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Radiographic Lung Volumes Predict Progression to COPD in Smokers with Preserved Spirometry in SPIROMICS

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TITLE PAGE

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ABSTRACT

The characteristics that predict progression to overt COPD in smokers without spirometric airflow obstruction are not clearly defined.

We conducted a post-hoc analysis of 849 current and former smokers (≥20 pack-years) with preserved spirometry from the SPIROMICS cohort who had baseline computed tomography (CT) scans of lungs and serial spirometry. We examined whether CT-derived lung volumes representing air trapping could predict adverse respiratory outcomes and more rapid decline in spirometry to overt COPD using mixed effect linear modeling.

Among these subjects with normal forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC), CT-measured residual volume to total lung capacity ratio (RV_{CT}/TLC_{CT}) varied widely, from 21% to 59%. Over 2.5±0.7 years of follow-up, subjects with higher RV_{CT}/TLC_{CT} had a greater differential rate of decline in FEV_1/FVC; those in the upper RV_{CT}/TLC_{CT} tertile had a 0.66% [95%CI=0.06%-1.27%] faster rate of decline per year compared to those in the lower tertile (P=0.015) regardless of demographics, baseline spirometry, respiratory symptoms score, smoking status (former versus current), or smoking burden (pack-years). Accordingly, subjects with higher RV_{CT}/TLC_{CT} were more likely to develop spirometric COPD (odds ratio=5.7 [95%CI=2.4-13.2] in upper versus lower RV_{CT}/TLC_{CT} tertile; P<0.001). Other CT indices of air trapping showed similar patterns of association with lung function decline; however, when all CT indices of air trapping, emphysema, and airway disease were included in the same model, only RV_{CT}/TLC_{CT} retained its significance.

Increased air trapping based on radiographic lung volumes predicts accelerated spirometry decline and progression to COPD in smokers without obstruction.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous disease that affects only a fraction of those who smoke tobacco.[1-4] Although nearly all smokers have

evidence of chronic airway inflammation,[5,6] only about 20% of them develop chronic airflow obstruction that meets the definition of COPD.[1] The origin of this widely variable susceptibility to develop COPD has not been well elucidated, and the ability to identify which smokers without airflow obstruction are at the highest risk for development of respiratory problems and lung function decline is of great interest for prognostication and intervention purposes.

Air trapping, defined as abnormally increased volume of air remaining in the lungs at the end of exhalation, is a manifestation of obstructive lung disease and is associated with increased dyspnea, reduced functional capacity, and higher mortality.[7,8] However, its consequence in those at risk for COPD but with preserved spirometry (normal FEV_1/FVC) demands further examination. A recent retrospective study of the United States Veterans Administration electronic health records showed abnormal lung volumes and air trapping, as measured by plethysmography, to be present in over 30% of smokers with preserved spirometry and to be associated with adverse respiratory outcomes and progression to spirometric COPD.[9] However, there has been no prospective validation of the utility of lung volumes as predictor of future lung function decline and progression to overt COPD.

In this study, we hypothesized that in individuals at risk for COPD due to smoking but with preserved spirometry, those with increased ratio of residual volume (RV) to total lung capacity (TLC), an index that represents air trapping, would have faster rates of lung function decline and progression to develop spirometric COPD. To examine this hypothesis, we used CT-derived measures of lung volumes and clinical data prospectively collected on current and former smokers without COPD from the National Heart, Lung, and Blood Institute-funded Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS),[10] and investigated whether CT measures of lung volumes representing air trapping could predict subsequent development of spirometric COPD and increased morbidity. We also examined whether other CT indices of air trapping, emphysema, and

airway disease had additional contributions towards the above outcomes beyond that from lung volumes.

METHODS

Study Design

The SPIROMICS multicenter observational study enrolled 2,981 participants from 2010 through 2015.[10] The study included persons 40 to 80 years of age who were either never-smoking healthy persons or current and former smokers who had a smoking history ≥20 pack-years, with or without a clinical diagnosis of obstructive lung disease. Participants were categorized using the Global Initiative on Obstructive Lung Disease (GOLD) staging system according to the results on spirometry performed before and after four inhalations each of albuterol at a dose of 90 μg per inhalation and ipratropium at a dose of 18 μg per inhalation.[11] Current and former smokers who had a concomitant diagnosis of asthma were not excluded. Respiratory symptoms, exacerbation history, exercise capacity by 6-minute walk distance (6-MWD) testing, and computed tomography (CT) scans of the lung were obtained, and subjects were followed for a target follow-up time of 3 years with planned annual serial spirometry and symptoms questionnaires, as previously described.[10,12] Lung volumes representing air trapping were measured from full inspiratory (TLC) and full expiratory (RV) CT imaging of lungs. Other CT indices of air trapping, emphysema, and airway disease were also measured as described below.

From the 849 current and former smokers with preserved spirometry (FEV_1/FVC ≥0.70 after bronchodilator use and FVC equal to or above the predicted lower limit of normal [≥LLN]),[13] complete data for this analysis were available for 814 subjects (**Figure 1**). CT-measured lung volumes with high confidence in their accuracy were available from 618 of the 814 subjects as described in **Supplemental Appendix** and shown in **Supplemental Figures S1** and **S2**. Using this cohort (described in **Supplemental Table S1**), we conducted a

post-hoc analysis to determine whether baseline radiographically-measured lung volumes representing air trapping (ratio of CT-measured RV to TLC or RV_{CT}/TLC_{CT}) could predict more rapid decline in spirometry to overt COPD and worse respiratory symptoms.

CT Indices of Lung Volumes, Air Trapping, Emphysema, and Small Airways

The detailed protocol and quality assessment of SPIROMICS CT scans have been described previously.[14] Briefly, SPIROMICS has an established quantitative CT lung assessment system (QCT-LAS), which includes scanner-specific imaging protocols for lung assessment at TLC and RV. Written breath-holding instructions were supplied to the CT technologists, who were instructed to coach the subject, as in a pulmonary function laboratory, to achieve both TLC and RV with a series of proceeding deep inspirations. To provide imaging speeds that allow proper breath-holds from subjects, only 64-detector rows or higher scanners were used.

In addition to RV_{CT}/TLC_{CT}, other CT indices of air trapping, including the percent of the lung voxels with attenuation <-856HU on the expiratory CT images (Exp_{-856})[15,16] and parametric response mapping of functional small airway disease (PRM^{fSAD})[17,18], were also used in the analysis. Moreover, measures of emphysema including the percent of the lung voxels on inspiratory CT images with attenuation < -950HU ($Insp_{-950}$) and parametric response mapping of emphysema (PRM^{EMPH})[17,18], and measures of airway disease including the average and thickest values for the square root of wall area of a hypothetical airway with 10mm internal perimeter (Pi10)[19] were also examined as additional predictors in the analysis.

Statistical and Data Analysis

The distribution of RV_{CT}/TLC_{CT} was computed and its correlations with airflow obstruction indices (FEV_1/FVC and FEV_1) were examined using the Pearson correlation test.

To control for age, sex, height, and weight covariates when examining the raw RV_{CT}/TLC_{CT} values, partial correlations corrected for covariates were derived and examined.[20] To examine these distributions in more details, airflow indices were partitioned in 5% increments, and summary statistics were calculated across each partition.

Outcome variables including spirometric indices, symptoms (Modified Medical Research Council Dyspnea Scale [mMRC], COPD Assessment Test [CAT], Saint George's Respiratory Questionnaire [SGRQ], and Short Form 12-item Survey [SF12]), the Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) index, exercise capacity (6-MWD test), and respiratory exacerbations (frequency and time to event) were examined longitudinally. Changes in the outcomes were calculated by subtracting the subsequent visits (V2, V3, or V4) outcome values from those of baseline visit (V1), and then analyzed using mixed effect modeling as described below.

Because there are no validated reference values for CT-measured lung volumes, we divided the subjects into three equal groups based on their RV_{CT}/TLC_{CT} to form distinct categories of low, intermediate, and high RV_{CT}/TLC_{CT}, with the assumption that low and high RV_{CT}/TLC_{CT} tertile groups would likely represent those subjects with normal and abnormal lung volumes, respectively. We used these tertile groups in the analysis as a categorical variable that would represent risk of progression to spirometric COPD.

The effects of RV_{CT}/TLC_{CT} (both as a continuous and as a categorical variable) on changes in outcomes were examined using mixed effect linear regression, with a nested random subject and study site effect, and fixed effect variables, including age, sex, height, weight, smoking status (current versus former), smoking burden (pack-years of smoking), corresponding baseline lung function or symptom or activity measurements (for example, baseline FEV_1/FVC when evaluating change in FEV_1/FVC as an outcome, or baseline

mMRC when evaluating change in mMRC as an outcome), and follow-up time to repeat outcome measurement as described in the **Supplementary Appendix**. Interaction models were fit with the inclusion of the main effect for (1) follow-up time and (2) smoking status (current versus former smoker), and their interactions with RV_{CT}/TLC_{CT} strata. To demonstrate statistical significance, P-values from mixed-effect linear regression modeling, as well as the 95% confidence intervals (95% CI) for comparisons of each RV_{CT}/TLC_{CT} category effect estimate to that of the reference value, were calculated.

The analysis of association between progression to spirometric COPD and RV_{CT}/TLC_{CT} was performed using mixed effect logistic regression modeling with a nested random time and site effect, and fixed effect variables including age, sex, height, weight, smoking status (former versus current smoking), and smoking burden (pack-years of smoking).

To examine the relevance of RV_{CT}/TLC_{CT} in the risk prediction model for COPD development, we performed receiver operating characteristic (ROC) analysis, and calculated its incremental contribution to the model beyond that of other covariates.

Cox proportional hazards regression modeling was used to analyze the association of RV_{CT}/TLC_{CT} and CT indices of air trapping with time to the first hospitalization. In addition, the association of those indices with number of severe respiratory exacerbations, as defined by number of emergency room and hospital admissions, were analyzed using mixed effect Poisson regression modeling to determine the incident rate ratios (IRR) of such events with consideration of follow-up time and study site.

We performed sensitivity analyses by simultaneous inclusion of variables that could act as confounders as additional terms in the regression models including hip-to-waist ratio and bronchodilator responsiveness (≥12% and ≥200 mL increase in FEV_1 after bronchodilator

administration). Separate sensitivity analyses were performed to evaluate the effect of presence or absence of respiratory symptoms (as measured by CAT questionnaire score of < versus ≥10) on associations of RV_{CT}/TLC_{CT} and other CT air trapping indices with lung function outcomes. Additional sensitivity analyses were also performed by excluding patients with specific characteristics that could act as confounders, including smoking status (current versus former smoker), obesity, or asthma separately.

RESULTS

Correlation between Baseline Lung Volumes and Airflow Indices

Among the 618 subjects with high concordance between VC_{CT} and SVC, baseline RV_{CT}/TLC_{CT} had weak to moderate inverse correlations with baseline FEV_1/FVC and FEV_1 (covariate-corrected correlations of 0.21 and 0.28, respectively; P<0.001) (**Figure 2**) (**Supplementary Table S2**). Nevertheless, RV_{CT}/TLC_{CT} had a wide distribution across normal ranges of these airflow indices spanning from 21% to 59%. This distribution corresponded to maximum coefficient of variations (standard deviation to mean ratio) of 19.3% and 20.5% across 5% (percent predicted) increments of FEV_1/FVC and FEV_1, respectively (**Figure 2**).

Association of Lung Volumes with Progression to Spirometric COPD

Follow-up spirometry was available in 496 out of 618 subjects with high VC_{CT} and SVC concordance. The median follow-up time from baseline spirometry (V1) to the last spirometry available was 2.7 years (interquartile range from 2.0 to 3.0 years and total range from 0.5 to 4.2 years; average follow-up time was 2.5±0.7 years). Among the 496 subjects with at least one follow-up spirometry, 295 had two and 157 had three follow-up spirometries (**Table 1)**. The average raw value of RV_{CT}/TLC_{CT} was 40%±7% for the entire cohort, and 33%±3%, 40%±2%, and 48%±4% for the low, intermediate, and high tertiles, respectively.

Overall, 16.7% of the 496 subjects progressed to meet the spirometric definition of COPD during the median 2.7 years of follow up (unadjusted proportions of 6.2%, 16.1%, and 27.7% for low, intermediate, and high RV_{CT}/TLC_{CT} groups) (**Table 1**).

During this follow-up period, and after adjustment for covariates (age, sex, height, weight, smoking status, smoking burden, and baseline FEV_1/FVC), FEV_1/FVC ratio declined in an RV_{CT}/TLC_{CT}-dependent manner such that a 10% higher baseline RV_{CT}/TLC_{CT} was associated with a 1.1% higher absolute decline in FEV_1/FVC over the follow-up period (P<0.001) (**Table 2** and **3** and **Figure 3A**). Accordingly, subjects with higher baseline RV_{CT}/TLC_{CT} were more likely to develop spirometric COPD (**Table 4**). For example, a 1% higher absolute RV_{CT}/TLC_{CT} value on baseline CT resulted in 10.8% higher likelihood of developing spirometric COPD during the follow-up period (OR [95%CI]=1.108 [1.056-1.162]; P<0.001), which translates to nearly tripling the likelihood of developing COPD for every 10% higher RV_{CT}/TLC_{CT} (OR [95%CI]=2.779 [1.721-4.486]; P<0.001).

To better understand the risk associated with developing COPD in smokers with preserved spirometry, we examined the likelihood of lung function decline to spirometric COPD for subjects in low, intermediate, and high tertiles of RV_{CT}/TLC_{CT}. We found that subjects with high RV_{CT}/TLC_{CT} had greater decline compared to those with intermediate RV_{CT}/TLC_{CT}, and those with intermediate RV_{CT}/TLC_{CT} had greater decline compared to those with low RV_{CT}/TLC_{CT} (P=0.005) (**Table 3** and **Figure 4**). Overall, subjects with high RV_{CT}/TLC_{CT} (≥42.7% absolute value) were nearly 6 times more likely to develop COPD compared to those with low RV_{CT}/TLC_{CT} (≤36.6% absolute value) over the follow-up period (OR [95%CI]=5.689 [2.446-13.228]; P<0.001) (**Table 4**). Furthermore, ROC analyses showed that inclusion of RV_{CT}/TLC_{CT} in the models improved the area under the curve (AUC) beyond the contribution of other covariates (including age and sex) (**Supplemental Table S3**).

The RV_{CT}/TLC_{CT} and follow-up time interaction analysis showed the rate of decline in FEV_1/FVC to be greater in those with high RV_{CT}/TLC_{CT} compared to those with low (or intermediate) RV_{CT}/TLC_{CT} (a differential 0.66% [95%CI: 0.06%-1.27%] increase in the rate of decline per year; P=0.015) (**Figure 3B** and **Supplemental Table S4**).

The changes in FEV_1 and FVC (or FEF_{25-75} and FEF_{75}) were not statistically significantly different between the RV_{CT}/TLC_{CT} strata during the follow-up period. However, the decline in FEV_1/FVC was at least in part due to a relative increase in FVC among those with high RV_{CT}/TLC_{CT} compared to those with low RV_{CT}/TLC_{CT} (**Tables 2** and **3** and **Figure 4**).

Smoking status (current versus former smoker) or burden (pack-years of smoking) did not significantly contribute to any of the observed associations, nor did the interaction term between smoking status and RV_{CT}/TLC_{CT} (**Supplemental Table S5**).

Association of Other CT Measures of Air Trapping, Emphysema, and Airway Disease with Progression to Spirometric COPD

Similar to RV_{CT}/TLC_{CT}, PRM^{fSAD} and Exp_{-856} showed wide but less varied distributions across FEV_1/FVC and FEV_1 (**Supplemental Figures S3** and **S4**). Among the 496 subjects with high VC_{CT} and SVC concordance and follow-up data, FEV_1/FVC declined in PRM^{fSAD}- and Exp_{-856}-dependent manners such that those in high and intermediate tertiles for either PRM^{fSAD} or Exp_{-856} had greater decline compared to those in the low tertile (P-values of 0.038 and 0.035 for PRM^{fSAD} and Exp_{-856}, respectively, for FEV_1/FVC decline) (**Supplemental Tables S6**, **S7**, and **S8**). Accordingly, those in the groups with higher PRM^{fSAD} or Exp_{-856} were more likely to progress to develop spirometric COPD (**Supplemental Table S9**). Similar to what was observed with lung volumes, smoking status (current versus former smoker) or burden (pack-years of smoking) did not significantly

contribute to any of the observed associations, nor did the interaction terms between smoking status and PRM^{fSAD} or Exp_{-856} (**Supplemental Table S10**).

