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Lung volumes differentiate the predominance of emphysema *versus* airway disease phenotype in early COPD: an observational study of the COPDGene cohort

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Shareable abstract (@ERSpublications)
Lung volumes at the pre-COPD stage can identify diverging courses of disease progression and distinct clinical phenotypes. Their measurement should be more routinely incorporated in the assessment of the tobacco-exposed person at risk of COPD. https://bit.ly/3Xona5A

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Abstract

Rationale Lung volumes identify the "susceptible smokers" who progress to develop spirometric COPD. However, among susceptible smokers, development of spirometric COPD seems to be heterogeneous, suggesting the presence of different pathological mechanisms during early establishment of spirometric COPD. The objective of the present study was to determine the differential patterns of radiographic pathologies among susceptible smokers.

Methods We categorised smokers with preserved spirometry (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0) in the Genetic Epidemiology of COPD (COPDGene) cohort based on tertiles (low, intermediate and high) of lung volumes (either total lung capacity (TLC), functional residual capacity FRC or FRC/TLC) at baseline visit. We then examined the differential patterns of change in spirometry and the associated prevalence of computed tomography measured pathologies of emphysema and airway disease with those categories of lung volumes.

Results The pattern of spirometric change differed when participants were categorised by TLC *versus* FRC/TLC: those in the high TLC tertile showed stable forced expiratory volume in 1 s (FEV_1), but enlarging forced vital capacity (FVC), while those in the high FRC/TLC tertile showed decline in both FEV_1 and FVC. When participants from the high TLC and high FRC/TLC tertiles were partitioned into mutually exclusive groups, compared to those with high TLC, those with high FRC/TLC had lesser emphysema, but greater air trapping, more self-reported respiratory symptoms and exacerbation episodes and higher likelihood of progressing to more severe spirometric disease (GOLD stages 2–4 *versus* GOLD stage 1).

Conclusions Lung volumes identify distinct physiological and radiographic phenotypes in early disease among susceptible smokers and predict the rate of spirometric disease progression and the severity of symptoms in early COPD.

Introduction

COPD is a heterogeneous disease affecting only a fraction of people who have smoked tobacco (tobacco smoke-exposed persons) [1–4]. In addition, those tobacco-exposed persons who develop COPD do so through loss of lung function at variable rates [5]. The mechanisms underlying the variable susceptibility to development and progression of COPD are not well understood. Recently, we showed that lung volume indices that represent air trapping (such as the ratio of residual volume (RV) or functional residual capacity (FRC) to total lung capacity (TLC)) provide predictive information for identification of tobacco-exposed persons without spirometric obstruction (those with preserved spirometry or Global Initiative for Chronic

Obstructive Lung Disease (GOLD) stage 0) who will go on to develop airflow obstruction and symptomatic COPD, the so-called "susceptible smokers" [6, 7].

More recently, we showed that other lung volume indices, including TLC, vital capacity (VC) and inspiratory capacity (IC), can identify subgroups of susceptible smokers who have diverging patterns of spirometric disease progression [8]. Specifically, we showed that those susceptible smokers with larger baseline TLC, VC and IC were more likely to progress to milder spirometric disease (GOLD stage 1), while those with smaller baseline TLC, VC and IC were more likely to progress to more severe spirometric disease (GOLD stage 2) [8]. Although these observations are consistent with the heterogeneous nature of lung disease in COPD, the underlying mechanisms of these physiological observations remain unclear.

In this study, we aimed to understand the mechanisms underlying the interaction of lung volumes and airflow obstruction during the early disease development in COPD by examining the pathologies that are discernible on computed tomography (CT) thoracic imaging among susceptible smokers. Our hypothesis was that the susceptible smokers who progress to develop milder spirometric COPD have a predominant emphysematous phenotype while those who progress to develop moderate-to-severe spirometric disease have a predominant small airway disease phenotype. To investigate this hypothesis, we examined the baseline lung volumes, the differential patterns of change in spirometry, and the associated prevalence of CT-measured pathologies of emphysema and airway disease among tobacco-exposed persons with preserved spirometry (participants with baseline GOLD stage 0 disease) in the Genetic Epidemiology of COPD (COPDGene) cohort.

