Radiographic lung volumes predict progression to COPD in smokers with preserved spirometry in SPIROMICS

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Radiographic lung volumes and related computed tomography measures that represent air trapping are associated with an accelerated decline in lung function and can identify susceptible smokers at increased risk of progressing to overt COPD <http://bit.ly/32QqiKQ>

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ABSTRACT The characteristics that predict progression to overt chronic obstructive pulmonary disease (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 Subpopulations and Intermediate Outcome Measures in COPD Study (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 modelling.

Among these subjects with normal forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio, CT-measured residual volume (RV_{CT}) to total lung capacity (TLC_{CT}) ratio 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 with 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 (OR 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.

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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 dyspnoea, reduced functional capacity and higher mortality [7, 8]. However, its consequence in those at risk for COPD but with preserved spirometry (normal forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC) ratio) 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 >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 hypothesised 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 computed tomography (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 multicentre observational study enrolled 2981 participants from 2010 through 2015 [10]. The study included persons 40–80 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 categorised 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 μ g per inhalation and ipratropium at a dose of 18 μ g 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 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

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(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 ($FEV_1/FVC \geq 0.70$ after bronchodilator use and FVC equal to or above the predicted lower limit of normal [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 the supplementary appendix and shown in supplementary figures S1 and S2. Using this cohort (described in supplementary 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 (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 preceding 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 percentage of the lung voxels with attenuation < -856 HU 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 percentage of the lung voxels on inspiratory CT images with attenuation < -950 HU ($Insp_{-950}$) 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 10 mm internal perimeter (P_{110}) [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

FIGURE 1 Subject flow. 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.

covariates were derived and examined [20]. To examine these distributions in more detail, 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 dyspnoea scale (mMRC), COPD assessment test (CAT), Saint George's Respiratory Questionnaire (SGRQ) and Short Form 12-item Survey (SF12)), body-mass index, airflow obstruction, dyspnoea 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 analysed using mixed effect modelling 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 (e.g. 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 modelling, as well as the 95% confidence intervals 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 modelling 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 modelling was used to analyse the association of RV_{CT}/TLC_{CT} and CT indices of air trapping with time to the first hospitalisation. In addition, the association of those indices with number of severe respiratory exacerbations, as defined by number of emergency room and hospital admissions, were analysed using mixed-effect Poisson regression modelling 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 ($\geq 12\%$ 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 CT-measured vital capacity (VC_{CT}) and slow vital capacity (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).

FIGURE 2 Correlation between computed tomography-measured residual volume to total lung capacity ratio (RV_{CT}/TLC_{CT}) and forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) or FEV₁ in smokers with preserved spirometry. Boxplots show the distribution of RV_{CT}/TLC_{CT} [raw value] by 5% increments in FEV₁/FVC % predicted (Panel a), and 5% increments in FEV₁ % predicted (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} strata, respectively. The black line represents the regression line for all the points. 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.

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 $40 \pm 7\%$ for the entire cohort, and $33 \pm 3\%$, $40 \pm 2\%$ and $48 \pm 4\%$ 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, respectively; table 1).

During this follow-up period, and after adjustment for covariates (age, sex, height, weight, smoking status, smoking burden and baseline FEV₁/FVC), FEV₁/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 FEV₁/FVC over the follow-up period ($p < 0.001$) (tables 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 with those with intermediate RV_{CT}/TLC_{CT}, and those with intermediate RV_{CT}/TLC_{CT} had greater decline compared with those with low RV_{CT}/TLC_{CT} ($p = 0.005$) (table 3 and figure 4). Overall, subjects with high RV_{CT}/TLC_{CT} ($\geq 42.7\%$ absolute value) were nearly 6-times more likely to develop COPD compared with those with low RV_{CT}/TLC_{CT} ($\leq 36.6\%$ 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) (supplementary table S3).

The RV_{CT}/TLC_{CT} and follow-up time interaction analysis showed the rate of decline in FEV₁/FVC to be greater in those with high RV_{CT}/TLC_{CT} compared with 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 supplementary table S4).

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					
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
Female sex 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 % pred	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 % pred	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 % pred	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%} % pred	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 P _{i10}	3.701±0.082	3.692±0.083	3.697±0.080	3.715±0.083	0.030
Thickest P _{i10}	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

Continued

TABLE 1 Continued

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)
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 years	63.2±9.8	58.3±9.0	62.8±9.7	68.3±7.8	<0.001
Height 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 % pred	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 % pred	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 % pred	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%} % pred	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
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 1 year n (%)	58 (11.7)	9 (5.6)	23 (13.7)	26 (15.7)	0.010
After 2 years n (%)	59 (13.4)	7 (5.2)	23 (15.1)	29 (19.1)	0.001
After 3 years n (%)	53 (19.6)	6 (8.6)	19 (19.0)	28 (28.0)	0.006