Other CT indices of emphysema and airway disease examined, including PRM^{EMPH}, $Insp_{-950}$, and Pi10, were not associated with progression to spirometric COPD (**Supplemental Table S11**).

To better understand the importance of RV_{CT}/TLC_{CT} compared to other CT parameters, we included all CT-indices of air trapping, emphysema, and airway wall thickness in the same model along with RV_{CT}/TLC_{CT}. In this all-inclusive and fully adjusted model, RV_{CT}/TLC_{CT} (included as either a continuous or a categorical variable) was the only significant predictor for FEV_1/FVC decline and COPD development in smokers with preserved spirometry (**Supplemental Table S12**).

Association of Lung Volumes with Exercise Capacity, Symptoms, and Respiratory Exacerbations

Among the 496 subjects with high VC_{CT} and SVC concordance and follow-up data, the subjects with higher RV_{CT}/TLC_{CT} (intermediate and high tertiles) walked a shorter distance on their subsequent 6-MWD testing compared to those with low RV_{CT}/TLC_{CT} (P=0.041) (**Tables 2** and **3**). For example, subjects with high and intermediate RV_{CT}/TLC_{CT} had a differential 6-MWD decline of 15 m and 19 m, respectively, compared to those with low RV_{CT}/TLC_{CT}, reflecting an absolute decline in 6-MWD distance of 22 m to 30 m in those with higher RV_{CT}/TLC_{CT} (**Supplemental Table S13**).

Similarly, subjective assessments of physical activity as measured by SF12 and SGRQ questionnaires showed a higher decline in the self-described level of subject activity in those with high and intermediate RV_{CT}/TLC_{CT} compared to those with low RV_{CT}/TLC_{CT} although this effect was not statistically significant when measured by SGRQ activity score

(P=0.138) (**Tables 2** and **3**). Other CT indices of air trapping (PRM^{fSAD} or Exp_{-856}) were not associated with changes in exercise capacity (**Supplemental Tables S6** and **S7**).

Higher RV_{CT}/TLC_{CT} was statistically significantly associated with worsening respiratory symptom scores measured only by mMRC (P=0.031). Changes in symptoms measured by SGRQ and CAT, although in the hypothesized direction, were not statistically significant (**Tables 2** and **3**). The BODE index also showed a trend towards an RV_{CT}/TLC_{CT}-dependent worsening with higher RV_{CT}/TLC_{CT}, but this did not reach statistical significance (P=0.074). Other CT indices (PRM^{fSAD} or Exp_{-856}) were not associated with changes in respiratory symptoms (**Supplemental Tables S6** and **S7**).

The time and RV_{CT}/TLC_{CT} interaction analyses were not statistically significant with any of the measured exercise or symptoms score outcomes (**Supplemental Tables S4**).

Among the 618 subjects with high VC_{CT} and SVC concordance, a total of 36 subjects had severe respiratory exacerbation events (including emergency department and hospital admissions). Neither the number of those events nor the time to the first hospitalization was significantly different between the tertiles of RV_{CT}/TLC_{CT}, PRM^{fSAD}, or Exp_{-856} (**Supplemental Table S14**).

Sensitivity Analyses

Among the 496 subjects with high VC_{CT} and SVC concordance and follow-up data, 37.1% of patients were obese (BMI >30), 16.7% had asthma diagnoses, and 12.1% had bronchodilator responsiveness. Sensitivity analyses with exclusion of patients with obesity, asthma, or bronchodilator responsiveness did not change any of the observed associations with the exception of one of the outcomes (the continuous RV_{CT}/TLC_{CT} model of progression to COPD measured at V3) becoming non-significant (P=0.097) when obese subjects were excluded. Sensitivity analyses with simultaneous inclusion of bronchodilator responsiveness (in terms of FEV_1) and hip-to-waist ratio in the models did not affect any of the observed

associations except for change in 6-MWD test, which showed similar but a non-significant association (P=0.072). Inclusion of symptom score (CAT < or ≥10) in the models along with RV_{CT}/TLC_{CT} or other CT indices of air trapping (PRM^{fSAD} or Exp_{-856}) did not affect the observed associations.

Furthermore, use of lower limit of normal (LLN) criteria for diagnosis of COPD, instead of fixed ratio per GOLD criteria, produced similar associations between RV_{CT}/TLC_{CT} and outcomes (**Supplemental Tables S15, S16,** and **S17**).

Finally, sensitivity analysis with inclusion of all 814 subjects regardless of their VC_{CT} and SVC concordance did not affect the overall associations of RV/TLC with lung function outcomes.

DISCUSSION

In this longitudinal study of a prospective cohort of smokers at risk for COPD but with preserved spirometry, we found radiographically-measured RV to TLC ratio (RV_{CT}/TLC_{CT}) to vary widely across the normal ranges of spirometric indices used for COPD definition (FEV_1/FVC and FEV_1). We then explored this wide variance and found patients with higher RV_{CT}/TLC_{CT} to have greater decline in lung function at a faster rate, greater likelihood of developing spirometric COPD, and greater reduction in exercise capacity compared to those with lower RV_{CT}/TLC_{CT}. The relationship between higher RV_{CT}/TLC_{CT} and worse respiratory symptoms as measured by respiratory questionnaires reached statistical significance only across one of the three survey tools used. These findings were robust, as adjustment of analyses for several possible confounders, including smoking status (current versus former smoker), smoking burden (pack-years of smoking), obesity (including hip-to-waist ratio), concomitant asthma, respiratory symptoms score (score of < versus ≥10 on CAT questionnaire), or bronchodilator responsiveness, did not change the observed associations. Furthermore, CT indices of air trapping including PRM^{fSAD} and Exp_{-856} also showed similar

patterns of association with the FEV_1/FVC decline and progression to COPD. Remarkably, when all CT parameters of air trapping, emphysema, and airway disease were analyzed together in the same model, the RV_{CT}/TLC_{CT} was the only significant predictor for lung function decline and progression to spirometric COPD in smokers with preserved spirometry.

In a previous retrospective study of electronic health records from the Veterans Health Administration,[9] we found plethysmographically-measured RV/TLC, as well as other lung volume indices that represent air trapping (such as the ratio of functional residual capacity [FRC] to TLC), to predict morbidity and progression to COPD in smokers with preserved spirometry. The current study increases our confidence in those conclusions by providing prospective validation of the findings of that study, and expands our understanding of multi-dimensionality of susceptibility to develop COPD. Overall, these findings indicate the predictive usefulness of lung volume measurements, regardless of whether determined radiographically or physiologically, and argue for use of air trapping parameters for prognostication in those at risk for COPD.

Given the baseline differences in spirometric indices between those with higher and lower RV_{CT}/TLC_{CT} in this cohort, a possible explanation for the faster rate of lung function decline may simply be that those with higher RV_{CT}/TLC_{CT} had longer duration or higher amount of smoking, causing them to have more prolonged or more severe lung damage. However, the association of RV_{CT}/TLC_{CT} with progression to COPD was unaffected by adjustment for baseline lung function, smoking status (being former versus current smoker), or the amount of smoking (pack-years) in these unobstructed subjects with a minimum of 20 pack-years of smoking. Indeed, these data suggest that once at least 20 pack-years of smoking has been achieved, even smoking cessation does not affect the subsequent lung function decline in those unobstructed smokers who have developed air trapping. Overall, these findings suggest that distinct underlying biological mechanisms may be involved in

determining susceptibility of smokers to develop COPD as has been previously suggested in "the Dutch hypothesis",[21] and that lung volumes representing air trapping may provide early evidence for identifying the "susceptible" smokers.

An interesting finding in this study is the manner by which the FEV_1/FVC ratio declined in those with high RV_{CT}/TLC_{CT} to reach the threshold to be considered COPD (that is, FEV_1/FVC <0.70). Although the differential changes in FEV_1 or FVC across RV_{CT}/TLC_{CT} strata did not reach statistical significance, there appeared to be contributions from decline in FEV_1 and increase in FVC as seen in **Figure 4**. Our previous retrospective study of electronic health records from the Veterans Health Administration,[9] showed statistically significant change only in FVC (and no change in FEV_1) to contribute to the decline in FEV_1/FVC seen with higher RV/TLC and air trapping. Together, these findings may implicate increase in FVC as the important mechanism responsible for progression to spirometric COPD in the early stages of the disease. It is remarkable, however, that despite the trend of increases in FVC in those with higher RV_{CT}/TLC_{CT}, there was not an increasing trend in the expiratory time on spirometry, and in fact, the expiratory time was shorter in those with higher baseline RV_{CT}/TLC_{CT} and higher FVC on follow-up spirometry. These findings may indicate that regional loss of lung elastance with subsequent expansion of chest wall and increased TLC may contribute to the higher FVC and development of spirometric COPD.[9]

Our study has several limitations. First, although in some subjects, assessing lung volumes using CT imaging was challenging, the majority of subjects had accurate RV and TLC measurements as we demonstrated by the high concordance between radiographically- and physiologically-measured vital capacity. The cases of lung volume measurement inaccuracy by CT may be due to the challenges with breath-hold maneuvers during the full inspiratory and expiratory CT imaging. Remarkably, the strength of the associations of lung volumes representing air trapping with lung function decline and COPD development was so

robust that inclusion of all subjects versus stringent inclusion of only those with high VC_{CT} and SVC concordance did not affect the study findings. Second, only limited number of repeat spirometries and relatively short duration of follow-up were available from the SPIROMICS cohort. Nevertheless, it is indeed remarkable that statistically significant changes in lung function albeit being small were detected within the available follow-up duration. Lastly, while we found higher RV_{CT}/TLC_{CT} to be associated with faster decline in lung function and exercise capacity over the follow-up period, we found statistically significant worsening of symptoms via only one of the three respiratory questionnaires used in SPIROMICS. However, other questionnaires did show a similar albeit non-significant trend towards worsening symptoms with higher RV_{CT}/TLC_{CT}. This may be due to the relatively short duration of follow-up available and/or the limited sensitivity of the survey tools that were used to assess the symptoms. A longer follow-up period may then provide further convincing evidence regarding the symptoms progression.

In conclusion, in smokers with preserved spirometry, radiographic lung volumes representing air trapping prospectively predict higher rate of spirometry decline and COPD development, and may be predictive of more rapid decline in exercise capacity and respiratory symptoms associated with COPD. Further investigation of underlying biological mechanisms involved in development of air trapping should be useful in understanding the susceptibility to develop COPD at its early stages.

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FIGURE LEGEND

Figure 1- Subject Flow. Abbreviations: CT= computed tomography; SVC= slow vital capacity; VC_{CT}= CT-measured vital capacity; RV_{CT}/TLC_{CT}= CT-measured residual volume to total lung capacity ratio.

Figure 2- Correlation between RV_{CT}/TLC_{CT} and FEV_1/FVC or FEV_1 in smokers with preserved spirometry. Relationship between CT-measured RV/TLC (RV_{CT}/TLC_{CT}) and FEV_1/FVC (% predicted), or FEV_1 (% predicted). Boxplots show the distribution of RV_{CT}/TLC_{CT} (raw value) by 5% increments in FEV_1/FVC % predicated (Panel **A**), and 5% increments in FEV_1 % predicated (Panel **B**). Subjects were stratified into tertiles of RV_{CT}/TLC_{CT} represented by green, blue, and magenta for low, intermediate, and high RV_{CT}/TLC_{CT} tertiles, respectively. The black line represents the regression line for all the points. Abbreviations- CT: computed tomography; TLC: total lung capacity; RV: residual volume; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Figure 3- Comparison of Change in Spirometry from Different SPIROMICS Visits Across CT-measured RV/TLC (RV_{CT}/TLC_{CT}) Strata. Line graphs of FEV_1/FVC values predicted from mixed-effect regression modeling ("fitted values") through time across RV_{CT}/TLC_{CT} strata. Subjects were stratified into tertiles of RV_{CT}/TLC_{CT} represented by green, blue, and magenta for low, intermediate, and high RV_{CT}/TLC_{CT} tertiles, respectively. The tick marks on the x-axes represent the time that each spirometry was performed during the course of the study. Panel A shows the change in FEV_1/FVC (predicted from the main model) and panel B shows the difference in rate of FEV_1/FVC change per year (predicted from the spirometry follow-up time interaction model). Abbreviation: FEV_1= forced expiratory volume in 1 second; FVC= forced vital capacity.

Figure 4- Comparison of Change in Airflow Indices on Follow-up Spirometry Across CT-measured RV/TLC (RV_{CT}/TLC_{CT}) Strata. Graphs represent means and 95% confidence intervals for change in airflow indices across RV_{CT}/TLC_{CT} strata relative to the reference group (subjects in the lowest tertile of RV_{CT}/TLC_{CT}) from mixed effect linear

regression modeling with adjustment for age, sex, height, weight, smoking status (former versus current), baseline lung function, and time to follow-up spirometry. Subjects were stratified into tertiles of RV_{CT}/TLC_{CT} represented by green, blue, and magenta for low, intermediate, and high RV_{CT}/TLC_{CT} tertiles, respectively. Abbreviation: Ref= reference value; FEV_1= forced expiratory volume in 1 second; FVC= forced vital capacity; FEF_{25-75}= maximum airflow at mid-lung volume; FEF_{75}= maximum airflow after 75% of lung volume exhaled.

TABLES

Table 1- Characteristics of smoker subjects with preserved spirometry who had follow-up spirometry.

Characteristics	All Subjects	Subjects with Low RV_{CT}/TLC_{CT}	Subjects with Intermediate RV_{CT}/TLC_{CT}	Subjects with High RV_{CT}/TLC_{CT}	P-value (ANOVA)
Demographics					
Number Who Had Follow-up Spirometry (N)	496	162	168	166	
Age (years)	61.1±9.6	56.4±8.9	60.7±9.5	66.0±7.9	<0.001
Sex [Female n (%)]	261 (52.6%)	73 (45.1%)	90 (53.6%)	98 (59.0%)	0.038
Height (cm)	169.4±9.2	170.6±9.3	169.7±9.1	167.9±9.1	0.021
BMI (kg/m^2)	28.9±5.1	29.4±4.7	28.7±5.2	28.6±5.3	0.329
Years of Follow-up	2.5±0.7	2.4±0.7	2.5±0.6	2.6±0.6	0.079
Current Smoker [n (%)]	232 (46.8%)	86 (53.1%)	75 (44.6%)	71 (42.8%)	0.138
Smoking History (pack-years)	43.4±23.4	40.5±26.1	43.1±21.1	46.5±22.6	0.065
Baseline Spirometric Indices					
FEV_1 (L)	2.81±0.69	3.13±0.69	2.80±0.60	2.50±0.63	<0.001
FEV_1 (% predicted)	98±12	102±12	97±12	95±12	<0.001
FVC (L)	3.63±0.89	3.97±0.91	3.64±0.80	3.29±0.84	<0.001
FVC (% predicted)	97±12	100±12	97±12	94±12	<0.001
FEV_1/FVC (%)	77±5	79±5	77±4	76±5	<0.001
FEV_1/FVC (% predicted)	100±6	101±7	100±6	100±6	0.089
FEF_{25-75} (L)	2.68±0.98	3.22±1.05	2.59±0.84	2.25±0.77	<0.001
FEF_{25-75} (% predicted)	107±34	117±38	103±29	101±33	<0.001
FEF_{75} (L)	0.97±0.47	1.21±0.53	0.92±0.38	0.78±0.36	<0.001
Expiratory Time on Spirometry (s)	9.66±3.43	9.62±3.38	10.10±3.69	9.25±3.16	0.077
Reversibility in FEV_1 (mL)	160±143	154±142	158±132	166±154	0.769
Reversibility in FEV_1 (%)	6±6	5±5	6±5	7±7	0.007
Bronchodilator responsiveness by FEV_1 [n (%)]	60 (12.1%)	12 (7.4%)	20 (11.9%)	28 (16.9%)	0.031
SVC (L)	3.69±0.94	4.04±0.96	3.70±0.83	3.32±0.89	<0.001