Methods

Study design

The COPDGene study is a United States-based multicentre observational prospective study designed to identify genetic factors associated with COPD that has enrolled 10 263 current and former smokers with or without a reported COPD diagnosis [9]. The COPDGene study inclusion criteria were: non-Hispanic White or African-American, current or former smokers ($\geqslant$10 pack-years) and age 45–80 years. Participants reporting a medical diagnosis of active lung diseases other than asthma, emphysema, chronic bronchitis or COPD were excluded (*e.g.* lung cancer). The goals of the COPDGene study have been to characterise phenotypes of tobacco smokers using spirometry, chest CT scans (at full inspiration (TLC) and normal exhalation (FRC)), medical history and questionnaires regarding respiratory symptoms and to perform genome-wide association studies. Local institutional review board approvals to enrol participants in COPDGene study were obtained and all participants provided informed consent to participate in the study.

Baseline (visit 1 (V1)) data were derived from all enrolled participants who had a history of smoking tobacco, had undergone pre- and post-bronchodilator spirometry (two inhalations of albuterol 90 µg per inhalation with repeat spirometry 15 min later) and had baseline chest CT imaging with radiographic lung volumes (TLC and FRC) available. Participants with preserved ratio and impaired spirometry (PRISm) were not included in this analysis. Follow-up data were derived from participants who had completed their 5- and 10-year follow-up visits (visits 2 (V2) and 3 (V3), respectively) and had pre- and post-bronchodilator spirometry and chest CT imaging with radiographic lung volumes (TLC and FRC) available.

CT indices of lung volumes, air trapping, emphysema and small airways

The detailed protocol and quality assessment of COPDGene CT scan imaging have been described previously [10]. Briefly, participants underwent two volumetric chest CT examinations, one at full inspiration (TLC) and one at the end of a relaxed exhalation (FRC). Three manufacturers and 11 different CT scanner models were used in the study including those with 16-detector (1083 participants), 40-detector (12 participants), 64-detector (1667 participants) and 128-detector (1300 participants) scanners [9]. Anonymised scans were transferred to a central imaging laboratory for quantitative analysis using a standardised protocol with image reconstruction at sub-millimetre slice thickness with smooth and edge-enhancing algorithms [9–11].

For our study, we used the following CT-measured parameters: CT-measured TLC and FRC and their ratio (FRC/TLC), CT indices of air trapping (including the percentage of the lung voxels with attenuation <-856 HU on the expiratory CT images (Exp_{-856}) [12, 13] and parametric response mapping of air trapping ($PRM^{airtrapping}$) [14, 15]), 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}) [14, 15]) and measures of airway disease (including the mean value for the square root of wall area of a hypothetical airway with 10 mm internal perimeter (Pi10) [16]).

Pulmonary function testing

The detailed protocol and quality assessment of COPDGene lung function measurements have been described previously [9]. Briefly, spirometry was performed following the American Thoracic Society (ATS) guidelines and using the EasyOne spirometer (ndd Medical Technologies, Andover, MA, USA) [17]. Spirometry was performed at baseline before and then repeated after the administration of 180 µg of inhaled albuterol. Peak expiratory flow, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and forced mid-expiratory flow were obtained for all participants. The percent-predicted values for FEV_1 and FVC were calculated using the third National Health and Nutrition Examination Survey reference values [18]. The ratio of FEV_1 to FVC was calculated using the absolute measurements in litres, and a ratio <0.70 at baseline was used to diagnose spirometric COPD, and severity of the disease was graded per the GOLD recommendations [19].

In addition to spirometry, plethysmography was performed on a subset of participants (n=432) at a single site (National Jewish Health, Denver, CO, USA). Plethysmography was performed in the seated position using an nSpire body plethysmograph (nSpire Health, Longmont, CO, USA) [20] according to the ATS and European Respiratory Society guidelines [17, 21–25]. Percent predicted of normal values for lung volumes were calculated using Global Lung Function Initiative and Stocks- and Quanjer-predicted formulas [18, 26, 27].

Data management and analysis

To examine the accuracy of the CT-measured FRC, TLC and FRC/TLC, correlations between CT-measured and plethysmographically measured lung volumes from the 432 participants who had plethysmographic data available were assessed by Pearson correlation coefficient and linear regression analysis. All further analyses were performed using the CT-measured lung volumes.

Currently, no validated reference values for CT-measured lung volumes are available. Thus, to account for common covariates, adjusted lung volumes were derived by computing the "residual" values from linear regression modelling of the absolute lung volumes over age, sex, height and weight, and were then used in further analysis.