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF_{25–75%}: forced expiratory flow at 25–75% of FVC; FEF_{75%}: forced expiratory flow at 75% of FVC; 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 P_{i10} : square root of wall area of a hypothetical airway with 10 mm 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}: percentage of the lung voxels with attenuation <–856 Hounsfield Unit on the expiratory CT images; Insp_{–950}: percentage of the lung voxels on inspiratory CT images with attenuation <–950 Hounsfield Units; 6-MWD: 6-minute walk distance; BODE: body-mass index, airflow obstruction, dyspnoea, and exercise capacity index; CAT: COPD assessment test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: Saint George's Respiratory Questionnaire; SF12: Short Form 12-Item Survey. [#]: At least one follow-up spirometry was available for a subgroup of the patients. Reference equations: measures of pulmonary function and % predicted of normal values were calculated using Crapo-predicted formulae [22–24]. Bronchodilator responsiveness was defined as ≥12% and ≥200 mL increase in FEV₁ after bronchodilator administration.

TABLE 2 Associations of changes in lung function or symptoms with computed tomography-measured residual volume/total lung capacity (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

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. FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75%}: forced expiratory flow at 25-75% of FVC; FEF_{75%}: forced expiratory flow at 75% of FVC; 6-MWD: 6-minute walk distance test; BODE: body-mass index, airflow obstruction, dyspnoea and exercise capacity; CAT: COPD assessment test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: Saint George's Respiratory Questionnaire; SF12: Short Form 12-Item survey. p-values are from mixed-effect linear regression modelling with a nested random subject and site effect. Significant associations are shown in bold.

The changes in FEV₁ and FVC (or forced expiratory flow at 25-75% of FVC (FEF_{25-75%}) and forced expiratory flow at 75% of FVC (FEF_{75%})) were not statistically significantly different between the RV_{CT}/TLC_{CT} strata during the follow-up period. However, the decline in FEV₁/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} (supplementary 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^{ISAD} and Exp₋₈₅₆ showed wide but less varied distributions across FEV₁/FVC and FEV₁ (supplementary figures S3 and S4). Among the 496 subjects with high VC_{CT} and SVC concordance and follow-up data, FEV₁/FVC declined in PRM^{ISAD} - and Exp₋₈₅₆-dependent manners such that those in high and intermediate tertiles for either PRM^{ISAD} or Exp₋₈₅₆ had greater decline compared to those in the low tertile (p-values of 0.038 and 0.035 for PRM^{ISAD} and Exp₋₈₅₆, respectively, for FEV₁/FVC decline) (supplementary tables S6, S7 and S8). Accordingly, those in the groups with higher PRM^{ISAD} or Exp₋₈₅₆ were more likely to progress to develop spirometric COPD (supplementary 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^{ISAD} or Exp₋₈₅₆ (supplementary table S10).

Other CT indices of emphysema and airway disease examined, including PRM^{EMPH}, Insp₋₉₅₀ and P₁₁₀, were not associated with progression to spirometric COPD (supplementary table S11).

To better understand the importance of RV_{CT}/TLC_{CT} compared with other CT parameters, we included all measured 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 FEV₁/FVC decline and COPD development in smokers with preserved spirometry (supplementary table S12).

TABLE 3 Associations of changes in lung function or symptoms with computed tomography-measured residual volume/total lung capacity (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	0.525
	Intermediate	−23.7	−65.2 to 18.5	
	Low	Ref.		
FVC mL	High	29.3	−35.1 to 94.5	0.623
	Intermediate	4.6	−53.9 to 62.7	
	Low	Ref.		
FEV ₁ /FVC %	High	−1.43	−2.31 to −0.57	0.005
	Intermediate	−0.91	−1.69 to −0.12	
	Low	Ref.		
FEF _{25–75%} mL	High	−86.2	−185.5 to 12.2	0.164
	Intermediate	−77.4	−165.7 to 11.4	
	Low	Ref.		
FEF _{75%} mL	High	−53.2	−107.8 to 1.0	0.127
	Intermediate	−42.7	−91.7 to 6.7	
	Low	Ref.		
Expiratory time s	High	0.13	−0.55 to 0.81	0.120
	Intermediate	0.60	−0.02 to 1.21	
	Low	Ref.		
6-MWD m	High	−15.4	−32.2 to 1.2	0.041
	Intermediate	−19.4	−34.6 to −4.2	
	Low	Ref.		
BODE index	High	0.20	0.02 to 0.39	0.074
	Intermediate	0.16	−0.01 to 0.32	
	Low	Ref.		
CAT score	High	−0.007	−1.208 to 1.202	0.999
	Intermediate	−0.019	−1.133 to 1.089	
	Low	Ref.		
mMRC	High	0.175	0.025 to 0.327	0.031
	Intermediate	0.172	0.033 to 0.311	
	Low	Ref.		
SGRQ total score	High	1.68	−0.72 to 4.12	0.312
	Intermediate	0.18	−2.05 to 2.45	
	Low	Ref.		
SGRQ symptom score	High	1.99	−1.84 to 6.02	0.604
	Intermediate	1.23	−2.33 to 4.88	
	Low	Ref.		
SGRQ activity score	High	3.28	0.10 to 6.50	0.138
	Intermediate	1.49	−1.51 to 4.45	
	Low	Ref.		
SGRQ impact score	High	0.99	−1.31 to 3.32	0.692
	Intermediate	0.34	−1.77 to 2.47	
	Low	Ref.		
SF12 physical component	High	−0.74	−1.72 to 0.20	0.231
	Intermediate	−0.67	−1.56 to 0.19	
	Low	Ref.		

