-sectional area of 5 cm\(^2\), to bifurcate and eventually connect with the alveoli with a total surface area of 130 m\(^2\).\(^{(13)}\) Although this fractal nature is vital for efficient gas flow and diffusion, abnormalities induced by narrowing and loss of airways, and changes in curvature and branching angles can impact outcomes in disease. Even mild asymmetries in the branching patterns of successive generations can create large variations in ventilation at the terminal segments, resulting in inefficiency of gas exchange.\(^{(15, 16)}\) Indeed, exhaled aerosol patterns
demonstrate fractal behavior, suggesting an influence of fractal patterns on airflow and particle deposition. (31) Although branching morphogenesis is initiated early in-utero during embryogenesis, the patterns might influence deposition of cigarette smoke and other environmental agents, and potentiate a series of events marked by lung injury and further impact on fractals. It is postulated that there is a clock mechanism for airway branching in the developmental period that is key in timing the rate of embryonic airway bud extension and thus the inter-branch distance. (32) Once emphysema has set in, it likely plays a role in changing the fractals as a result of peribronchial emphysema exerting mechanical effects. Emphysema adjacent to the airways can change the branching able by pushing the airways away from the area of emphysema, especially if this is associated with local air trapping due to poor elastic recoil. For example, emphysema present within the arc of a branch point may widen the branching angle, whereas emphysema that is laterally present may cause the branching angle to narrow. In addition, the presence of emphysema adjacent to the airways may also predispose the airways to collapse, due to the untethering of airways. (33, 34)

Our finding of the importance of AFD in participants without overt airflow obstruction is of particular clinical importance. Multiple recent studies have shown that approximately half the subjects at risk for COPD but without airflow obstruction on spirometry have evidence for structural disease on CT. (35, 36) The strong associations of AFD with respiratory-quality of life and functional capacity support these earlier studies. In addition, AFD can be used to predict disease progression measured by lung function decline as well as mortality in these subjects. Studies of mild disease show that airway loss occurs early in COPD, findings that likely explain the loss of fractal dimension. (22)
AFD has been previously measured on silicone rubber airway casts made from autopsy samples of asthmatic airways, and fatal asthmatics had lower fractal dimensions compared to those with non-fatal asthma, and controls without asthma. (20) Casts from the fatal asthma cases showed substantial remodeling with tapering of segments, irregularity of airways and ridges. Casts from non-fatal asthma were visually not different compared with controls, but AFD was substantially lower in these cases compared with controls. (20) In contrast to these studies on airway casts, our results extend the application of fractal analysis to non-invasive CT image reconstruction of airway trees to quantify airway remodeling in COPD. We found that AFD was lower in those with COPD compared with normal participants of roughly similar age, and there was a progressive decrease in AFD with worsening disease stages (p<0.001). A reduction in AFD reflects either a loss of the complex branching pattern, perhaps due to loss of airways, or a progressive narrowing of the airways. Recent studies have demonstrated this loss of airways in vitro as well as on CT images, and this loss of airways has an impact on clinical outcomes. (21, 23, 37) This loss of complexity has also been shown in emphysema progression in mice using fractal analysis. (33, 38) In this study, we found that AFD provides additional prognostic information over that provided by current Euclidean-based measures of airway remodeling.

We also found that fractal dimensions can be used to stratify mortality risk in smokers, and this risk-stratification provides information that is different from the traditional spirometry-based severity grading. Indeed, a substantial number of participants in groups III and IV had GOLD 0 or 1 disease. Although both groups III and IV were characterized by a higher than median percentage of peribronchial emphysema, the additional mortality risk seen in group IV suggests that low AFD is associated with the worst survival rates. The discordance between low AFD groups and mild GOLD stages with differences in outcomes suggests that AFD provides
prognostic information that is different from that provided by GOLD alone. Although the reasons for this association remain to be investigated, it could be the culmination of the adverse influence of low AFD and its implications towards airflow dynamics, cigarette smoke and other particle deposition, inefficiencies in ventilation and gas exchange and perhaps deposition of inhaled medications as well. These findings, in combination with the association between AFD and lung function decline suggest that low AFD is associated with greater risk of disease progression.