Regression modelling was done using lung volumes as continuous and categorical variables. Stratification of lung volumes into categorical variables were done based on our previous studies from electronic health records of patients with history of smoking but preserved spirometry (GOLD-0), which showed that approximately one-third of such patients had lung volumes greater than their predicted upper limit of normal values [6]. Based on those findings, and considering the lack of reference values for CT-measured lung volumes for their stratification as normal and abnormal, we stratified the participants into three equal categories of low, intermediate and high tertiles using their adjusted lung volumes (*i.e.* tertiles of FRC, tertiles of TLC and tertiles of FRC/TLC).

Longitudinal outcome of developing spirometric COPD were assessed at the 5-year follow-up visit (V2) and analysed with respect to the adjusted lung volumes (TLC, FRC and FRC/TLC) tertiles using mixed-effect logistic modelling. Longitudinal changes in spirometric indices (FEV_1, FVC and FEV_1/FVC) were calculated by subtracting the subsequent visit (V2) values from the baseline visit (V1) values and analysed with respect to the adjusted lung-volume tertiles using mixed-effect linear modelling. All models were adjusted for age, sex, height, weight, smoking status (current *versus* former), smoking burden (pack-years) and years between the visits as fixed effects, and study site as the random effect. Additionally, models for spirometric indices were also adjusted for their respected spirometric index baseline value (for example, the model for change in FEV_1 included baseline FEV_1 from V1 as a covariate in the model). Distributions of subsequent GOLD stages at V2 with respect to the lung-volume tertiles were summarised and compared using one-way ANOVA with Tukey–Kramer *post hoc* test for multiple-group comparisons.

Because the high tertiles of TLC and FRC/TLC seemed to provide diverging predictive models for change in spirometric indices, we then generated mutually exclusive categories of high TLC (but no high FRC/TLC) and high FRC/TLC (but no high TLC), as well as a third category that included those with both high TLC and high FRC/TLC, and compared the baseline characteristics and longitudinal outcomes between these categories.

CT-related mechanistic measures ($Insp_{-950}$, PRM^{emph}, Exp_{-856}, $PRM^{airtrapping}$ and Pi10) and characteristics and outcomes including bronchodilator responsiveness, exercise capacity (6-min walk distance), symptoms (modified Medical Research Council dyspnoea scale (mMRC), cough and St George's Respiratory

Questionnaire (SGRQ)), and self-reported severe exacerbations were examined at baseline and subsequent visits using mixed-effect logistic or linear modelling (for binary or continuous dependent variables, respectively) with adjustment for age, sex, height, weight, smoking status (current *versus* former) and smoking burden (pack-years) as fixed effects, and study site as the random effect.

Data management, distribution analysis, and mixed-effect regression were done in R (version 4.0.1; R Foundation for Statistical Computing, Vienna, Austria). Figures were generated in GraphPad Prism (version 9.0.0; GraphPad Software, San Diego, CA, USA).

Results

Participants' characteristics

Figure 1 shows the participant selection flow for this study. From the original 10 720 participants in COPDGene study, 4409 were categorised to have preserved spirometry (GOLD-0), of whom, 2159 had complete follow-up data available at 5-year visit (table 1 and supplementary table S1). At baseline visit, those 2159 participants were 51% female, 49% current smokers, had a mean±SD age 58±8 years and 37±20 pack-years of smoking history. 20% had bronchodilator responsiveness by FEV_1. 13% proceeded to develop spirometric COPD by the 5-year follow-up visit. Lung volume indices (TLC, FRC and FRC/TLC) had a wide distribution across spirometric indices (FEV_1 and FEV_1/FVC) among smokers with preserved spirometry (figure 2).

Correlation between radiographically and physiologically measured lung volumes

The characteristics of the 432 COPDGene participants who had plethysmography are shown in the supplementary table S2. Among those 432 participants, CT-measured TLC and FRC were closely correlated with plethysmographically measured TLC and FRC (correlation coefficients of 0.94 and 0.91, respectively), and were closely associated in linear regression models (β=1.02 and 1.32, respectively; $p<0.001$) (figure 3).