IC (L)	2.80±0.72	3.02±0.72	2.82±0.67	2.56±0.70	<0.001
IRV (L)	1.91±0.67	2.08±0.70	1.92±0.64	1.72±0.61	<0.001
Baseline CT Indices					
TLC_{CT} (L)	4.73±1.08	4.86±1.09	4.74±1.06	4.58±1.08	0.062
RV_{CT} (L)	1.88±0.50	1.59±0.39	1.87±0.43	2.17±0.51	<0.001
RV/TLC_{CT} (%)	40±7	33±3	40±2	48±4	<0.001
VC_{CT} (L)	2.84±0.76	3.27±0.75	2.86±0.65	2.41±0.62	<0.001
Average Pi10	3.701±0.082	3.692±0.083	3.697±0.080	3.715±0.083	0.030
Thickest Pi10	3.815±0.114	3.809±0.112	3.806±0.101	3.829±0.126	0.142
PRM^{EMPH}	0.35±1.07	0.22±0.80	0.25±0.65	0.59±1.51	0.002
PRM^{fSAD}	6.93±6.22	3.33±3.10	6.02±4.79	11.25±7.14	<0.001
Exp_{-856}	6.46±6.03	3.11±2.92	5.67±4.52	10.54±7.19	<0.001
$Insp_{-950}$	1.82±2.04	1.91±2.36	1.69±1.51	1.88±2.16	0.580
Activity Levels and Symptom Scores					
6-MWD (m)	442.1±90.6	453.2±89.2	442.5±92.3	430.7±89.5	0.080
BODE Index	0.40±0.76	0.36±0.69	0.44±0.84	0.39±0.74	0.609
CAT Score	10.9±8.2	9.7±7.0	12.0±8.6	10.79±8.79	0.032
mMRC	0.71±0.81	0.71±0.84	0.74±0.86	0.68±0.75	0.812
SGRQ Total Score	23.5±18.8	21.5±16.0	25.9±20.6	23.1±19.4	0.116
SGRQ Symptom Score	35.5±25.7	33.2±23.5	38.1±27.8	35.3±25.6	0.235
SGRQ Activity Score	32.9±23.3	30.9±21.1	35.8±25.4	31.9±23.1	0.147
SGRQ Impact Score	14.9±16.7	12.6±13.2	17.0±18.2	15.2±18.0	0.068
SF12 Physical Component	51.1±6.3	51.7±5.8	50.5±7.1	51.0±6.0	0.221
SF12 Physical Functioning	50.8±7.0	51.4±6.3	50.0±7.5	50.9±7.0	0.181
Follow-up Spirometry §					
Age at Follow-up Spirometry (years)	63.2±9.8	58.3±9.0	62.8±9.7	68.3±7.8	<0.001
Height at Follow-up Spirometry (cm)	169.0±9.9	169.8±11.3	169.5±8.9	167.6±9.3	0.098
FEV_1 (L)	2.69±0.69	3.00±0.68	2.67±0.61	2.40±0.64	<0.001
FEV_1 (% predicted)	96±14	100±12	95±14	94±14	<0.001
FVC (L)	3.57±0.90	3.87±0.90	3.57±0.84	3.28±0.87	<0.001

FVC (% predicted)	98±14	100±13	97±14	97±16	0.133
FEV_1/FVC (%)	75±6	78±5	75±6	73±6	<0.001
FEV_1/FVC (% predicted)	98±8	100±7	98±8	97±8	<0.001
FEF_{25-75} (L)	2.41±1.02	2.98±1.06	2.31±0.89	1.96±0.82	<0.001
FEF_{25-75} (% predicted)	98±34	108±32	94±31	91±35	<0.001
FEF_{75} (L)	0.83±0.46	1.07±0.50	0.79±0.41	0.65±0.34	<0.001
Expiratory Time on Spirometry (s)	11.03±4.82	10.59±4.51	11.37±4.69	11.11±5.20	0.328
Number of Subjects Who Progressed to Spirometric COPD at Follow-up Visits					
Visit 2 [n (%)]	58 (11.7%)	9 (5.6%)	23 (13.7%)	26 (15.7%)	0.010
Visit 3 [n (%)]	62 (21.0%)	7 (8.8%)	19 (18.5%)	36 (32.1%)	<0.001
Visit 4 [n (%)]	34 (21.4%)	6 (13.6%)	14 (25.5%)	14 (23.3%)	0.329
Last Follow-up [n (%)]	83 (16.7%)	10 (6.2%)	27 (16.1%)	46 (27.7%)	<0.001
After One Years [n (%)]	58 (11.7%)	9 (5.6%)	23 (13.7%)	26 (15.7%)	0.010
After Two Years [n (%)]	59 (13.4%)	7 (5.2%)	23 (15.1%)	29 (19.1%)	0.001
After Three Years [n (%)]	53 (19.6%)	6 (8.6%)	19 (19.0%)	28 (28.0%)	0.006

Footnote: Data from subjects with follow-up spirometry from each CT-measured RV/TLC (RV_{CT}/TLC_{CT}) tertile are presented as mean ± standard deviation or number of patients with positive value for the variable (n) out of the total number of patients (N) and percentage of patients (%). **§** At least one follow-up spirometry was available for a subgroup of the patients. Reference equations: measures of pulmonary function and percent predicted of normal values were calculated using Crapo predicted formulas.[22-24] Bronchodilator responsiveness was defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilators administration. Abbreviations: BMI=body mass index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; SVC=slow vital capacity; IC=inspiratory capacity; IRV=inspiratory reserve volume; CT=computed tomography; TLC_{CT}=CT-measured total lung capacity; RV_{CT}=CT-measured residual volume; VC_{CT}=CT-measured vital capacity; Average Pi10= the average for the square root of wall area of a hypothetical airway with 10mm internal perimeter ;

Thickest Pi10= the thickest values for the square root of wall area of a hypothetical airway with 10mm internal perimeter ; PRM^{EMPH}=parametric response mapping of functional small airway disease as measures of emphysema; PRM^{fSAD}=parametric response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; $Insp_{-950}$=percent of the lung voxels on inspiratory CT images with attenuation < -950 Hounsfield Units; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

Table 2- Associations of changes in lung function or symptoms with CT-measured RV/TLC (RV_{CT}/TLC_{CT}).

Outcome Parameters	Parameter Estimate for RV_{CT}/TLC_{CT} (%)	95% CI	P-value
FEV_1 (mL)	-1.98	-4.92 to 0.98	0.193
FVC (mL)	1.64	-2.43 to 5.81	0.436
FEV_1/FVC (%)	**-0.11**	**-0.17 to -0.06**	**<0.001**
FEF_{25-75} (mL)	**-7.72**	**-13.94 to -1.56**	**0.015**
FEF_{75} (mL)	**-3.91**	**-7.30 to -0.55**	**0.024**
Expiratory Time (s)	-0.002	-0.045 to 0.041	0.927
6-MWD (m)	-0.75	-1.82 to 0.31	0.170
BODE Index	**0.012**	**0.001 to 0.024**	**0.040**
CAT Score	0.006	-0.070 to 0.082	0.879
mMRC	0.008	-0.001 to 0.018	0.098
SGRQ Total Score	0.046	-0.108 to 0.204	0.566
SGRQ Symptom Score	-0.038	-0.285 to 0.228	0.768
SGRQ Activity Score	0.17	-0.03 to 0.37	0.098
SGRQ Impact Score	-0.001	-0.146 to 0.145	0.984
SF12 Physical Component	-0.04	-0.10 to 0.02	0.163
SF12 Physical Functioning	-0.07	-0.14 to 0.01	0.074

Footnote: Association of changes in lung function and symptoms outcomes with RV_{CT}/TLC_{CT} were estimated using mixed-effect linear regression models with adjustment for age, sex, height, weight, smoking status, smoking burden, and random effects from length of follow-up and study sites. Abbreviations: CI=confidence interval; CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test;

mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

*P-values are from mixed-effect linear regression modeling with a nested random subject and site effect.

Table 3- Associations of changes in lung function or symptoms with CT-measured RV/TLC (RV_{CT}/TLC_{CT}) strata.

Outcome Parameters	RV_{CT}/TLC_{CT} Strata	Differences in estimates	95% CI	P-value *
FEV_1 (mL)				
	High	-20.2	-66.8 to 26.3	
	Intermediate	-23.7	-65.2 to 18.5	0.525
	Low	--	--	
FVC (mL)				
	High	29.3	-35.1 to 94.5	
	Intermediate	4.6	-53.9 to 62.7	0.623
	Low	--	--	
FEV_1/FVC (%)				
	High	**-1.43**	**-2.31 to -0.57**	
	Intermediate	**-0.91**	**-1.69 to -0.12**	**0.005**
	Low	--	--	
FEF_{25-75} (mL)				
	High	-86.2	-185.5 to 12.2	
	Intermediate	-77.4	-165.7 to 11.4	0.164
	Low	--	--	
FEF_{75} (mL)				
	High	-53.2	-107.8 to 1.0	
	Intermediate	-42.7	-91.7 to 6.7	0.127
	Low	--	--	
Expiratory Time (s)				
	High	0.13	-0.55 to 0.81	
	Intermediate	0.60	-0.02 to 1.21	0.120
	Low	--	--	
6-MWD (m)				
	High	**-15.4**	**-32.2 to 1.2**	
	Intermediate	**-19.4**	**-34.6 to -4.2**	**0.041**
	Low	--	--	
BODE Index				
	High	0.20	0.02 to 0.39	
	Intermediate	0.16	-0.01 to 0.32	0.074
	Low	--	--	
CAT Score				
	High	-0.007	-1.208 to 1.202	
	Intermediate	-0.019	-1.133 to 1.089	0.999
	Low	--	--	
mMRC				
	High	**0.175**	**0.025 to 0.327**	
	Intermediate	**0.172**	**0.033 to 0.311**	**0.031**
	Low	--	--	
SGRQ Total Score				
	High	1.68	-0.72 to 4.12	
	Intermediate	0.18	-2.05 to 2.45	0.312
	Low	--	--	
SGRQ Symptom Score				
	High	1.99	-1.84 to 6.02	
	Intermediate	1.23	-2.33 to 4.88	0.604
	Low	--	--	
SGRQ Activity Score				
	High	3.28	0.10 to 6.50	
	Intermediate	1.49	-1.51 to 4.45	0.138
	Low	--	--	
SGRQ Impact Score				
	High	0.99	-1.31 to 3.32	
	Intermediate	0.34	-1.77 to 2.47	0.692

	Low	--	--	
SF12 Physical Component				
	High	-0.74	-1.72 to 0.20	
	Intermediate	-0.67	-1.56 to 0.19	0.231
	Low	--	--	
SF12 Physical Functioning				
	High	**-1.39**	**-2.58 to -0.26**	
	Intermediate	**-1.33**	**-2.39 to -0.30**	**0.022**
	Low	--	--	

Footnote: Association of changes in lung function and symptoms outcomes with RV_{CT}/TLC_{CT} strata were estimated using mixed-effect linear regression models with adjustment for age, sex, height, weight, smoking status, smoking burden, and random effects from length of follow-up time and study site. Abbreviations: CI= confidence interval; CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

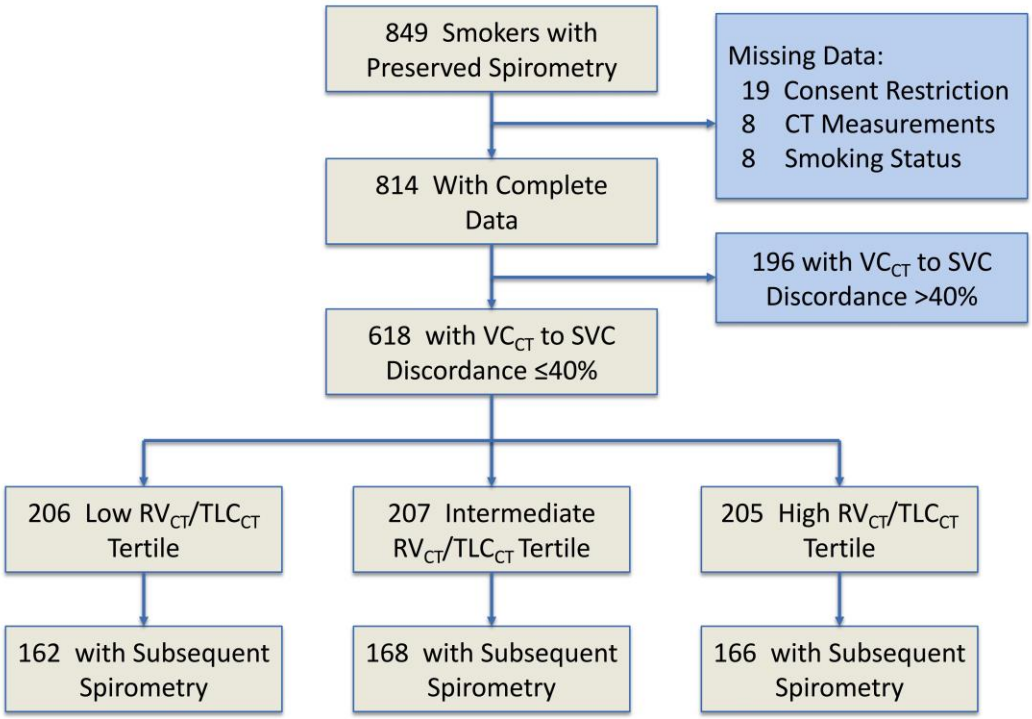
*P-values are from mixed-effect linear regression modeling with a nested random subject and site effect.

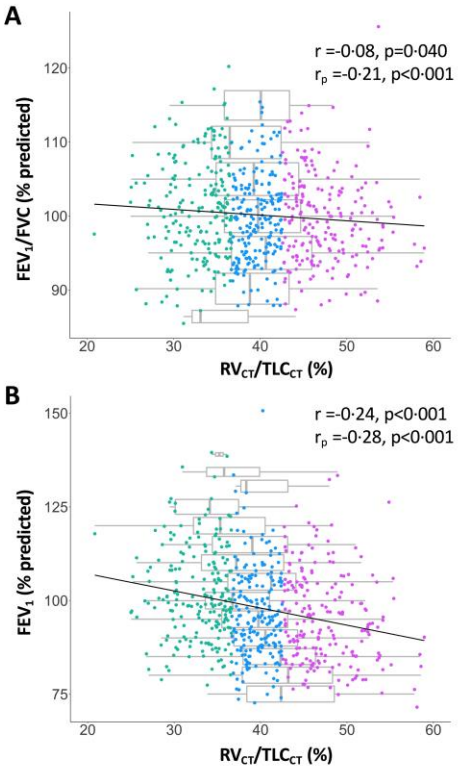
Table 4- Association of spirometric COPD development with CT-measured RV/TLC (RV_{CT}/TLC_{CT}).