Our study has a number of strengths. The COPDGene study is a cohort of well characterized participants that included normal controls as well as smokers with a wide spectrum of disease severity. We showed the utility of this novel measure independent of traditional measures of airway narrowing. Participants were extensively phenotyped with stringent quality control for spirometry and CT. Our study also has a few limitations. We used cubes to fill the airways and measured AFD, whereas the use of other shapes such as 3D triangles could result in slightly different AFD values. However, box counting with cubes has been previously used and provides robust values for AFD. As AFD is a global measure of airway branching complexity, minor alterations in airway structure may be missed; however, these early changes are also likely to be missed using existing metrics that measure geometric averages. All airway measures can be affected by the volume of acquisition, the display field of view, and spatial resolution of CTs, and more efforts are being made to standardize CT acquisition protocols to minimize these factors. 3D CT resolution is continuing to increase and will drive improvements in AFD accuracy in the future by enabling the use of smaller cube sizes. We did not adjust outcomes for medication data, but no medication has been shown to alter disease outcomes such as lung function decline and mortality. Finally, we calculated all-cause mortality as mortality causes have not been adjudicated.
Conclusions

We found that the fractal dimension of the airway tree as a measure of airway remodeling in smokers is associated with respiratory morbidity including exacerbations as well as lung function decline, and informs mortality risk, beyond that inferred from airway wall thickness. Fractal dimensions may prove useful for phenotyping patients by providing a unique CT signature for modeling particle deposition, and targeting drug delivery devices.

Methods

Participants

We included participants enrolled in the Genetic Epidemiology of COPD (COPDGene) study, which is a large multicenter clinical trial involving non-smokers, and current and former smokers between ages 45 and 80 years with a smoking history of at least 10 pack-years; details of this study have been previously published.(39) We included 10,300 participants at baseline and the first 5000 participants who returned for a follow-up visit after approximately 5 years (CONSORT diagram in Supplemental Figure 1). At baseline and at follow-up, participants underwent extensive phenotypic characterization including demographics, computed tomography (CT) imaging, and pre and post bronchodilator spirometry. The presence of airflow obstruction was confirmed when the post-bronchodilator ratio of the forced expiratory volume in the first second (FEV₁) to the forced vital capacity (FVC) was <0.70. The Global initiative for Obstructive Lung Disease (GOLD) recommendations were used to classify the severity of airflow obstruction.(1) All participants performed a six-minute walk test (6MWD) to assess functional capacity, and the St. George’s Respiratory Questionnaire (SGRQ) was used to assess disease-specific impact on quality of life.(40) Acute exacerbations were defined using a modified
version of the Epidemiology Standardization Project questionnaire (American Thoracic Society–Division of Lung Disease-78).(41, 42) Exacerbations were defined as worsening in respiratory status with increase in dyspnea, cough or sputum production that lasted at least 48 hours and required the use of either antibiotics and/or systemic steroids. Those exacerbations that resulted in hospitalization were categorized as severe exacerbations. Lung function change was assessed by the annualized change in FEV₁ from enrollment to follow-up. We also obtained data on all-cause mortality on longitudinal follow-up. All participants provided written informed consent prior to enrollment and the COPDGene study protocol was approved by the University of Alabama at Birmingham Institutional Review Boards (IRB) for Human Use (F070712014), and the IRBs of all 21 participating study centers (Details in Supplement).

CT Imaging

We analyzed volumetric CT scans acquired at baseline using multi-detector CT scanners at full inspiration (Total Lung Capacity, TLC). Voxels < -950HU on inspiratory scans were labelled as regions with emphysema and voxels < -856HU on expiratory scans were labelled as regions of air trapping. Pulmonary WorkStation 2 software (VIDA Diagnostics, Inc., Coralville, IA, USA) was used to segment the lungs and to reconstruct the 3D airway tree up to the 6th generation from the inspiratory CT image using an automated region-growing algorithm.(43, 44) Completeness of the airway tree was visually assessed, and manual corrections were performed in the case of discrepancies. Airway wall remodeling was quantified by estimating the square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm (Pi10).(9, 25)

Airway Fractal Dimension (AFD)

The fractal complexity of the segmented airway luminal tree was measured by the Airway Fractal Dimension (AFD) using the Minkowski-Bougliand box-counting dimension
(also known as Kolmogorov dimension). Details are provided in the Supplement, and in **Supplemental Figure 2**. Briefly, the segmented airway tree was converted to a binary image for processing. Cubes of progressively increasing side length “s” (initial value of s = 1; increasing in powers of 2 to a maximum encompassing the image size) were iteratively overlaid over the binary airway mask and the number of cubes ‘N’ overlapping with the airway were identified at each iteration. The number of cubes required to cover the airway is related to the size of the cube by an inverse power law. The slope of the least-squares best-fit regression line between the $\log(N)$ and $\log(1/s)$ was computed to derive the AFD. The greater the complexity of how the branches fill space, the greater the AFD. **Figure 3** shows representative examples of the AFD of subjects with varying severity of emphysema. All fractal computations were performed using MATLAB software (Math Works, Natick, MA).