Association of lung volumes with progression to spirometric COPD

In age-, sex-, height- and weight-adjusted linear regression models, higher TLC, FRC and FRC/TLC were statistically significantly associated with the greater decline in FEV_1/FVC regardless of whether lung volume indices were included as continuous (supplementary table S3) or categorical (low, intermediate,

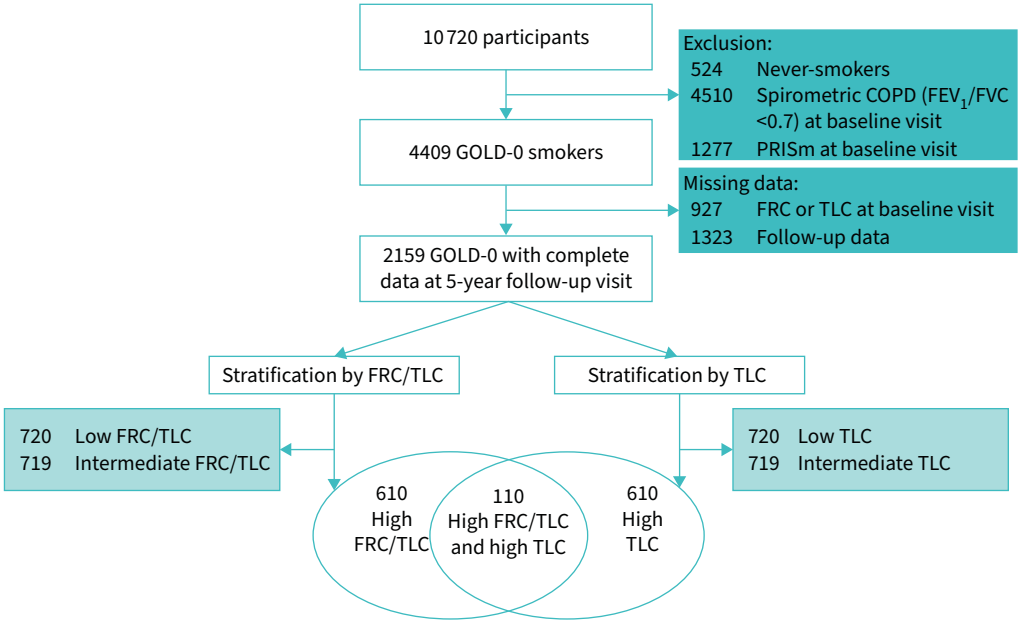

FIGURE 1 Participant flow through the study protocol. GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FRC: functional residual capacity; TLC: total lung capacity.

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TABLE 1 Participant characteristics