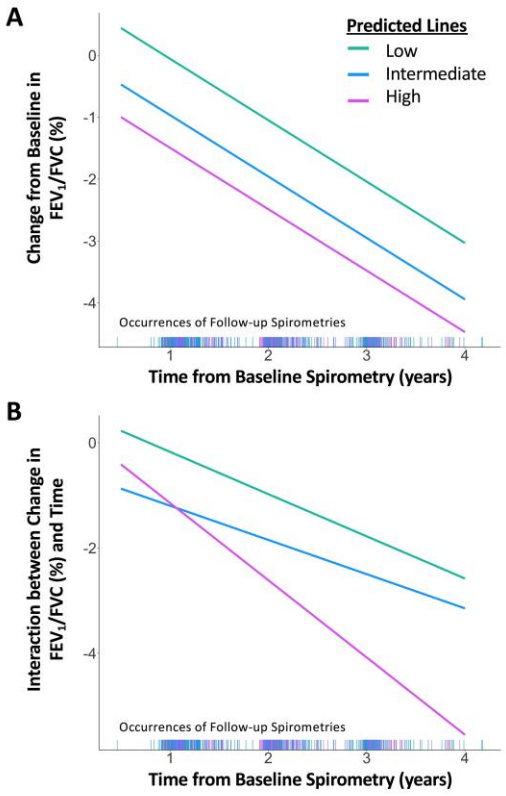
Development of Spirometric COPD				
RV_{CT}/TLC_{CT}	Spirometric COPD Progression at V2	Spirometric COPD Progression at V3	Spirometric COPD Progression at V4	Spirometric COPD Progression on Last Follow-up §
N	496	295	157	496
Continuous model				
RV_{CT}/TLC_{CT} (%)	**1.081 [1.028-1.136] P=0.002**	**1.091 [1.034-1.151] P=0.001**	1.048 [0.971-1.130] P=0.230	**1.108 [1.056-1.162] P<0.001**
Categorical model				
High RV_{CT}/TLC_{CT}	**3.178 [1.296-7.794] P=0.012**	**4.854 [1.832-12.860] P=0.001**	1.749 [0.460-6.647] P=0.412	**5.689 [2.446-13.228] P<0.001**
Intermediate RV_{CT}/TLC_{CT}	**2.763 [1.183-6.452] P=0.019**	2.420 [0.921-6.361] P=0.073	2.955 [0.822-10.625] P=0.097	**2.966 [1.298-6.775] P=0.010**
Low RV_{CT}/TLC_{CT} (Reference)	--	--	--	--

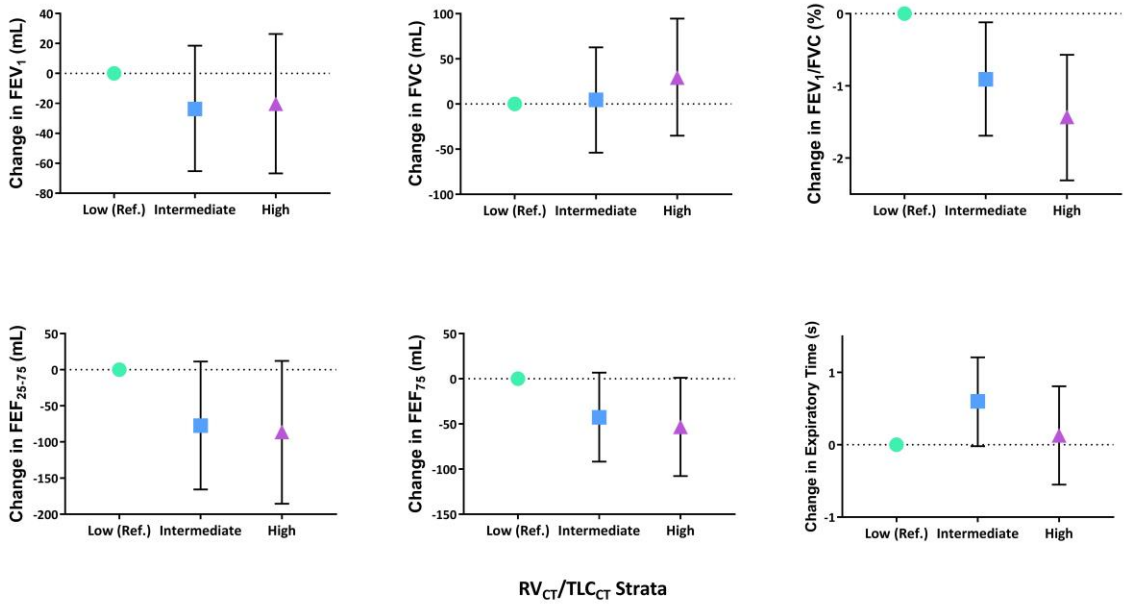
Footnote: Association of development of spirometric COPD with RV_{CT}/TLC_{CT} was estimated using mixed effect logistic regression models with adjustment for age, sex, height, weight, smoking status, smoking burden, and random effects from length of follow-up and study sites. The models odds ratio (OR) with 95% confidence intervals and P-values are shown in the table. P-values are from mixed effect logistic regression with random effect. Significant associations are shown in bold. **§** Follow-up spirometry from the last available post-bronchodilator spirometry from any of the V2, V3, or V4

visits. Abbreviations: CT= computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio.


849 Smokers with Preserved Spirometry
Missing Data:
19 Consent Restriction
8 CT Measurements
8 Smoking Status
814 With Complete Data
196 with VC_{CT} to SVC Discordance >40%
618 with VC_{CT} to SVC Discordance ≤40%
206 Low RV_{CT}/TLC_{CT} Tertile
207 Intermediate RV_{CT}/TLC_{CT} Tertile
205 High RV_{CT}/TLC_{CT} Tertile
162 with Subsequent Spirometry
168 with Subsequent Spirometry
166 with Subsequent Spirometry


A
r =-0·08, p=0·040
r_p =-0·21, p<0·001
FEV_1/FVC (% predicted)
120
110
100
90
20
30
40
50
60
RV_{CT}/TLC_{CT} (%)
B
r =-0·24, p<0·001
r_p =-0·28, p<0·001
FEV_1 (% predicted)
150
125
100
75
20
30
40
50
60
RV_{CT}/TLC_{CT} (%)


A
Predicted Lines
Low
Intermediate
High
Change from Baseline in FEV1/FVC (%)
0
-1
-2
-3
-4
Occurrences of Follow-up Spirometries
1
2
3
4
Time from Baseline Spirometry (years)
B
Interaction between Change in FEV1/FVC (%) and Time
0
-2
-4
Occurrences of Follow-up Spirometries
1
2
3
4
Time from Baseline Spirometry (years)


Change in FEV_1 (mL)
40
20
0
-20
-40
-60
-80
Low (Ref.) Intermediate High
Change in FVC (mL)
100
50
0
-50
-100
Low (Ref.) Intermediate High
Change in FEV_1/FVC (%)
0
-1
-2
Low (Ref.) Intermediate High
Change in FEF_{25-75} (mL)
50
0
-50
-100
-150
-200
Low (Ref.) Intermediate High
Change in FEF_{75} (mL)
50
0
-50
-100
-150
Low (Ref.) Intermediate High
Change in Expiratory Time (s)
1
0
-1
Low (Ref.) Intermediate High
RV_{CT}/TLC_{CT} Strata

Supplementary Appendix

Radiographic Lung Volumes Predict Progression to COPD in Smokers with Preserved Spirometry in SPIROMICS

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3. Detailed Methods and Data Analysis

CT Indices of Lung Volumes, Air Trapping, Emphysema, and Small Airways

The detailed protocol and quality assessment of SPIROMICS CT scans have been described previously.[1] Briefly, SPIROMICS has an established quantitative CT lung assessment system (QCT-LAS), which includes scanner-specific imaging protocols for lung assessment at TLC and RV. Written breath-holding instructions were supplied to the CT technologists, who were instructed to coach the subject, as in a pulmonary function laboratory, to achieve both TLC and RV with a series of proceeding deep inspirations. To provide imaging speeds that allow proper breath-holds from subjects, only 64-detector rows or higher scanners were used.

CT indices of air trapping, including the percent of the lung voxels with attenuation <-856HU on the expiratory CT images (Exp_{-856})[2,3] and parametric response mapping of functional small airway disease (PRM^{fSAD})[4,5], were used in the analysis as replacement predictors for RV_{CT}/TLC_{CT}.

In addition, measures of emphysema including the percent of the lung voxels on inspiratory CT images with attenuation < -950HU ($Insp_{-950}$) and parametric response mapping of emphysema (PRM^{EMPH})[4,5], and measures of airway disease including the average and thickest values for the square root of wall area of a hypothetical airway with 10mm internal perimeter (Pi10)[6] were also examined as additional predictors in the models.

Data Analysis

Initial assessment of CT-measured lung volumes showed that in a few subjects, the CT-measured RV (RV_{CT}) values were greater than the TLC (TLC_{CT}) values, resulting CT-

measured vital capacity (VC_{CT}) values less than zero, which suggested that these subjects had performed poorly on their full expiratory and/or inspiratory breath-hold maneuvers.

While the lung volumes measurements with VC_{CT} values less than zero were clearly erroneous, the possible measurement error in other VC_{CT} values that were not negative but were small remained questionable with concerns on whether those subjects really had low VC or their measurements were erroneous. Various approaches were considered and tested, including one to only include the subjects whose TLC_{CT}, RV_{CT}, or VC_{CT} values on the subsequent (second) visit CT scan, done about a year later, changed less than 10% or 20% from the first CT scan values (**Supplemental Figure S1**). At the end, the best approach seemed to be an approach to use correlation of CT-measured VC with physiologically-measured VC. As presented in **Supplemental Figure S2**, various discordant cutoffs were entertained, and at the end, an arbitrary cutoff of 40% concordance was chosen based on the fact that this cutoff generated a 90% correlation between the measurements of remaining subjects.

To increase our confidence in CT-measured lung volumes, we examined the distributions of CT-measured vital capacity (VC_{CT}), calculated from CT-measured metrics of TLC (TLC_{CT}) and RV (RV_{CT}), and spirometrically-measured slow VC (SVC). Studies have shown that CT-measured lung volumes, even though obtained in the supine position, could closely approximate plethysmographically-measured lung volumes, which are routinely obtained in seated position.[7-10] Thus, to optimize the accuracy of TLC_{CT} and RV_{CT} measurements and eliminate uninterpretable results, we examined various thresholds of concordance between VC_{CT} and SVC measurements for each subject, which identified subgroups with high levels of correlation between the overall distributions of VC_{CT} and SVC as described in **Supplemental Appendix** and shown in **Supplemental Figure S2**. Based on that examination, subjects with >40% discordance between their individual VC_{CT} and SVC

measurements were excluded from the analysis. To understand the effect of this exclusion, we also performed a sensitivity analysis that included all subjects regardless of their VC_{CT} and SVC discordance.

The distribution of CT-measured RV/TLC (RV_{CT}/TLC_{CT}) was computed and its correlation with airflow obstruction indices (FEV_1/FVC and FEV_1) were examined using the Pearson correlation test. To control for age, sex, and height covariates when examining the raw RV_{CT}/TLC_{CT} values, partial correlations corrected for covariates were derived and examined.[11] To examine these distributions in more details, airflow indices were partitioned in 5% increments, and summary statistics were calculated across each partition.

Outcome variables including spirometric indices, symptoms (Modified Medical Research Council Dyspnea Scale (mMRC), COPD Assessment Test (CAT), Saint George's Respiratory Questionnaire (SGRQ), and Short Form 12-item Survey (SF12)), the Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) index, exercise capacity (6-Minute Walk Distance (6-MWD) test), and respiratory exacerbations (frequency and time to event) were examined longitudinally. Changes in the outcomes were calculated by subtracting the subsequent visits (V2, V3, or V4) outcome values from those of baseline visit (V1) values, and then analyzed using mixed effect modeling as described below.

Because there are no validated reference values for CT-measured lung volumes, we divided the subjects into three equal groups based on their RV_{CT}/TLC_{CT} to form distinct categories of low, intermediate, and high RV_{CT}/TLC_{CT}, with the assumption that low and high RV_{CT}/TLC_{CT} tertile groups would likely represent those subjects with normal and abnormal lung volumes, respectively. We used these tertile groups in the analysis as a categorical variable that would represent risk of progression to spirometric COPD.

The effects of RV_{CT}/TLC_{CT} (as a continuous or a categorical variable) on changes in outcomes were examined using mixed effect linear regression, with a nested random subject and site effect, and fixed effect variables, including age, sex, height, weight, smoking status (current versus former), smoking burden (pack-years of smoking), baseline lung function (FEV_1/FVC), and follow-up time to repeat outcome measurement as described below. Interaction models were fit with the inclusion of the main effect for follow-up time or smoking status (current versus former smoker), and their interaction with RV_{CT}/TLC_{CT} strata. To demonstrate statistical significance, P-values from mixed-effect linear regression modeling with a nested random subject and site effect, as well as the 95% confidence intervals (95% CI) for comparisons of each RV_{CT}/TLC_{CT} category effect estimate to that of the reference value, were calculated.

Mixed-effect linear models accounting for repeated measures, with a nested random subject and site effects and a covariance structure, were used to evaluate the impact of RV_{CT}/TLC_{CT} strata on the outcomes. The covariance structure assigned is the standard variance component matrix where a distinct variance component is assigned to each effect for the matrix. RV_{CT}/TLC_{CT} was treated initially as a continuous variable, and then as a categorical (3-level) variable, in all regression models. Baseline measurement and time were controlled for in the models. The main effects model for this design was:

$$Y_{ijkt} = \mu + \tau_k + \beta_{ij} + \theta_t + \varepsilon_{ijkt}$$

where Y_{ijkt} is the change in the outcome measure (change from baseline V1 to follow-up visits) for subject *i* at center *j* in RV_{CT}/TLC_{CT} stratum k (or for value k of RV_{CT}/TLC_{CT} in the continuous model) at time *t*, μ is the intercept, τ is the effect of RV_{CT}/TLC_{CT} stratum/value *k*, β is the effect of subject *i* in center *j*, θ is the effect of time *t*, and the ε_{ijkt} are independent and identically distributed Gaussian random errors. The tables that present the regression results

(**Tables 2** and **3** and other Supplemental Tables) report the mixed model effect estimates (and confidence interval) along with the associated P-values. Additional terms were included in the model for covariate adjustment including age, sex, height, weight, smoking status (former versus current smoking), smoking burden (pack-years of smoking), and baseline lung function (FEV_1/FVC).

When there was a statistically significant effect of RV_{CT}/TLC_{CT} on an outcome, the RV_{CT}/TLC_{CT} by time interaction was assessed to determine whether the RV_{CT}/TLC_{CT} effect was consistent across the follow-up times. The interaction model for this design was:

$$Y_{ijkt} = \mu + \tau_k + \beta_{ij} + \theta_t + \tau\theta_{kt} + \varepsilon_{ijkt}$$

where $\tau\theta_{kt}$ is the interaction effect of RV_{CT}/TLC_{CT} stratum/value *k* at time *t*, and the other terms are as defined above.

Similarly, the RV_{CT}/TLC_{CT} by smoking status interaction was assessed to determine whether the RV_{CT}/TLC_{CT} effect was consistent in former versus current smokers. The interaction model for this design was:

$$Y_{ijkt} = \mu + \tau_k + \beta_{ij} + \theta_t + \tau\zeta_{ks} + \varepsilon_{ijkts}$$

where $\tau\zeta_{ks}$ is the interaction effect of RV_{CT}/TLC_{CT} stratum/value *k* for smoking status *s*, and the other terms are as defined above.

For analysis of development of spirometric COPD, because the time from baseline (V1) spirometry to any of the follow-up visits spirometry (V2, V3, V4, or last visit) did not reflect the time at which the subject actually developed spirometric COPD, year increments to follow-up spirometry was included in the model as the random effect variable. Thus, the analysis of association between progression to spirometric COPD and RV_{CT}/TLC_{CT} was performed using mixed effect logistic regression modeling with a nested random time and

site effect, and fixed effect variables including age, sex, height, weight, smoking status (former versus current smoking), and smoking burden (pack-years of smoking).

To examine the relevance of RV_{CT}/TLC_{CT} in the risk prediction model for COPD development, we performed receiver operating characteristic (ROC) analysis with adjustment for age, sex, height, weight, smoking status, smoking burden, and follow-up time. We then calculated the incremental contribution of RV_{CT}/TLC_{CT} to the model beyond other covariates. In particular, we examined the separate and combined effects of age and RV_{CT}/TLC_{CT} as predictors of COPD development by calculating the area under the curve (AUC or C-statistics) as well as Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Cox proportional hazards regression modeling was used to analyze the association of RV_{CT}/TLC_{CT} and CT indices of air trapping with time to the first hospitalization. In addition, the association of those indices with number of severe exacerbations as defined by number of emergency department and hospital admissions were analyzed using mixed effect Poisson regression modeling to examine the incident rate ratios (IRR) of such events with consideration of follow-up time and study site.

All models included raw values of lung function and were adjusted internally for age, sex, height, weight, smoking status, smoking burden, and follow-up time based on an *a priori* decision. The FEV_1/FVC and RV_{CT}/TLC_{CT} ratios were presented as percentages of the absolute ratios (for example, 70% instead of 0.70) and then adjusted internally for covariates.