**Simulation of Airway Loss:**

As AFD can be affected by airway narrowing and loss of airways, both processes commonly seen in COPD, we simulated these processes in a representative subject’s airways. The change in AFD in the case of airway loss was estimated by iteratively cutting down distal branches with specific lumen diameter per iteration (**Figure 2**). Similarly, in the case of airway narrowing, a distance map was initially calculated on the airway mask and an iterative binary thinning algorithm was implemented to simulate airway narrowing.

**Peribronchial Emphysema**

As airway branching angles can potentially be affected by emphysema adjacent to the airways with resultant mechanical forces, and this can influence the fractal dimension (AFD), we further quantified the percentage of peribronchial emphysema within 5mm of the airway tree (**Supplemental Figure 3**).
Grouping of COPD subjects using AFD and % Peribronchial Emphysema

As AFD can be influenced by innate airway geometry, airway remodeling, and peribronchial emphysema, we divided participants into four groups based on median AFD and median % peribronchial emphysema estimated from all subjects in the cohort, after excluding never-smokers (Figure 1A). Groups I and III are comprised of participants with AFD greater than the median and with % peribronchial emphysema lower and higher than the median, respectively. Groups II and IV are comprised of participants with AFD lower than the median and with low and high % peribronchial emphysema, respectively.

Statistical Analysis

The parametric Pearson’s test was used to calculate correlations between AFD and lung function. Univariate and multivariable regression analyses were performed to test associations between AFD and respiratory morbidity (SGRQ and 6MWD), FEV₁/FVC, FEV₁, and FEV₁ change, after adjustment for age, race, gender, smoking status, pack-years of smoking, body-mass-index (BMI), CT emphysema (%), CT air trapping (%), Pi10, and CT scanner type. All models were also adjusted for baseline FEV₁ except in estimating the associations for FEV₁ and FEV₁/FVC. Multivariable models for FEV₁ change included baseline FEV₁ in addition to the above mentioned variables. Using the aforementioned groups based on combinations of dichotomized AFD and % peribronchial emphysema, we compared mortality rates using Kaplan-Meier survival analysis with log-rank test. To enable comparisons between the various radiological parameters and their associations with outcomes, we “normalized” the CT parameters by scaling and centering them by (value-mean)/SD. Thus, a 1 unit increase in a normalized metric is 1 SD. These results are presented separately in the Supplement. The
association between AFD and exacerbations were assessed using negative binomial regression models with adjustment for age, race, sex, BMI, pack-years of smoking, current smoking status, FEV$_1$ and emphysema. The Cox proportional hazards model was used to calculate adjusted hazard ratios for each group compared with group I as reference, after adjustment for age, race, gender, and pack-years of smoking. A two-sided p-value <0.05 was considered significant for all analyses. All analyses were performed using Statistical Package for the Social Sciences (SPSS V 24.0, SPSS, Chicago, Illinois, USA) and R statistical software (V 3.2).
# Table 1: Baseline Demographics of participants (n=8135)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.9 (9.0)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>3731 (45.8%)</td>
</tr>
<tr>
<td>African-American (%)</td>
<td>2503 (30.7%)</td>
</tr>
<tr>
<td>Body-mass-index (kg/m²)</td>
<td>28.3 (5.9)</td>
</tr>
<tr>
<td>Smoking Pack-years</td>
<td>44.6 (24.9)</td>
</tr>
<tr>
<td>Current Smokers (%)</td>
<td>4121 (50.6%)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.28 (0.9)</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>77.6 (27.0)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.3 (1.0)</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>89.4 (18.1)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.6 (0.1)</td>
</tr>
<tr>
<td>GOLD Severity</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3961 (48.6%)</td>
</tr>
<tr>
<td>1</td>
<td>721 (8.8%)</td>
</tr>
<tr>
<td>2</td>
<td>1755 (21.5%)</td>
</tr>
<tr>
<td>3</td>
<td>1052 (12.9%)</td>
</tr>
<tr>
<td>4</td>
<td>541 (6.6%)</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>105 (1.2%)</td>
</tr>
<tr>
<td>CT Emphysema %</td>
<td>6.78 (10.1)</td>
</tr>
<tr>
<td>CT Air Trapping %</td>
<td>23.37 (20.5)</td>
</tr>
<tr>
<td>Pi10</td>
<td>3.67 (0.13)</td>
</tr>
<tr>
<td>Airway Fractal Dimension</td>
<td>1.49 (0.1)</td>
</tr>
<tr>
<td>Peribronchial Emphysema, %</td>
<td>2.30 (3.1)</td>
</tr>
</tbody>
</table>
All values expressed as mean (SD) unless specified otherwise. SD = Standard deviation. FEV₁ = Forced expiratory volume in the first second. FVC = Forced vital capacity. GOLD = Global Initiative for Chronic Obstructive Lung Disease. CT = Computed tomography. HU = Hounsfield Units. Pi₁₀ = Square root of wall area of a theoretical airway with 10mm luminal perimeter)
Table 2: Multivariable associations of Airway Measures with lung function and respiratory morbidity (n = 8030)