	GOLD-0	High adjusted FRC/TLC and high adjusted TLC	High adjusted FRC/TLC	High adjusted TLC	p-value (high FRC/TLC *versus* high TLC)
Demographics					
Participants	2159	110	610	610	
Age (years)	57.9±8.4	59.5±8.7	56.8±8.5	57.3±7.8	0.499
Female	1108 (51.3)	51 (46.4)	332 (54.4)	286 (46.9)	0.022
Height (cm)	170.0±9.4	171.0±10.1	169.8±9.6	170.6±9.4	0.316
BMI ($kg \cdot m^{-2}$)	29.2±5.7	28.4±6.3	29.3±6.1	29.3±5.9	0.995
Current smoker	1064 (49.3)	63 (57.3)	392 (64.3)	243 (39.8)	<0.001
Smoking history (pack-years)	37.0±20.4	48.0±25.7	37.2±21.4	36.4±19.4	0.787
Baseline spirometry					
FEV_1 (L)	2.88±0.68	3.02±0.76	2.70±0.64	3.21±0.68	<0.001
FEV_1 (% pred)	98±12	98±13	95±11	103±12	<0.001
FVC (L)	3.67±0.89	3.98±0.98	3.43±0.84	4.16±0.88	<0.001
FVC (% pred)	96±12	99±12	94±11	102±11	<0.001
FEV_1/FVC	0.79±0.05	0.76±0.04	0.79±0.05	0.77±0.05	<0.001
FEV_1/FVC (% pred)	101±6	98±5	101±7	100±6	0.061
$FEF_{25-75\%}$ (L)	2.75±0.99	2.48±0.92	2.65±0.96	2.88±0.95	<0.001
$FEF_{25-75\%}$ (% pred)	103±31	92±27	100±31	104±29	0.078
Bronchodilator responsiveness in FEV_1 (mL)	93.0±152.2	126.3±151.6	75.4±176.9	121.9±143.6	<0.001
Bronchodilator responsiveness in FEV_1 (%)	3.7±5.9	4.8±6.0	3.5±7.6	4.2±4.8	0.152
Bronchodilator responsiveness by FEV_1	422 (19.5)	10 (9.1)	54 (8.9)	33 (5.4)	0.046
Baseline CT indices					
FRC (L)	2.77±0.67	3.85±0.79	2.89±0.64	2.95±0.58	0.236
TLC (L)	5.43±1.25	6.42±1.17	4.68±0.98	6.45±1.12	<0.001
FRC/TLC (%)	52±9	60±5	62±6	46±5	<0.001
IC (L)	2.66±0.87	2.57±0.54	1.79±0.48	3.50±0.72	<0.001
Pi10	1.96±0.41	2.02±0.40	2.17±0.47	1.82±0.34	<0.001
PRM^{emph}	0.80±1.57	1.65±2.65	0.72±1.68	1.02±1.60	0.001
$PRM^{airtrapping}$	9.16±6.98	15.83±10.19	10.89±8.37	8.81±6.04	<0.001
Exp_{-856}	10.40±8.46	19.24±12.15	12.57±9.30	10.38±7.86	<0.001
$Insp_{-950}$	2.20±2.80	2.66±3.32	1.21±1.93	3.35±3.41	<0.001
Visit 2					
Participants	2159	110	610	610	
Follow-up (years)	5.6±0.8	5.5±0.7	5.7±0.9	5.6±0.7	0.080
Progression to COPD	280 (13.0)	38 (34.5)	70 (11.5)	94 (15.4)	0.127
Annualised change in FEV_1 (mL)	−43±48	−59±49	−42±53	−47±47	0.165
Annualised % change in FEV_1 (%)	−1.48±1.65	−2.02±1.59	−1.52±1.90	−1.45±1.42	0.763
Annualised change in FVC (mL)	−42±64	−49±67	−40±70	−48±62	0.075
Annualised % change in FVC (%)	−1.13±1.74	−1.26±1.56	−1.14±1.97	−1.14±1.46	0.999
Annualised % change in FEV_1/FVC (%)	−0.33±1.16	−0.78±1.29	−0.36±1.24	−0.30±1.06	0.650

Continued

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TABLE 1 Continued

	GOLD-0	High adjusted FRC/TLC and high adjusted TLC	High adjusted FRC/TLC	High adjusted TLC	p-value (high FRC/TLC *versus* high TLC)
Visit 3					
Participants	480	23	113	140	
Follow-up (years)	10.0±0.4	10.0±0.3	9.9±0.3	10.1±0.4	<0.001
Progression to COPD	86 (17.9)	12 (10.9)	21 (3.4)	27 (4.4)	0.989
Annualised change in FEV_1 (mL)	−39±26	−43±25	−39±27	−43±29	0.507
Annualised % change in FEV_1 (%)	−1.77±1.45	−1.97±1.59	−1.92±1.58	−1.71±1.46	0.515
Annualised change in FVC (mL)	−37±37	−38±23	−35±43	−43±37	0.301
Annualised % change in FVC (%)	−1.27±1.32	−1.20±0.93	−1.34±1.64	−1.28±1.13	0.934
Annualised % change in FEV_1/FVC (%)	−0.48±0.92	−0.72±1.46	−0.59±1.01	−0.40±0.88	0.294

Data are presented as n, mean±SD or n (%), unless otherwise stated. Reference equations: percent predicted of normal values of spirometry and lung volumes were calculated using the third National Health and Nutrition Examination Survey, Global Lung Function Initiative and Quanjer predicted formulas [18, 27]. Bronchodilator responsiveness was defined as ⩾12% and ⩾200 mL increase in forced expiratory volume in 1 s (FEV_1) after bronchodilator administration. GOLD: Global Initiative for Chronic Obstructive Lung Disease; FRC: functional residual capacity; TLC: total lung capacity; BMI: body mass index; FVC: forced vital capacity; $FEF_{25-75\%}$: maximum airflow at mid-lung volume; CT: computed tomography; IC: inspiratory capacity; Pi10: the mean for the 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; $PRM^{airtrapping}$: PRM of percentage air trapping; Exp_{-856}: percentage of the lung voxels with attenuation <−856 HU on the expiratory CT images; $Insp_{-950}$: percentage of the lung voxels on inspiratory CT images with attenuation <−950 HU.