Sensitivity analyses were performed by inclusion of variables that could act as confounders as additional terms in the regression models including hip-to-waist ratio and bronchodilator responsiveness ($\geq$12% and $\geq$200 mL increase in FEV_1 after bronchodilator administration). Separate sensitivity analyses were performed to evaluate the effect of

presence or absence of respiratory symptoms (as measured by CAT questionnaire score of < or ≥10) on associations of RV_{CT}/TLC_{CT} and other CT air trapping indices with lung function outcomes. Additional sensitivity analyses were also done by excluding subjects with specific characteristics that could act as confounders including smoking status (current versus former smoker), obesity, or asthma separately.

Line graphs were produced using GraphPad Prism (version 7.0c; GraphPad Software Inc., La Jolla, CA, USA). Data management, figure generation, mixed effect linear regression, and Cox proportional hazards regression analyses were done using R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). Other data analyses were conducted in STATA (version 14.1; StataCorp LP, College Station, TX, USA).

4. Supplemental Tables

Table S1- Characteristics of former and current smoking subject with preserved spirometry who had complete dataset and acceptable radiographic lung volume measurements.

Characteristics	All subjects	Subjects with low RV_{CT}/TLC_{CT}	Subjects with intermediate RV_{CT}/TLC_{CT}	Subjects with high RV_{CT}/TLC_{CT}	P-value (ANOVA)
Demographics					
N	618	206	207	205	
Age (years)	60.4±9.6	55.7±8.8	60.3±9.1	65.2±8.5	<0.001
Sex [Female n (%)]	325 (52.6%)	93 (45.1%)	111 (53.6%)	121 (59.0%)	0.017
Height (cm)	169.3±9.3	170.4±9.1	169.7±9.1	167.8±9.6	0.015
BMI (kg/m^2)	28.9±5.1	29.4±4.7	28.8±5.2	28.6±5.3	0.286
Years of Follow-up	2.2±0.9	2.1±0.9	2.3±0.8	2.3±0.9	0.203
Current Smoker [n (%)]	307 (49.7%)	118 (57.3%)	98 (47.3%)	91 (44.4%)	0.023
Smoking History (pack-years)	42.6±22.2	40.0±24.0	42.4±20.6	45.4±21.5	0.048
Airflow Indices					
FEV_1 (L)	2.82±0.70	3.14±0.68	2.80±0.65	2.53±0.65	<0.001
FEV_1 (% predicted)	98±13	102±12	96±12	95±12	<0.001
FVC (L)	3.65±0.91	3.98±0.89	3.66±0.86	3.32±0.87	<0.001
FVC (% predicted)	98±12	101±12	97±12	95±12	<0.001
FEV_1/FVC (%)	77±5	79±5	77±4	76±5	<0.001
FEV_1/FVC (% predicted)	100±6	101±7	99±6	100±6	0.005
FEF_{25-75} (L)	2.69±0.98	3.23±1.03	2.57±0.84	2.26±0.80	<0.001
FEF_{25-75} (% predicted)	106±33	116±36	101±29	100±31	<0.001
FEF_{75} (L)	0.98±0.48	1.23±0.55	0.91±0.38	0.79±0.38	<0.001
Expiratory Time	9.68±3.46	9.70±3.47	10.02±3.64	9.31±3.22	0.108

(s)					
Reversibility in FEV_1 (mL)	165±146	154±138	163±143	177±156	0.276
Reversibility in FEV_1 (%)	7±6	5±5	7±6	8±8	<0.001
Bronchodilator responsiveness by FEV_1 [n (%)]	78 (12.6%)	13 (6.3%)	27 (13.0%)	38 (18.5%)	<0.001
SVC (L)	3.70±0.95	4.04±0.94	3.71±0.89	3.34±0.89	<0.001
IC (L)	2.79±0.72	3.00±0.70	2.83±0.71	2.54±0.69	<0.001
IRV (L)	1.90±0.66	2.06±0.67	1.93±0.66	1.72±0.59	<0.001
CT-measured Lung Volume Indices					
TLC_{CT} (L)	4.74±1.08	4.84±1.04	4.78±1.11	4.59±1.09	0.046
RV_{CT} (L)	1.88±0.51	1.59±0.38	1.89±0.45	2.17±0.52	<0.001
RV_{CT}/TLC_{CT} (%)	40±7	33±3	40±2	48±4	<0.001
VC_{CT} (L)	2.85±0.75	3.25±0.71	2.88±0.67	2.41±0.62	<0.001
Average Pi10	3.702±0.082	3.695±0.081	3.699±0.081	3.710±0.083	0.150
Thickest Pi10	3.813±0.110	3.812±0.108	3.805±0.100	3.822±0.122	0.251
PRM^{EMPH}	0.34±1.01	0.20±0.75	0.24±0.64	0.56±1.42	<0.001
PRM^{fSAD}	6.91±6.39	3.18±3.09	6.20±5.12	11.26±7.29	<0.001
Exp_{-856}	6.38±6.08	2.98±2.88	5.82±4.82	10.38±7.21	<0.001
$Insp_{-950}$	1.77±1.95	1.80±2.20	1.70±1.58	1.81±2.04	0.833
Activity Levels and Symptom Scores					
6-MWD (m)	438.9±96.2	447.3±88.1	444.3±106.5	425.0±91.9	0.038
BODE Index	0.41±0.79	0.37±0.69	0.44±0.85	0.42±0.82	0.644
CAT Score	11.1±8.1	10.1±7.2	12.3±8.5	10.8±8.5	0.021
mMRC	0.70±0.80	0.69±0.82	0.74±0.86	0.68±0.73	0.721
SGRQ Total Score	23.8±18.6	22.1±15.8	26.2±20.2	23.2±19.4	0.082
SGRQ Symptom Score	36.4±25.8	34.5±23.7	39.0±27.6	35.7±25.8	0.202
SGRQ Activity Score	32.8±23.1	31.3±21.0	35.5±25.0	31.7±23.0	0.131
SGRQ Impact Score	15.2±16.6	12.9±13.1	17.4±17.9	15.3±18.0	0.026
SF12 Physical Component	50.9±6.4	51.3±6.1	50.5±6.8	50.9±6.2	0.436

SF12 Physical Functioning	50.7±6.9	51.1±6.4	50.1±7.4	50.9±7.1	0.283

Footnote: Subjects were stratified into tertiles of CT-measured RV/TLC (RV_{CT}/TLC_{CT}): low (minimum value to 36.6%); intermediate (36.6% to 42.6%); and high (42.6% to maximum value). Data are presented as mean ± standard deviation or number of patients with positive value for the variable (n) out of the total number of patients (N) and percentage of patients (%). Reference equations: measures of pulmonary function and percent predicted of normal values were calculated using Crapo predicted formulas.[12-14] Bronchodilator responsiveness was defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilators administration. Abbreviations: BMI=body mass index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; SVC=slow vital capacity; IC=inspiratory capacity; IRV=inspiratory reserve volume; CT=computed tomography; TLC_{CT}=CT-measured total lung capacity; RV_{CT}=CT-measured residual volume; VC_{CT}=CT-measured vital capacity; Average Pi10= the average for the square root of wall area of a hypothetical airway with 10mm internal perimeter ; Thickest Pi10= the thickest values for the square root of wall area of a hypothetical airway with 10mm internal perimeter ; PRM^{EMPH}=parametric response mapping of functional small airway disease as measures of emphysema; PRM^{fSAD}=parametric response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; $Insp_{-950}$=percent of the lung voxels on inspiratory CT images with attenuation < -950 Hounsfield Units; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD

Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

Table S2- Correlation of CT-measured RV/TLC (RV_{CT}/TLC_{CT}) with airflow indices.

	Uncorrected correlation with RV_{CT}/TLC_{CT} (%)		**Corrected correlation with RV_{CT}/TLC_{CT} (%)**	
Correlation w RV_{CT}/TLC_{CT} (%)	**r**	**P-value**	**r_p**	**P-value**
Absolute Values				
FEV_1/FVC (%)	-0.24	**<0.001**	-0.18	<**0.001**
FEV_1 (L)	-0.40	**<0.001**	-0.32	**<0.001**
FVC (L)	-0.34	**<0.001**	-0.25	**<0.001**
FEF_{25-75} (L/s)	-0.43	**<0.001**	-0.29	**<0.001**
% Predicted Values				
FEV_1/FVC (% predicted)	-0.08	**0.040**	-0.21	<**0.001**
FEV_1 (% predicted)	-0.24	**<0.001**	-0.28	**<0.001**
FVC (% predicted)	-0.21	**<0.001**	-0.18	**<0.001**
FEF_{25-75} (% predicted)	-0.19	**<0.001**	-0.28	**<0.001**
	Uncorrected correlation with PRM^{fSAD}		**Corrected correlation with PRM^{fSAD}**	
Correlation w PRM^{fSAD}	**r**	**P-value**	**r_p**	**P-value**
Absolute Values				
FEV_1/FVC (%)	-0.33	**<0.001**	-0.25	<**0.001**
FEV_1 (L)	0.02	0.619	-0.001	0.987
FVC (L)	0.10	**0.013**	0.11	**0.009**
FEF_{25-75} (L/s)	-0.20	**<0.001**	-0.20	**<0.001**
% Predicted Values				
FEV_1/FVC (% predicted)	-0.09	**0.036**	-0.26	<**0.001**
FEV_1 (% predicted)	0.03	0.421	0.005	0.907
FVC (% predicted)	0.09	**0.027**	0.14	**0.001**
FEF_{25-75} (% predicted)	-0.10	**0.024**	-0.21	**<0.001**
	Uncorrected correlation with Exp_{-856}		**Corrected Correlation with Exp_{-856}**	
Correlation w Exp_{-856}	**r**	**P-value**	**r_p**	**P-value**
Absolute Values				
FEV_1/FVC (%)	-0.31	**<0.001**	-0.23	<**0.001**
FEV_1 (L)	0.01	0.759	-0.02	0.646
FVC (L)	0.09	**0.021**	0.09	**0.031**
FEF_{25-75} (L/s)	-0.20	**<0.001**	-0.19	**<0.001**
% Predicted Values				
FEV_1/FVC (% predicted)	-0.09	**0.024**	-0.24	<**0.001**
FEV_1 (% predicted)	0.02	0.600	-0.006	0.891
FVC (% predicted)	0.08	**0.046**	0.12	**0.003**
FEF_{25-75} (% predicted)	-0.10	**0.014**	-0.19	**<0.001**

Footnote: Correlation coefficients were tested among airflow indices and RV_{CT}/TLC_{CT} controlling for age, height, weight, and sex in the cohort with preserved spirometry. N= 618.

Abbreviations- CT=computed tomography, TLC=total lung capacity; RV=residual volume;

r=correlation coefficient; r_p=partial correlation, which is the correlation coefficient between the dependent variable and the targeted independent variable with the effect of other controlling random variables removed; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume.

Table S3- Comparison of indices in models assessing risk of developing spirometric COPD.

Models	AUC	AIC	BIC
Base model	0.76	433.6	471.4
Base model + age	0.78	429.3	471.4
Base model + RV_{CT}/TLC_{CT}	0.80	409.9	452.0
Base model + age + RV_{CT}/TLC_{CT}	0.80	411.8	458.1

Footnote: Evaluations of the models were assessed with receiver operating characteristic (ROC) analysis. The base model for predicting progression to spirometric COPD contained all other covariates including sex, height, weight, smoking status, smoking burden, and length of follow-up except for age or RV_{CT}/TLC_{CT}. Higher AUC and lower AIC and BIC indicate an improved model. Abbreviations: CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; AUC=area under the curve; AIC=Akaike Information Criterion; and BIC=Bayesian Information Criterion.

Table S4- Effect of follow-up time interaction on association of CT-measured RV/TLC (RV_{CT}/TLC_{CT}) with changes in lung function or symptoms.

Outcome parameters	RV_{CT}/TLC_{CT} strata × F/U time	Differences in estimates	95% CI	P-value *
FEV_1/FVC (%)				
	High	**-0.66**	**-1.27 to -0.06**	
	Intermediate	**0.15**	**-0.46 to 0.77**	**0.015**
	Low	--	--	
6-MWD (m)				
	High	-0.53	-13.57 to 12.81	
	Intermediate	6.61	-6.93 to 20.45	0.507
	Low	--	--	
mMRC				
	High	0.12	-0.005 to 0.243	
	Intermediate	0.03	-0.098 to 0.158	0.140
	Low	--	--	
SF12 Physical Functioning				
	High	0.53	-0.23 to 1.31	
	Intermediate	0.63	-0.16 to 1.43	0.244
	Low	--	--	

Footnote: Association of changes in lung function and symptoms outcomes with RV_{CT}/TLC_{CT} strata along with RV_{CT}/TLCCT interaction with follow-up time were estimated using mixed-effect models. Abbreviations: CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council

Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

*P-values from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S5- Effect of smoking status interaction on association of CT-measured RV/TLC (RV_{CT}/TLC_{CT}) with changes in lung function or symptoms.

Outcome parameters	RV_{CT}/TLC_{CT} strata × smoking status	Differences in estimates	95% CI	P-value *
FEV_1/FVC (%)				
	High	0.17	-1.34 to 1.69	
	Intermediate	-0.10	-1.61 to 1.41	0.935
	Low	--	--	
6-MWD (m)				
	High	0.52	-29.09 to 30.04	
	Intermediate	13.76	-16.07 to 43.28	0.587
	Low	--	--	
mMRC				
	High	-0.04	-0.31 to 0.23	
	Intermediate	0.11	-0.16 to 0.39	0.493
	Low	--	--	
SF12 Physical Functioning				
	High	1.11	-0.89 to 3.12	
	Intermediate	-1.11	-3.11 to 0.90	0.094
	Low	--	--	

Footnote: Association of changes in lung function and symptoms outcomes with RV_{CT}/TLC_{CT} strata along with the RV_{CT}/TLC_{CT} interaction with smoking status (current smoker versus not) were estimated using mixed-effect models. Abbreviations: CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

*P values from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S6- Association of changes in lung function or symptoms with parametric response mapping of functional small airway disease (PRM^{fSAD}) strata.

Outcome parameters	PRM^{fSAD} strata	Differences in estimates	95% CI	P-value *
FEV_1 (mL)				
	High	-45.27	-94.27 to 3.49	
	Intermediate	-13.20	-55.99 to 29.59	0.178
	Low	--	--	
FVC (mL)				
	High	-7.80	-77.56 to 61.97	
	Intermediate	22.12	-39.03 to 83.27	0.594
	Low	--	--	
FEV_1/FVC (%)				
	High	**-1.15**	**-2.10 to -0.20**	
	Intermediate	**-0.92**	**-1.73 to -0.10**	**0.038**
	Low	--	--	
FEF_{25-75} (mL)				
	High	-128.5	-235.1 to -22.0	
	Intermediate	-49.4	-140.8 to 41.9	0.058
	Low	--	--	
FEF_{75} (mL)				
	High	**-69.37**	**-127.00 to -12.16**	
	Intermediate	**-9.96**	**-60.05 to 37.80**	**0.035**
	Low	--	--	
Expiratory Time (s)				
	High	0.11	-0.61 to 0.84	
	Intermediate	0.51	-0.13 to 1.15	0.237
	Low	--	--	
6-MWD (m)				
	High	-3.38	-21.63 to 14.67	
	Intermediate	-1.20	-16.89 to 14.57	0.934
	Low	--	--	
BODE Index				
	High	0.05	-0.14 to 0.25	
	Intermediate	0.01	-0.16 to 0.18	0.863
	Low	--	--	
CAT Score				
	High	-0.001	-1.303 to 1.327	
	Intermediate	0.599	-0.541 to 1.742	0.473
	Low	--	--	
mMRC				
	High	0.05	-0.11 to 0.21	
	Intermediate	0.04	-0.10 to 0.18	0.819
	Low	--	--	
SGRQ Total Score				
	High	0.09	-2.55 to 2.74	
	Intermediate	1.62	-0.70 to 3.95	0.277
	Low	--	--	
SGRQ Symptom Score				
	High	-1.93	-6.15 to 2.56	
	Intermediate	-0.41	-4.14 to 3.39	0.643
	Low	--	--	

SGRQ Activity Score				
	High	1.33	-2.20 to 4.93	
	Intermediate	2.46	-0.63 to 5.58	0.303
	Low	--	--	
SGRQ Impact Score				
	High	0.52	-1.91 to 3.00	
	Intermediate	1.76	-0.36 to 3.90	0.236
	Low	--	--	
SF12 Physical Component				
	High	0.01	-1.03 to 1.01	
	Intermediate	0.32	-0.57 to 1.21	0.701
	Low	--	--	
SF12 Physical Functioning				
	High	0.22	-1.02 to 1.44	
	Intermediate	0.37	-0.70 to 1.44	0.794
	Low	--	--	

Footnote: Association of changes in lung function and symptoms outcomes with PRM^{fSAD} strata were estimated using mixed-effect models. Abbreviations: PRM^{fSAD}=parametric response mapping of functional small airway disease; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ= Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

*P values from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S7- Association of changes in lung function or symptoms with percent of the lung voxels with attenuation <-856HU on the expiratory CT images (Exp_{-856}) strata.