<table>
<thead>
<tr>
<th>Pi10</th>
<th>Airway Fractal Dimension (AFD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted for Pi10</td>
</tr>
<tr>
<td></td>
<td>β (95% CI)</td>
</tr>
<tr>
<td>FEV₁ (L)*</td>
<td>-1.85 (-1.95, -1.76)</td>
</tr>
<tr>
<td>FEV₁/FVC*</td>
<td>-0.19 (-0.20, -0.17)</td>
</tr>
<tr>
<td>Six-minute walk distance (ft)**</td>
<td>-343.52 (-410.11, -276.93)</td>
</tr>
<tr>
<td>SGRQ**</td>
<td>19.00 (15.42, 22.58)</td>
</tr>
</tbody>
</table>

Pi10 = Square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm

β = Regression co-efficient. CI = Confidence Interval.

FEV₁ = Forced expiratory volume in the first second. FVC = Forced vital capacity. SGRQ = St. George’s Respiratory Questionnaire.

*All models adjusted for age, race, gender, smoking status, pack years, body mass index, %CT Emphysema, %CT Gas Trapping, and CT scanner type.

**Models adjusted for adjusted for baseline FEV₁ at baseline in addition to age, race, gender, smoking status, pack years, body mass index, %CT Emphysema, %CT Gas Trapping, and CT scanner type.
### Table 3: Multivariable associations of Airway Measures with lung function and respiratory morbidity subjects without airflow obstruction (n = 3961)

<table>
<thead>
<tr>
<th></th>
<th>Pi10</th>
<th>Airway Fractal Dimension (AFD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>FEV(_1) (L)*</td>
<td>-0.69</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(-0.83, -0.55)</td>
<td></td>
</tr>
<tr>
<td>FEV(_1)/FVC*</td>
<td>0.03</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(0.01, 0.05)</td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance (ft)**</td>
<td>-254.94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(-360.07, -149.82)</td>
<td></td>
</tr>
<tr>
<td>SGRQ**</td>
<td>13.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(7.61, 18.63)</td>
<td></td>
</tr>
<tr>
<td>Change in FEV(_1) after 5-year follow up ‡</td>
<td>4.71</td>
<td>0.676</td>
</tr>
<tr>
<td></td>
<td>(-17.43, 26.87)</td>
<td></td>
</tr>
</tbody>
</table>

Pi10 = Square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm

β = Regression co-efficient. CI = Confidence Interval.

FEV\(_1\) = Forced expiratory volume in the first second. FVC = Forced vital capacity. SGRQ = St. George’s Respiratory Questionnaire.

*adjusted for age, race, gender, smoking status, pack years, body mass index, %CT Emphysema, %CT Gas Trapping, and CT scanner type.

**Models adjusted for adjusted for baseline FEV\(_1\) at baseline in addition to age, race, gender, smoking status, pack years, body mass index, %CT Emphysema, %CT Gas Trapping, and CT scanner type.

‡ adjusted for age, race, gender, smoking status, pack years, body mass index, FEV\(_1\) at baseline, %CT Emphysema, and CT scanner type.