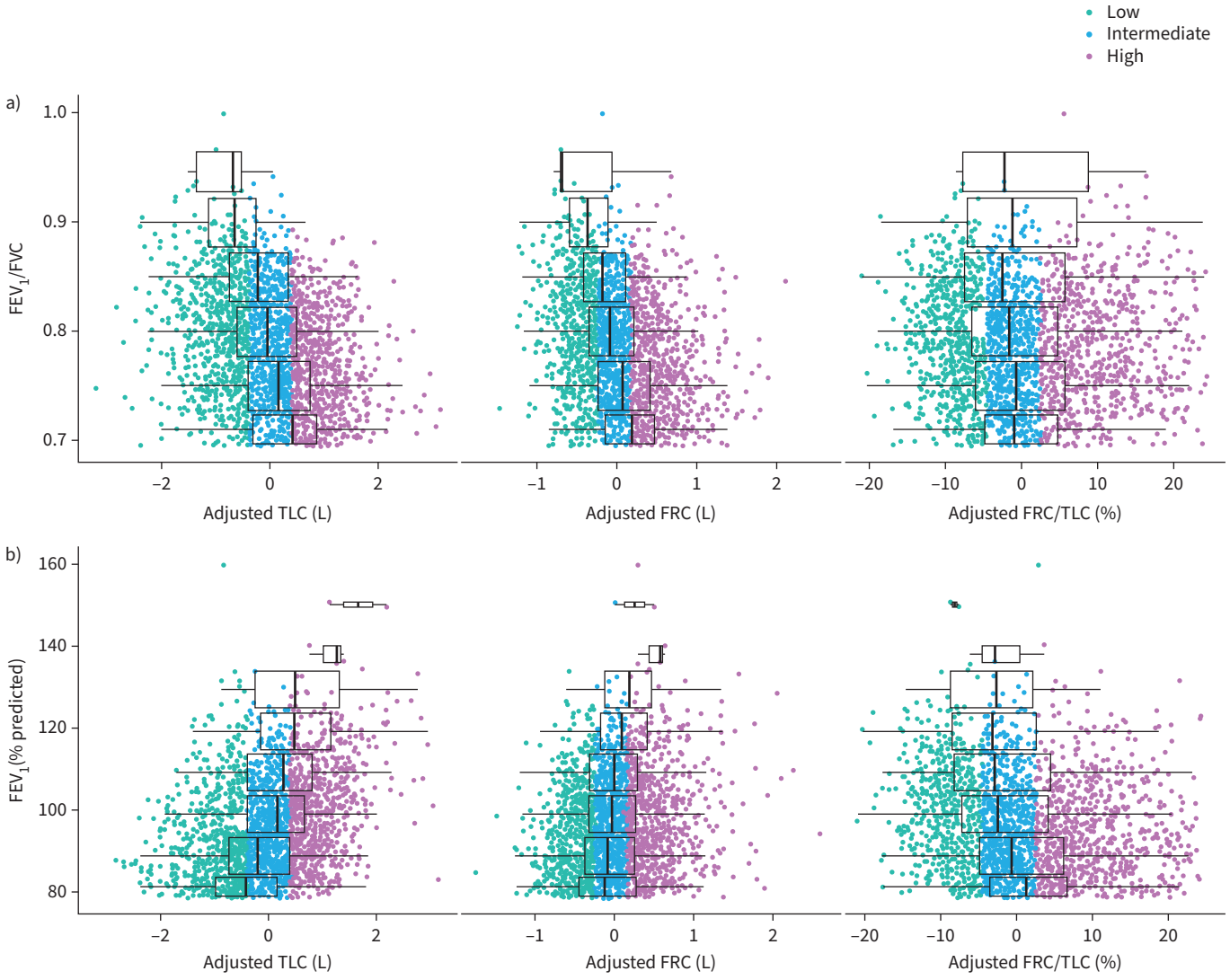

FIGURE 2 Distribution of lung volumes *versus* spirometry. Association between lung volumes (total lung capacity (TLC), functional residual capacity (FRC), FRC/TLC) and the spirometric indices a) forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) and b) FEV_1 in the baseline cohort. Boxplots represent distributions of age-, sex-, height- and weight-adjusted lung volumes against 5% increments in FEV_1/FVC or FEV_1. Participants' lung volumes (TLC, FRC and FRC/TLC) were stratified into tertiles of low, intermediate and high.

high tertile) variables (all p<0.038) (figure 4). Accordingly, higher TLC and FRC were associated with higher likelihood of developing spirometric COPD (p<0.001); the association of higher FRC/TLC with developing spirometric COPD did not reach statistical significance (p=0.10) (figure 4).