Outcome parameters	Exp_{-856} strata	Differences in stimates	95% CI	P-value *
FEV_1 (mL)				
	High	-57.14	-105.87 to -9.18	
	Intermediate	-19.83	-62.41 to 22.77	0.061
	Low	--	--	
FVC (mL)				
	High	-19.29	-88.70 to 50.13	
	Intermediate	21.97	-39.23 to 83.17	0.384
	Low	--	--	
FEV_1/FVC (%)				
	High	**-1.16**	**-2.11 to -0.21**	
	Intermediate	**-0.94**	**-1.76 to -0.13**	**0.035**
	Low	--	--	
FEF_{25-75} (mL)				
	High	-128.81	-233.84 to -23.78	
	Intermediate	-57.01	-147.11 to 33.09	0.055
	Low	--	--	
FEF_{75} (mL)				
	High	**-73.55**	**-131.46 to -16.20**	
	Intermediate	**-13.14**	**-63.16 to 36.52**	**0.024**
	Low	--	--	
Expiratory Time (s)				
	High	0.20	-0.53 to 0.92	
	Intermediate	0.31	-0.32 to 0.95	0.633
	Low	--	--	
6-MWD (m)				
	High	3.17	-15.07 to 21.17	
	Intermediate	4.56	-11.13 to 20.32	0.853
	Low	--	--	
BODE Index				
	High	-0.03	-0.23 to 0.17	
	Intermediate	-0.09	-0.26 to 0.09	0.589
	Low	--	--	
CAT Score				
	High	-0.28	-1.58 to 1.03	
	Intermediate	0.21	-0.93 to 1.35	0.690
	Low	--	--	
mMRC				
	High	0.03	-0.132 to 0.202	
	Intermediate	0.02	-0.128 to 0.166	0.928
	Low	--	--	
SGRQ Total Score				
	High	-1.33	-3.92 to 1.33	
	Intermediate	0.15	-2.14 to 2.46	0.419
	Low	--	--	
SGRQ Symptom Score				
	High	-3.40	-7.55 to 1.04	
	Intermediate	-1.84	-5.52 to 1.90	0.292
	Low	--	--	
SGRQ Activity Score				
	High	0.43	-3.08 to 3.98	
	Intermediate	0.49	-2.58 to 3.59	0.951
	Low	--	--	

SGRQ Impact Score				
	High	-0.91	-3.37 to 1.59	
	Intermediate	0.48	-1.67 to 2.64	0.449
	Low	--	--	
SF12 Physical Component				
	High	0.11	-0.94 to 1.13	
	Intermediate	0.42	-0.49 to 1.33	0.612
	Low	--	--	
SF12 Physical Functioning				
	High	0.24	-1.00 to 1.46	
	Intermediate	0.42	-0.67 to 1.49	0.752
	Low	--	--	

Footnote: Association of changes in lung function and symptoms outcomes with Exp_{-856} strata were estimated using mixed-effects models. Abbreviations: CT=computed tomography; Exp_{-856}=percent of the lung voxels with attenuation <-856HU on the expiratory CT images; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

*P values from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S8- Effect of follow-up time interaction on association of other CT measures of air trapping with changes in lung function.

Outcome parameters	Strata	Differences in estimates	95% CI	P value *
FEV_1/FVC (%)				
PRM^{fSAD} × F/U time	High	0.07	-0.52 to 0.65	
	Intermediate	-0.08	-0.72 to 0.55	0.896
	Low	--	--	
FEF_{75} (mL)				
PRM^{fSAD} × F/U time	High	21.68	-16.94 to 60.31	
	Intermediate	22.79	-19.08 to 64.66	0.447
	Low	--	--	
FEV_1/FVC (%)				
Exp_{-856} × F/U time	High	-0.04	-0.76 to -0.51	
	Intermediate	-0.13	-0.63 to 0.55	0.922
	Low	--	--	
FEF_{75} (mL)				
Exp_{-856} × F/U time	High	13.10	-26.37 to 52.31	
	Intermediate	3.13	-39.16 to 45.29	0.790
	Low	--	--	

Footnote: Association of CT measures of air trapping strata and changes in lung function and symptoms outcomes along with their interaction with follow-up time were estimated using mixed-effects models. Abbreviations: PRM^{fSAD}=parametric response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

*P values from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S9- Association of COPD development with CT-measured lung volumes and air trapping strata.

Development of Spirometric COPD				
	Spirometric COPD Progression at V2	Spirometric COPD Progression at V3	Spirometric COPD Progression at V4	Spirometric COPD Progression on Last Follow-up §
N	496	295	157	496
Categorical model				
High RV_{CT}/TLC_{CT}	**3.178 [1.296-7.794] P=0.012**	**4.854 [1.832-12.860] P=0.001**	1.749 [0.460-6.647] P=0.412	**5.689 [2.446-13.228] P<0.001**
Intermediate RV_{CT}/TLC_{CT}	**2.763 [1.183-6.452] P=0.019**	2.420 [0.921-6.361] P=0.073	2.955 [0.822-10.625] P=0.097	**2.966 [1.298-6.775] P=0.010**
Low RV_{CT}/TLC_{CT} (Reference)	--	--	--	--
High PRM^{fSAD}	**5.705 [2.050-15.879] P=0.001**	**6.836 [2.327-20.080] P<0.001**	1.572 [0.418-5.910] P=0.503	**5.374 [2.306-12.526] P<0.001**
Intermediate PRM^{fSAD}	**4.658 [1.827-11.875] P=0.001**	**5.329 [2.013-14.104] P=0.001**	2.820 [0.815-9.751] P=0.102	**3.530 [1.649-7.558] P=0.001**
Low PRM^{fSAD} (Reference)	--	--	--	--
High Exp_{-856}	**6.663 [2.316-19.172] P<0.001**	**6.011 [2.115-17.087] P=0.001**	2.024 [0.520-7.871] P=0.309	**4.732 [2.041-10.972] P<0.001**
Intermediate Exp_{-856}	**3.937 [1.465-10.575] P=0.007**	**3.895 [1.473-10.297[P=0.006**	1.608 [0.468-5.529] P=0.451	**2.686 [1.239-5.826] P=0.012**
Low Exp_{-856} (Reference)	--	--	--	--

Footnote: Association of development of spirometric COPD with CT-measured lung volumes and air trapping strata were estimated using mixed effect logistic regression analyses with adjustment for age, sex, height, weight, smoking status, and random effects from length of follow-up and sites. The models odds ratio (OR) with 95% confidence intervals and P-values are shown in the table. Values are presented as OR (95% confidence interval) with p-value. P-values are from mixed effect logistic and linear regression with random effect. Significant

associations are shown in bold. **§** Follow-up spirometry from the last available post-bronchodilator spirometry from any of the V2, V3, or V4 visits. Abbreviations- CT: computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; PRM^{fSAD}=parametric response mapping of functional small airway disease; $Exp._{856}$=percent of the lung voxels with attenuation <-856HU on the expiratory CT images.

Table S10- Effect of smoking status interaction on association of other CT measures of air trapping with changes in lung function.

	Strata	Differences in Estimates	95% CI	P value *
Changes in FEV_1/FVC (%)				
PRM^{fSAD} * Smoking Status	High	0.52	-1.16 to 2.18	
	Intermediate	-0.33	-1.92 to 1.26	0.626
	Low	--	--	
Changes in FEF_{75} (mL)				
PRM^{fSAD} * Smoking Status	High	32.55	-71.40 to 136.04	
	Intermediate	12.44	-85.84 to 110.37	0.830
	Low	--	--	
Changes in FEV_1/FVC (%)				
Exp_{-856} * Smoking Status	High	0.76	-0.92 to 2.42	
	Intermediate	-0.87	-2.50 to 0.77	0.135
	Low	--	--	
Changes in FEF_{75} (mL)				
Exp_{-856} * Smoking Status	High	32.51	-71.96 to 136.27	
	Intermediate	-36.42	-138.00 to 64.24	0.395
	Low	--	--	

Footnote: Association of CT measures of air trapping strata and changes in lung function and symptoms outcomes along with their interaction with smoking status were estimated using mixed-effects models. Abbreviations: PRM^{fSAD}=parametric response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

*P values from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S11- Association of COPD development with CT measures of lung disease.

Development of Spirometric COPD				
	Spirometric COPD Progression at V2	Spirometric COPD Progression at V3	Spirometric COPD Progression at V4	Spirometric COPD Progression on Last Follow-up §
N	496	295	157	496
Continuous model				
RV_{CT}/TLC_{CT} (%)	**1.081 [1.028-1.136] P=0.002**	**1.091 [1.034-1.151] P=0.001**	1.048 [0.971-1.130] P=0.230	**1.107 [1.056-1.160] P<0.001**
IC (L)	0.927 [0.527-1.632] P=0.794	0.821 [0.451-1.494] P=0.519	1.001 [0.408-2.458] P=0.998	0.671 [0.392-1.147] P=0.145
IRV (L)	0.638 [0.366-1.112] P=0.113	0.603 [0.332-1.094] P=0.096	0.922 [0.376-2.258] P=0.859	0.639 [0.383-1.065] P=0.086
Average Pi10	0.364 [0.007-17.889] P=0.611	1.195 [0.024-60.268] P=0.929	1.046 [0.002-570.985] P=0.989	0.189 [0.006-6.401] P=0.354
Thickest Pi10	1.474 [0.127-17.148] P=0.757	3.161 [0.178-56.074] P=0.433	3.593 [0.044-294.465] P=0.569	3.071 [0.305-30.962] P=0.341
PRM^{EMPH}	1.194 [0.954-1.493] P=0.122	1.026 [0.800-1.317] P=0.838	0.987 [0.704-1.383] P=0.938	1.213 [0.959-1.535] P=0.108
PRM^{fSAD}	**1.069 [1.021-1.119] P=0.005**	**1.084 [1.027-1.145] P=0.004**	1.035 [0.949-1.128] P=0.441	**1.094 [1.046-1.145] P<0.001**
Exp_{-856}	**1.075 [1.026-1.125] P=0.002**	**1.072 [1.017-1.131] P=0.010**	1.035 [0.951-1.126] P=0.429	**1.092 [1.044-1.143] P<0.001**
$Insp_{-950}$	**1.143 [1.011-1.292] P=0.033**	1.020 [0.880-1.182] P=0.794	1.041 [0.838-1.294] P=0.715	1.110]0.978-1.260] P=0.106

Footnote: Association of development of spirometric COPD with several CT measures of disease in COPD were estimated using mixed effect logistic regression analyses with adjustment for age, sex, height, weight, smoking status, and random effects from length of follow-up and sites. The models odds ratio (OR) with 95% confidence intervals and P-values are shown in the table. Values are presented as OR (95% confidence interval) with P-value. P-values are from mixed effect logistic and linear regression with random effect. Significant associations are shown in bold. **§** Follow-up spirometry from the last available post-

bronchodilator spirometry from any of the V2, V3, or V4 visits. Abbreviations- CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; IC=inspiratory capacity; IRV=inspiratory reserve volume; Average Pi10= the average for the square root of wall area of a hypothetical airway with 10mm internal perimeter; Thickest Pi10= the thickest values for the square root of wall area of a hypothetical airway with 10mm internal perimeter; PRM^{EMPH}=parametric response mapping of functional small airway disease as measures of emphysema; PRM^{fSAD}=parametric response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; $Insp_{-950}$=percent of the lung voxels on inspiratory CT images with attenuation < -950 Hounsfield Units.

Table S12 - Combined model with inclusion of all CT parameters of air trapping, emphysema, and airway disease in the same model.

Combined Continuous Models			
N=496	**Progression to Spirometric COPD on Last Follow-up §**		
	Odds Ratio	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	**1.109**	**1.035 to 1.188**	**0.003**
Average Pi10	0.151	0.002 to 9.178	0.367
PRM^{EMPH}	1.169	0.636 to 2.151	0.615
PRM^{fSAD}	1.365	0.783 to 2.381	0.273
Exp_{-856}	0.725	0.394 to 1.332	0.300
$Insp_{-950}$	1.130	0.845 to 1.511	0.409
N=476	**Changes in FEV_1 (mL)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	-3.06	-7.44 to 1.33	0.172
Average Pi10	-25.72	-265.96 to 214.52	0.834
PRM^{EMPH}	5.22	-34.81 to 45.25	0.798
PRM^{fSAD}	-10.08	-46.95 to 26.78	0.592
Exp_{-856}	12.38	-28.14 to 52.91	0.549
$Insp_{-950}$	-8.49	-26.16 to 9.18	0.346
N=476	**Changes in FVC (mL)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	1.49	-4.50 to 7.55	0.633
Average Pi10	-128.14	-4.78.72 to 221.39	0.482
PRM^{EMPH}	3.55	-52.04 to 59.57	0.902
PRM^{fSAD}	4.00	-47.76 to 54.91	0.879
Exp_{-856}	-3.48	-59.45 to 53.38	0.904
$Insp_{-950}$	6.27	-18.86 to 30.82	0.623
N=476	**Changes in FEV_1/FVC (%)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	**-0.15**	**-0.23 to -0.08**	**<0.001**
Average Pi10	-1.86	-6.81 to 3.13	0.467
PRM^{EMPH}	-0.22	-0.94 to 0.51	0.564
PRM^{fSAD}	-0.57	-1.23 to 0.10	0.098
Exp-856	0.67	-0.06 to 1.40	0.076
Insp-950	**-0.38**	**-0.71 to -0.06**	**0.023**
N=469	**Changes in 6-MWD (m)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	**-1.51**	**-3.04 to 0.03**	**0.054**
Average Pi10	35.87	-59.68 to 131.42	0.462
PRM^{EMPH}	-11.06	-25.56 to 3.44	0.135
PRM^{fSAD}	0.71	-12.75 to 14.17	0.917
Exp_{-856}	1.18	-13.63 to 15.98	0.876

$Insp_{-950}$	2.06	-4.50 to 8.62	0.538
N=460	**Changes in BODE Index**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	**0.02**	**0.01 to 0.04**	**0.007**
Average Pi10	0.41	-0.53 to 1.35	0.405
PRM^{EMPH}	0.03	-0.12 to 0.18	0.712
PRM^{fSAD}	-0.06	-0.20 to 0.08	0.408
Exp_{-856}	0.05	-0.11 to 0.20	0.569
$Insp_{-950}$	0.03	-0.04 to 0.10	0.423
N=469	**Changes in mMRC**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	**0.01**	**0.001 to 0.028**	**0.032**
Average Pi10	0.19	-0.58 to 0.96	0.639
PRM^{EMPH}	0.10	-0.03 to 0.23	0.118
PRM^{fSAD}	0.04	-0.08 to 0.16	0.546
Exp_{-856}	-0.06	-0.19 to 0.08	0.413
$Insp_{-950}$	0.004	-0.05 to 0.06	0.897
N=471	**Changes in SF12 Physical Functioning**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} (%)	**-0.11**	**-0.21 to -0.01**	**0.043**
Average Pi10	0.01	-6.25 to 6.09	0.997
PRM^{EMPH}	**-1.04**	**-1.99 to -0.06**	**0.037**
PRM^{fSAD}	-0.18	-1.07 to 0.73	0.704
Exp_{-856}	0.31	-0.69 to 1.29	0.544
$Insp_{-950}$	0.16	-0.28 to 0.58	0.470
Combined Categorical Model			
N=496	**Progression to Spirometric COPD on Last Follow-up §**		
	Odds Ratio	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	**5.110**	**1.794 to 14.557**	**0.002**
Intermediate	**3.087**	**1.286 to 7.413**	**0.012**
Low (Ref.)	--	--	--
Average Pi10	0.236	0.004 to 13.447	0.484
PRM^{EMPH}	1.173	0.630 to 2.183	0.614
PRM^{fSAD}	1.304	0.749 to 2.274	0.349
Exp_{-856}	0.780	0.426 to 1.426	0.419
$Insp_{-950}$	1.075	0.798 to 2.274	0.633
N=476	**Changes in FEV_1 (mL)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	-22.37	-84.32 to 38.24	
Intermediate	-26.97	-71.95 to 18.75	0.174
Low	--	--	
Average Pi10	-53.94	-298.67 to 199.72	0.661