Continued

TABLE 3 Continued

Outcome parameters	RV _{CT} /TLC _{CT} strata	Differences in estimates	95% CI	p-value
SF12 physical functioning				
	High	−1.39	−2.58 to −0.26	0.022
	Intermediate	−1.33	−2.39 to −0.30	
	Low	Ref.		

Association of changes in lung function and symptoms outcomes with computed tomography-measured residual volume/total lung capacity (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. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF_{25–75%}: forced expiratory flow at 25–75% of FVC; FEF_{75%}: forced expiratory flow at 75% of FVC; 6-MWD: 6-minute walk distance test; BODE: body-mass index, airflow obstruction, dyspnoea and exercise capacity; CAT: COPD assessment test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: Saint George's Respiratory Questionnaire; SF12: Short Form 12-Item survey; Ref: reference value. p-values are from mixed-effect linear regression modelling with a nested random subject and site effect. Significant associations are shown in bold.

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 with 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 with 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} (supplementary 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 with 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

FIGURE 3 Comparison of change in spirometry from different SPIROMICS visits across CT-measured RV/TLC (RV_{CT}/TLC_{CT}) strata. Line graphs of FEV₁/FVC values predicted from mixed-effect regression modelling ("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 FEV₁/FVC (predicted from the main model) and panel b shows the difference in rate of FEV₁/FVC change per year (predicted from the spirometry follow-up time interaction model). FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity.

TABLE 4 Association of spirometric COPD development with computed tomography-measured residual volume/total lung capacity (RV_{CT}/TLC_{CT})

Progression to spirometric COPD	At V2	At V3	At V4	On last follow-up [#]
Subjects 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}	Ref.	Ref.	Ref.	Ref.

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 with 95% confidence intervals and p-values are shown in the table. Ref: reference value. p-values are from mixed effect logistic regression with random effect. [#]: follow-up spirometry from the last available post-bronchodilator spirometry from any of the visit 2, visit 3, visit 4, (V2, V3, or V4) or the last follow-up visit available.

trapping (PRM^{fSAD} or Exp_{-856}) were not associated with changes in exercise capacity (supplementary 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 hypothesised 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

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 modelling 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. Ref: reference value; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF_{25-75%}: forced expiratory flow at 25–75% of FVC; FEF_{75%}: forced expiratory flow at 75% of FVC.

statistical significance ($p=0.074$). Other CT indices (PRM^{fSAD} or Exp_{-856}) were not associated with changes in respiratory symptoms (supplementary tables S6 and S7).

The time and $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ interaction analyses were not statistically significant with any of the measured exercise or symptoms score outcomes (supplementary table 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 hospitalisation was significantly different between the tertiles of $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$, PRM^{fSAD} , or Exp_{-856} (supplementary 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 ($\text{BMI} > 30$), 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 $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ 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 ($\text{CAT} < \text{or} \geq 10$) in the models along with $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ 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 criteria for diagnosis of COPD, instead of fixed ratio per GOLD criteria, produced similar associations between $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ and outcomes (supplementary 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 ($\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$) 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 $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ to have greater decline in lung function at a faster rate, greater likelihood of developing spirometric COPD, and greater reduction in exercise capacity compared with those with lower $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$. The relationship between higher $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ 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 $< \text{versus} \geq 10$ 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 analysed together in the same model, the $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ 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 $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ in this cohort, a possible explanation for the faster rate of lung function decline may simply be that those with higher $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ had longer duration or higher amount of smoking, causing them to have more prolonged or more severe lung damage. However, the association of $\text{RV}_{\text{CT}}/\text{TLC}_{\text{CT}}$ 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 FEV₁/FVC ratio declined in those with high RV_{CT}/TLC_{CT} to reach the threshold to be considered COPD (*i.e.* FEV₁/FVC <0.70). Although the differential changes in FEV₁ or FVC across RV_{CT}/TLC_{CT} strata did not reach statistical significance, there appeared to be contributions from decline in FEV₁ 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 in only FVC (and no change in FEV₁) to contribute to the decline in FEV₁/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 VC. The cases of lung volume measurement inaccuracy by CT may be due to the challenges with breath-hold manoeuvres 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 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 symptom 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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