Follow-up data was available in 2053 subjects.
Table 4: Comparison of Groups by Airway Fractal Dimensions and Peribronchial Emphysema

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (High AFD, Low Peribronchial Emphysema)</th>
<th>Group II (Low AFD, Low Peribronchial Emphysema)</th>
<th>Group III (High AFD, High Peribronchial Emphysema)</th>
<th>Group IV (Low AFD, High Peribronchial Emphysema)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.0 (8.4)</td>
<td>56.5 (8.4)</td>
<td>63.2 (8.5)</td>
<td>62.9 (8.5)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>831 (46.3%)</td>
<td>973 (56.0%)</td>
<td>664 (34.8%)</td>
<td>849 (49.3%)</td>
</tr>
<tr>
<td>African-American (%)</td>
<td>650 (36.2%)</td>
<td>698 (40.1%)</td>
<td>288 (15.1%)</td>
<td>361 (20.9%)</td>
</tr>
<tr>
<td>Body-mass-index kg/m²</td>
<td>28.1 (5.2)</td>
<td>30.6 (6.3)</td>
<td>26.7 (5.1)</td>
<td>28.2 (6.0)</td>
</tr>
<tr>
<td>Smoking Pack-years</td>
<td>38.5 (20.0)</td>
<td>40.9 (22.4)</td>
<td>48.1 (26.8)</td>
<td>51.7 (27.7)</td>
</tr>
<tr>
<td>Current Smokers (%)</td>
<td>1101 (61.4%)</td>
<td>1175 (67.6%)</td>
<td>651 (34.2%)</td>
<td>601 (34.9%)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.7 (0.7)</td>
<td>2.3 (0.7)</td>
<td>2.3 (1.0)</td>
<td>1.5 (0.8)</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>93.8 (15.9)</td>
<td>81.8 (20.2)</td>
<td>76.8 (27.9)</td>
<td>55.4 (26.2)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.6 (0.8)</td>
<td>3.2 (0.8)</td>
<td>3.6 (1.0)</td>
<td>2.9 (0.9)</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>94.8 (13.5)</td>
<td>89.1 (15.8)</td>
<td>92.2 (18.5)</td>
<td>80.4 (20.4)</td>
</tr>
</tbody>
</table>

All values expressed as mean (SD) unless specified otherwise. SD = Standard deviation. AFD = Airway Fractal Dimension.

FEV₁ = Forced expiratory volume in the first second. FVC = Forced vital capacity. GOLD = Global Initiative for Chronic Obstructive Lung Disease. CT = Computed tomography. HU = Hounsfield Units.
Figure 1: (A) Group definitions based on median values of Airway Fractal Dimensions (AFD) and percent peribronchial emphysema (PBE) estimated in 8030 COPD subjects. Participants were stratified into high and low above the median for each metric. (B) Distribution of severity of airflow obstruction by GOLD criteria in each group. (C) Kaplan-Meier survival curves for the 4 groups based on AFD and %peribronchial emphysema.

GOLD = Global Initiative for Chronic Obstructive Lung Disease.
Figure 2: Panel showing change in AFD sequentially with loss of small airway branches (Top Panel) and with progressive narrowing of airways (Bottom Panel). Changes shown are by simulation in a representative subject’s airways. 3D images projected as 2D for representation.
Figure 3: Panel showing segmented airway tree and Airway Fractal Dimension (AFD) in representative participants who are non-smoking normal, or with combinations of different degree of AFD and emphysema.
**Funding Source:** This study was supported by NHLBI grant K23HL133438 to SPB. The COPDGene study is supported by NIH Grant Numbers R01 HL089897 and R01 HL089856. MKH is supported by K24 HL138188. The COPDGene project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovion and GlaxoSmithKline.

**Author Contributions:**

*Study concept and design:* Bodduluri, Kizhakke-Puliyakote, Gerard and Bhatt

*Acquisition, analysis, or interpretation of data:* All authors

*Drafting of the manuscript:* Bodduluri, Kizhakke-Puliyakote, Gerard and Bhatt

*Critical revision of the manuscript for important intellectual content:* All authors

*Statistical analysis:* Bodduluri and Bhatt

*Study supervision:* All authors

**Acknowledgements**

See Supplemental Acknowledgments for details of COPDGene Investigators.

**Role of the funding source:** The funding source had no role in the design of this study, the analyses and interpretation of the data, or decision to submit results.
References