PRM^{EMPH}	4.13	-36.51 to 43.21	0.840
PRM^{fSAD}	-8.98	-45.47 to 27.22	0.632
Exp_{-856}	9.37	-30.09 to 49.30	0.648
$Insp_{-950}$	-5.09	-21.94 to 11.79	0.559
N=476	**Changes in FVC (mL)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	30.34	-55.84 to 116.53	
Intermediate	3.93	-60.00 to 67.86	0.633
Low			
Average Pi10	-135.64	-491.68 to 220.40	0.456
PRM^{EMPH}	2.95	-53.65 to 59.55	0.918
PRM^{fSAD}	3.51	-48.36 to 55.38	0.894
Exp_{-856}	-3.27	-59.93 to 53.38	0.909
$Insp_{-950}$	6.84	-17.46 to 31.14	0.581
N=476	**Changes in FEV_1/FVC (%)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	**-1.62**	**-2.73 to -0.51**	
Intermediate	**-1.07**	**-1.90 to -0.24**	**<0.001**
Low			
Average Pi10	-2.82	-7.80 to 2.17	0.271
PRM^{EMPH}	-0.26	-0.99 to 0.47	0.492
PRM^{fSAD}	-0.51	-1.18 to 0.16	0.139
Exp-856	0.54	-0.18 to 1.28	0.147
Insp-950	-0.26	-0.58 to 0.06	0.112
N=469	**Changes in 6-MWD (m)**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	**-21.27**	**-42.87 to 0.14**	
Intermediate	**-21.41**	**-37.61 to -5.07**	**0.037**
Low			
Average Pi10	25.87	-67.07 to 119.25	0.594
PRM^{EMPH}	-11.68	-25.81 to 2.74	0.115
PRM^{fSAD}	0.69	-12.47 to 14.06	0.919
Exp_{-856}	0.77	-13.86 to 15.15	0.918
$Insp_{-950}$	2.70	-3.53 to 8.89	0.402
N=460	**Changes in BODE Index**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	**0.27**	**0.04 to 0.50**	
Intermediate	**0.22**	**0.04 to 0.39**	**0.032**
Low			
Average Pi10	0.53	-0.41 to 1.46	0.282
PRM^{EMPH}	0.04	-0.12 to 0.19	0.637

PRM^{fSAD}	-0.07	-0.21 to 0.08	0.373
Exp_{-856}	0.06	-0.10 to 0.21	0.466
$Insp_{-950}$	0.01	-0.05 to 0.08	0.679
N=469	**Changes in mMRC**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	**0.24**	**0.04 to 0.43**	
Intermediate	**0.21**	**0.07 to 0.36**	**0.014**
Low			
Average Pi10	0.24	-0.52 to 1.01	0.544
PRM^{EMPH}	0.11	-0.02 to 0.24	0.097
PRM^{fSAD}	0.04	-0.08 to 0.15	0.542
Exp_{-856}	-0.05	-0.18 to 0.08	0.430
$Insp_{-950}$	-0.0001	-0.06 to 0.06	0.997
N=471	**Changes in SF12 Physical Functioning**		
	PE	95% CI	P-value
RV_{CT}/TLC_{CT} Strata			
High	**-1.80**	**-3.32 to -0.37**	
Intermediate	**-1.53**	**-2.67 to -0.45**	**0.017**
Low			
Average Pi10	-0.47	-6.59 to 5.50	0.880
PRM^{EMPH}	**-1.08**	**-2.03 to -0.10**	**0.030**
PRM^{fSAD}	-0.19	-1.08 to 0.71	0.677
Exp_{-856}	0.31	-0.68 to 1.28	0.536
$Insp_{-950}$	0.17	-0.24 to 0.58	0.419

Footnote: Association of development of spirometric COPD and changes in lung function and symptoms outcomes with the CT measures of disease in COPD were estimated using mixed effect logistic and linear regerssion models, respectively, with adjustment for age, sex, height, weight, smoking status, and random effects from length of follow-up and sites. The models odds ratio (OR) or parameter estimate (PE) with 95% confidence intervals and P-values are shown in the table. Significant associations are shown in bold. **§** Follow-up spirometry from the last available post-bronchodilator spirometry from any of the V2, V3, or V4 visits. Abbreviations- CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; Average Pi10= the average for the square root of wall area of a hypothetical airway with 10mm internal perimeter; PRM^{EMPH}=parametric response mapping of functional small airway disease as measures of emphysema; PRM^{fSAD}=parametric

response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; $Insp_{-950}$=percent of the lung voxels on inspiratory CT images with attenuation < -950 Hounsfield Units; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

Table S13- Comparison of changes in lung functions or symptoms between CT-measured RV/TLC (RV_{CT}/TLC_{CT}) strata.

Adjusted changes in outcomes from baseline (from regression models)	RV_{CT}/TLC_{CT} strata	95% CI of Differences from Reference	P-value
FEV_1/FVC (%)	-1.43	-1.46 to -0.39	<0.001
	-1.25	-1.22 to -0.27	0.002
	-0.50	Reference	Reference
6-MWD (m)	-22.35	-23.29 to -1.67	0.023
	-29.61	-28.78 to -10.72	<0.001
	-9.87	Reference	Reference
mMRC	0.004	-0.034 to 0.197	0.164
	0.030	-0.008 to 0.224	0.067
	-0.078	Reference	Reference
SF12 Physical Functioning	-0.76	-2.33 to -0.66	<0.001
	-0.38	-1.99 to -0.24	0.012
	0.73	Reference	Reference
Unadjusted changes in outcomes from baseline	**RV_{CT}/TLC_{CT} strata**	**95% CI**	**P-value**
FEV_1/FVC (%)	-3.0	-3.8 to -2.2	<0.001
	-2.1	-2.8 to -1.4	0.050
	-1.1	-1.7 to -0.5	Reference
6-MWD (m)	-30.26	-43.31 to -17.20	0.043
	-31.24	-44.19 to -18.28	0.033
	-11.47	-24.33 to 1.38	Reference
mMRC	0.097	-0.042 to 0.236	0.016
	0.054	-0.091 to 0.198	0.057
	-0.127	-0.245 to -0.009	Reference
SF12 Physical Functioning	-1.01	-1.84 to -0.18	0.083
	-0.55	-1.42 to 0.32	0.321
	0.10	-0.85 to 1.05	Reference

Footnotes: Predicted changes in lung functions and symptoms were estimated using mixed effect linear regression models with age, sex, height, weight, smoking status, and random effects from length of follow-up and sites with respect to RV_{CT}/TLC_{CT} tertiles.

Abbreviations: CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; 6-MWD= 6-minute walk distance test; mMRC=Modified Medical Research Council Dyspnea Scale; SF12=Short Form 12-Item Survey.

Table S14- Association of respiratory exacerbations with CT-measured lung volumes and air trapping strata.

Respiratory Exacerbations		
	Number of Severe Exacerbations	Time to the First Hospitalization
N	595	595
Categorical model		
High RV_{CT}/TLC_{CT}	1.206 [0.568-2.562] P=0.626	0.121 [0.013-1.153] P=0.066
Intermediate RV_{CT}/TLC_{CT}	0.948 [0.484-1.857] P=0.877	0.900 [0.212-3.827] P=0.887
Low RV_{CT}/TLC_{CT} (Reference)	--	--
High PRM^{fSAD}	1.163 [0.493-2.742] P=0.730	1.509 [0.260-8.751] P=0.647
Intermediate PRM^{fSAD}	0.417 [0.170-1.023] P=0.056	0.753 [0.138-4.097] P=0.742
Low PRM^{fSAD} (Reference)	--	--
High Exp_{-856}	1.326 [0.596-2.953] P=0.489]	0.774 [0.179-3.340] P=0.732
Intermediate Exp_{-856}	0.694 [0.347-1.385] P=0.300	0.363 [0.114-1.155] P=0.086
Low Exp_{-856} (Reference)	--	--

Footnote: Association of respiratory exacerbation with CT-measured lung volumes and air trapping strata were estimated using mixed effect Poisson regression and Cox Proportional Hazards regression analyses with adjustment for age, sex, height, weight, smoking status, and random effects from length of follow-up and sites. The results of associations between number of severe exacerbations or time to the first hospitalization were reported by incident

rate ratio (IRR) or hazard ratio (HR), respectively, with 95% confidence intervals and P-values in the table. Significant associations are shown in bold. Abbreviations- CT: computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; PRM^{fSAD}=parametric response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856HU on the expiratory CT images.

Table S15- Associations of change in lung function or symptoms with CT-measured RV/TLC (RV_{CT}/TLC_{CT}) using lower limit of normal (LLN) criteria.

Outcomes Parameters	Parameter estimate of RV_{CT}/TLC_{CT} (%)	95% CI	P-value
FEV_1 (mL)	-2.02	-4.49 to 0.49	0.114
FVC (mL)	0.50	-2.99 to 4.02	0.781
FEV_1/FVC (%)	**-0.09**	**-0.13 to -0.04**	**<0.001**
FEF_{25-75} (mL)	**-6.46**	**-11.45 to -1.48**	**0.011**
FEF_{75} (mL)	**-4.15**	**-6.81 to -1.50**	**0.002**
Expiratory Time (s)	0.02	-0.02 to 0.06	0.364
6-MWD (m)	-0.50	-1.39 to 0.37	0.265
BODE Index	0.006	-0.003 to 0.016	0.170
CAT Score	0.001	-0.060 to 0.062	0.976
mMRC	0.005	-0.003 to 0.013	0.192
SGRQ Total Score	-0.03	-0.15 to 0.10	0.641
SGRQ Symptom Score	-0.05	-0.25 to 0.16	0.628
SGRQ Activity Score	0.09	-0.07 to 0.26	0.257
SGRQ Impact Score	-0.06	-0.18 to 0.06	0.306
SF12 Physical Component	-0.04	-0.09 to 0.02	0.219
SF12 Physical Functioning	**-0.07**	**-0.14 to -0.003**	**0.043**

Footnote: Association of changes in lung function and symptoms outcomes with RV_{CT}/TLC_{CT} were estimated using mixed-effect linear regression models with adjustment for age, sex, height, weight, smoking status, smoking burden, and random effects from length of follow-up and study sites. Lower limit of normal (LLN) criteria was used for determination of COPD at baseline (N=649 with repeated spirometries). Abbreviations: CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; FEV_1=forced expiratory volume in 1 second; CI=confidence interval; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

*P-values are from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S16- Associations of change in lung function or symptoms with CT-measured RV/TLC (RV_{CT}/TLC_{CT}) strata using lower limit of normal (LLN) criteria.

Outcome Parameters	RV_{CT}/TLC_{CT} strata	Differences in estimates	95% CI	P-value *
FEV_1 (mL)				
	High	**-44.10**	**-85.66 to -2.21**	
	Intermediate	**-44.71**	**-81.36 to -7.61**	**0.044**
	Low	**--**	**--**	
FVC (mL)				
	High	-6.22	-65.78 to 53.35	
	Intermediate	-18.31	-71.91 to 35.28	0.778
	Low	--	--	
FEV_1/FVC (%)				
	High	**-1.38**	**-2.15 to -0.62**	
	Intermediate	**-0.93**	**-1.61 to -0.25**	**0.001**
	Low	--	--	
FEF_{25-75} (mL)				
	High	**-103.69**	**-188.27 to -19.33**	
	Intermediate	**-105.97**	**-180.06 to -31.68**	**0.014**
	Low	--	--	
FEF_{25-75} (mL)				
	High	**-68.64**	**-114.22 to -23.06**	
	Intermediate	**-55.77**	**-96.55 to -15.00**	**0.006**
	Low	**--**	**--**	
Expiratory Time (s)				
	High	0.25	-0.39 to 0.90	
	Intermediate	0.51	-0.07 to 1.09	0.221
	Low	--	--	
6-MWD (m)				
	High	0.16	-14.68 to 15.00	
	Intermediate	-2.05	-15.50 to 11.41	0.929
	Low	--	--	
BODE Index				
	High	0.01	-0.15 to 0.17	
	Intermediate	-0.06	-0.21 to 0.08	0.529
	Low	--	--	
CAT Score				
	High	-0.27	-1.30 to 0.79	
	Intermediate	-0.23	-1.17 to 0.71	0.862
	Low	--	--	
mMRC				
	High	0.04	-0.09 to 0.18	
	Intermediate	0.01	-0.11 to 0.13	0.778
	Low	--	--	
SGRQ Total Score				
	High	-0.32	-2.42 to 1.82	
	Intermediate	-0.72	-2.65 to 1.24	0.761
	Low	--	--	
SGRQ Symptom Score				
	High	0.26	-3.09 to 3.76	
	Intermediate	0.15	-2.92 to 3.31	0.988
	Low	--	--	
SGRQ Activity Score				
	High	0.85	-1.94 to 3.67	
	Intermediate	0.47	-2.09 to 3.05	0.839
	Low	--	--	

SGRQ Impact Score				
	High	-0.66	-2.65 to 1.36	
	Intermediate	-0.72	-2.53 to 1.12	0.724
	Low	--	--	
SF12 Physical Component				
	High	-0.79	-1.77 to 0.19	
	Intermediate	-0.60	-1.48 to 0.29	0.260
	Low	--	--	
SF12 Physical Functioning				
	High	**-1.37**	**-2.55 to -0.21**	
	Intermediate	**-1.12**	**-2.17 to -0.07**	**0.048**
	Low	--	--	

Footnote: Association of changes in lung function and symptoms outcomes with RV_{CT}/TLC_{CT} were estimated using mixed-effect linear regression models with adjustment for age, sex, height, weight, smoking status, smoking burden, and random effects from length of follow-up and study sites. Lower limit of normal (LLN) criteria was used for determination of COPD at baseline (N=649 with repeated spirometries). Abbreviations: CT=computed tomography; RV_{CT}/TLC_{CT}=CT-measured residual volume to total lung capacity ratio; FEV_1=forced expiratory volume in 1 second; CI=confidence interval; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled; 6-MWD= 6-minute walk distance test; BODE= The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; CAT=COPD Assessment Test; mMRC=Modified Medical Research Council Dyspnea Scale; SGRQ=Saint George's Respiratory Questionnaire; SF12=Short Form 12-Item Survey.

*P-values are from mixed-effect linear regression modeling with a nested random subject and site effect.

Table S17- Association of spirometric COPD development with CT-measured RV/TLC (RV_{CT}/TLC_{CT}) using lower limit of normal (LLN) criteria using lower limit of normal (LLN) criteria.

Development of Spirometric COPD				
RV_{CT}/TLC_{CT}	Spirometric COPD Progression at V2	Spirometric COPD Progression at V3	Spirometric COPD Progression at V4	Spirometric COPD Progression on Last Follow-up §
N	649	403	214	649
Categorical model				
High RV_{CT}/TLC_{CT}	**4.999 [1.940-12.878] P=0.001**	**5.591 [2.010-15.552] P=0.001**	**5.450 [1.261-23.557] P=0.023**	**3.571 [1.600-7.974] P=0.002**
Intermediate RV_{CT}/TLC_{CT}	**3.278 [1.318-8.151] P=0.011**	1.876 [0.676-5.203] P=0.227	2.398 [0.571-10.075] P=0.232	2.081 [0.957-4.528] P=0.065
Low RV_{CT}/TLC_{CT} (Reference)	--	--	--	--
Continuous model				
RV_{CT}/TLC_{CT} (%)	**1.081 [1.035-1.129] P<0.001**	**1.109 [1.055-1.165] P<0.001**	**1.072 [1.000-1.148] P=0.049**	**1.067 [1.023-1.112] P=0.002**

Footnote: Association of development of spirometric COPD with RV_{CT}/TLC_{CT} was estimated using mixed effect logistic regression models with adjustment for age, sex, height, weight, smoking status, smoking burden, and random effects from length of follow-up and study sites. Lower limit of normal (LLN) criteria was used for determination of COPD at baseline and on follow-up spirometry. The models odds ratio (OR) with 95% confidence intervals (CI) and P-values are shown in the table. P-values are from mixed effect logistic regression with random effect. Significant associations are shown in bold. **§** Follow-up spirometry from the last available post-bronchodilator spirometry from any of the V2, V3, or V4 visits.

Abbreviations: CT= computed tomography; RV_{CT}/TLC_{CT}= CT-measured residual volume to total lung capacity ratio.

5. Supplemental Figure

Figure S1- Association between CT-measured vital capacity (VC_{CT}) and slow vital capacity (SVC) in smokers with preserved spirometry. Scatter plots of VC_{CT} (L) and SVC (L) are shown with points that have varying percent of variability between the two CT measurements being indicated with a "×" and the remaining points with cyan blue circles. The cyan blue lines represent the regression lines for the remaining subjects after exclusion of those with the corresponding variability with correlation coefficient (r). The black dashed line is the identity line between the two different measurement methods.

Figure S2- Association between CT-measured vital capacity (VC_{CT}) and slow vital capacity (SVC) in smokers with preserved spirometry. Scatter plots of VC_{CT} (L) and SVC (L) are shown with points that have varying percent of discordance between the two methods of measurements being indicated with a "+" and the remaining points with cyan blue circles. The cyan blue lines represent the regression lines for the remaining subjects after exclusion of those with the corresponding discordance with correlation coefficient (r). The black dashed line is the identity line between the two different measurement methods.

Figure S3- Correlation between parametric response mapping of functional small airway disease (PRM^{fSAD}) and FEV_1/FVC or FEV_1 in smokers with preserved spirometry. Relationship between PRM^{fSAD} and FEV_1/FVC (% predicted), or FEV_1 (% predicted). Boxplots show the distribution of PRM^{fSAD} by 5% increments in FEV_1/FVC % predicated (Panel **A**), and 5% increments in FEV_1 % predicated (Panel **B**). Subjects were stratified into tertiles of PRM^{fSAD} represented by green, blue, and magenta for low, intermediate, and high PRM^{fSAD} tertiles, respectively. The black line represents the regression line for all the points. Abbreviations- PRM^{fSAD}: parametric response mapping of functional small airway disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Figure S4- Correlation between percent of the lung voxels with attenuation <-856HU on the expiratory CT images (Exp_{-856}) and FEV_1/FVC or FEV_1 in smokers with preserved spirometry. Relationship between Exp_{-856} and FEV_1/FVC (% predicted), or FEV_1 (% predicted). Boxplots show the distribution of Exp_{-856} by 5% increments in FEV_1/FVC % predicated (Panel **A**), and 5% increments in FEV_1 % predicated (Panel **B**). Subjects were stratified into tertiles of Exp_{-856} represented by green, blue, and magenta for low, intermediate, and high Exp_{-856} tertiles, respectively. The black line represents the regression line for all the points. Abbreviations- Exp_{-856}: percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

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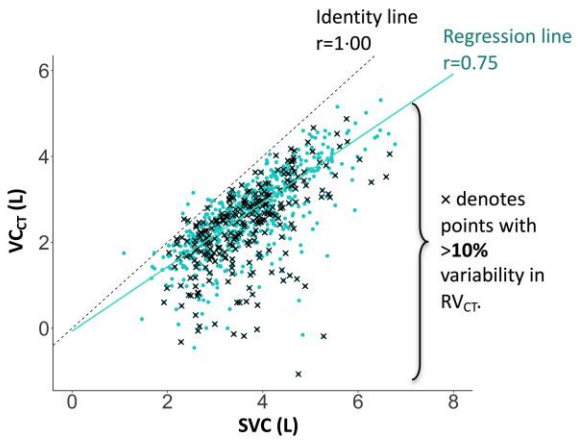
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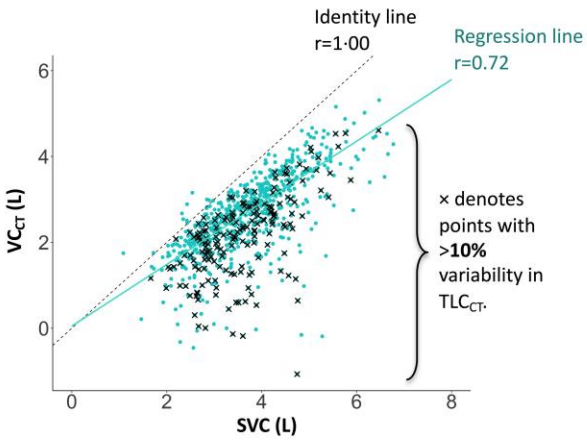
SVC (L)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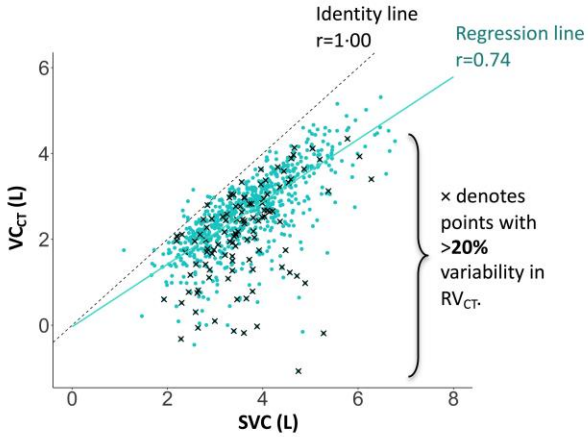
SVC (L)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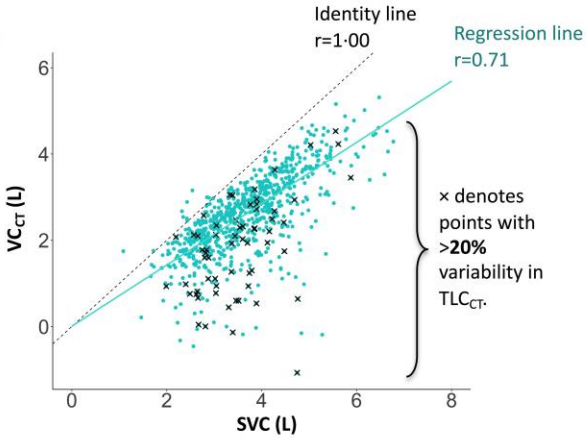
SVC (L)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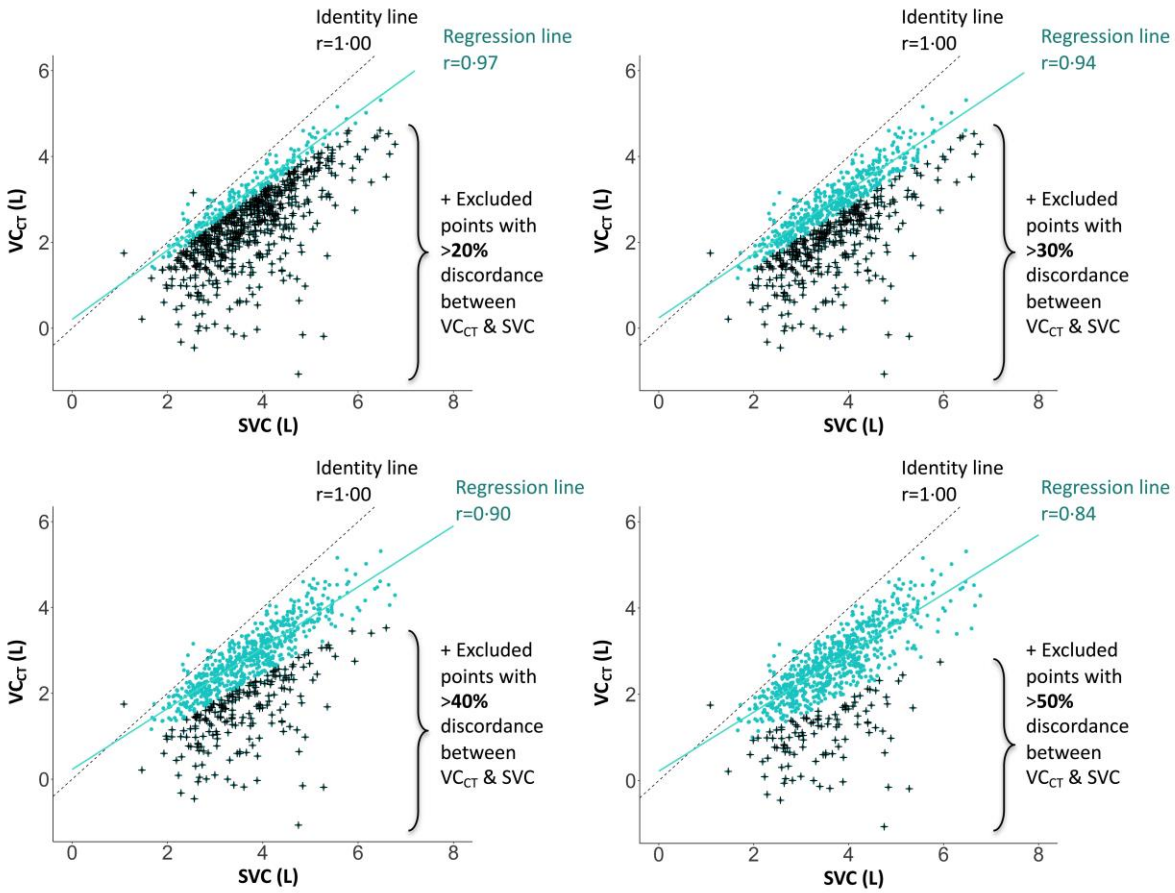
SVC (L)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SVC (L)
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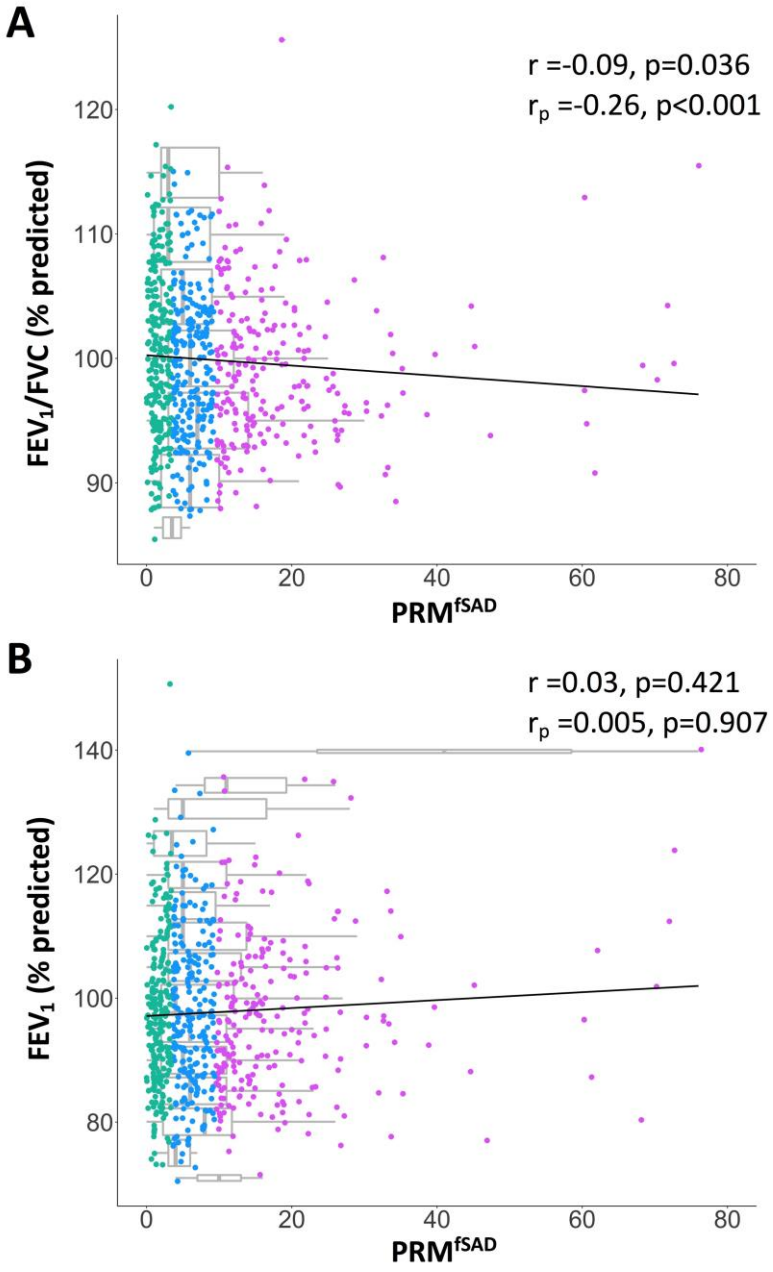
4
6
8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60
80
PRM^{fSAD}
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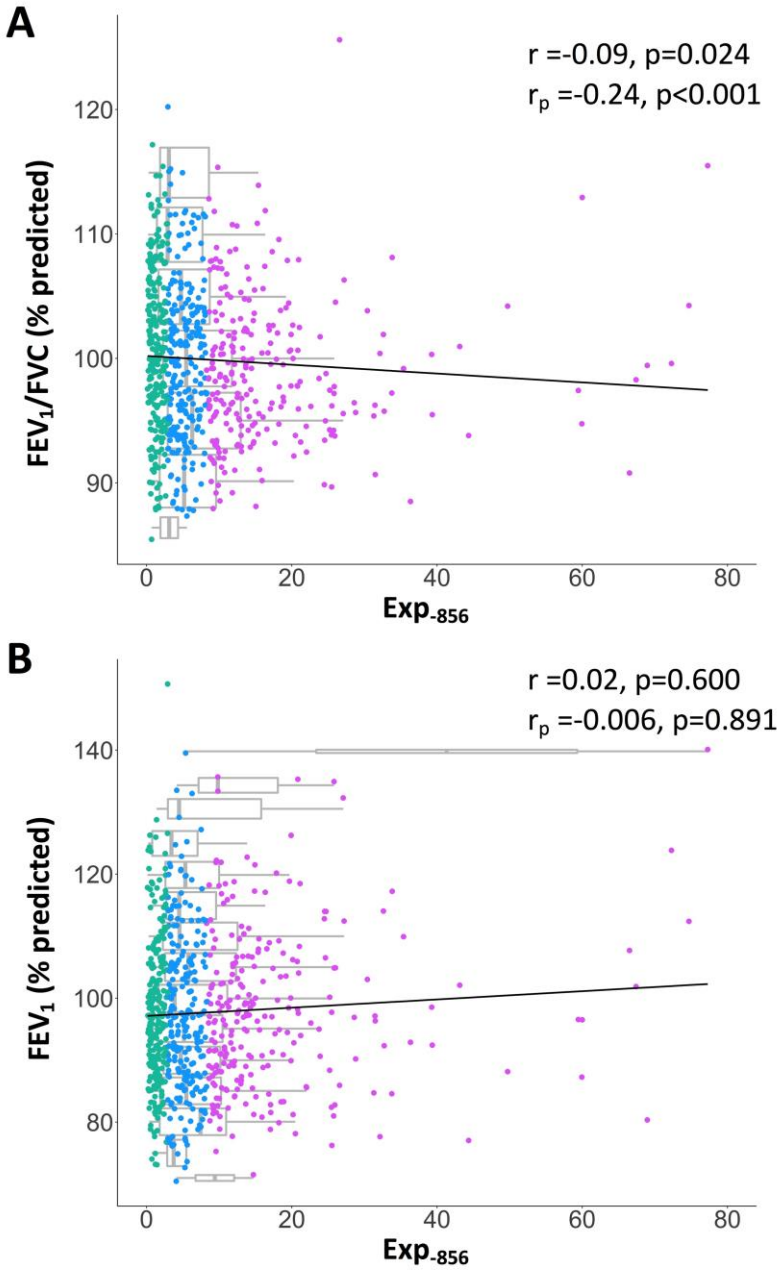
PRM^{fSAD}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40
60
80
Exp_{-856}
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120
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20
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80
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