Remarkably, the pattern of decline in FEV_1/FVC towards development of spirometric COPD was different when participants were categorised by TLC *versus* FRC/TLC: participants with higher TLC had a relatively stable FEV_1, but a relatively enlarging FVC over the 5-year follow-up time (p<0.001), while those with higher FRC/TLC had a relative decline in both FEV_1 and FVC over the 5-year follow-up time (p<0.002 and p<0.007, respectively) (figure 4).

The severity of spirometric COPD that was developed (*e.g.* by GOLD stage) was also distinct when participants were categorised by TLC *versus* FRC/TLC: those with higher TLC were more likely to develop GOLD-1 disease and less likely to develop PRISm or GOLD-2 disease. Conversely, those with higher FRC/TLC were less likely to develop GOLD-1 disease, but more likely to develop PRISm and GOLD-2 disease (figure 5).

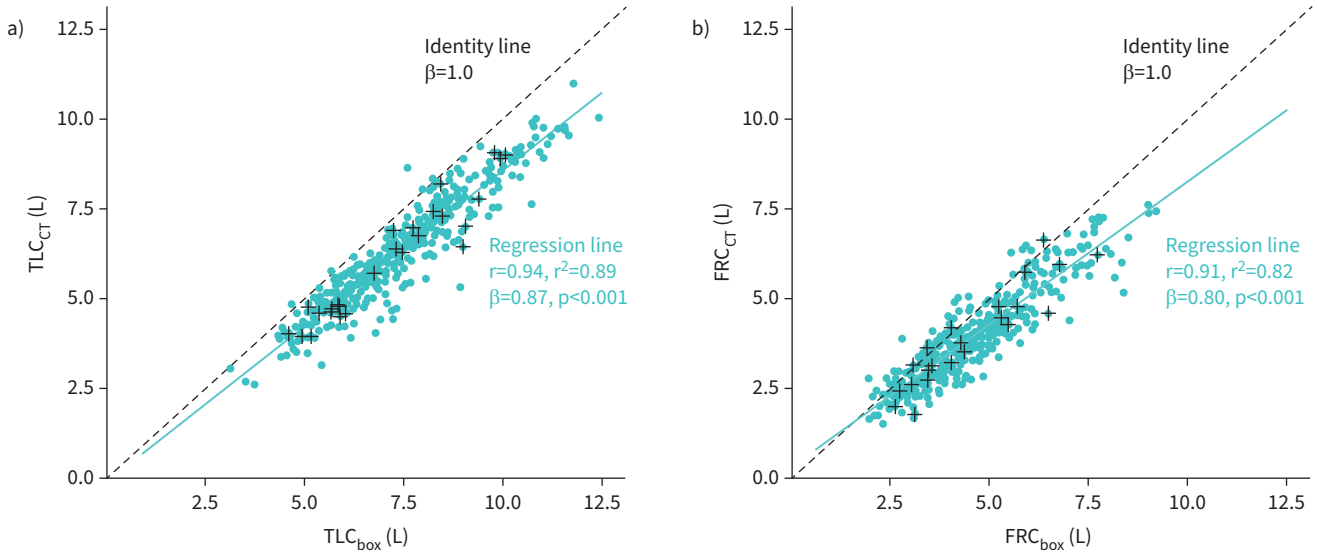

FIGURE 3 Correlation between plethysmographic and computed tomography (CT)-measured lung volumes. The charts show a linear relationship between plethysmographically measured (box) and CT-measured a) total lung capacity (TLC) and b) functional residual capacity (FRC) among a subgroup of 432 participants in the COPDGene study who had plethysmography in addition to CT imaging. +: denotes those whose plethysmography and CT imaging were done >1 year apart; r: coefficient of correlation; β: regression coefficient; r^2: coefficient of determination. p-values are from regression models.

When categorised by FRC, the spirometric changes were more similar to categorisation by TLC than to categorisation by FRC/TLC (figure 4).

While fewer datapoints from 10-year follow-up visit were available (n=480), similar trends of associations were observed, although some were no longer significant (supplementary figures S1 and S2).

Stratification for comparing categories of TLC versus *FRC/TLC*

Because of the distinct pattern of spirometric evolution when participants were stratified by their baseline TLC *versus* FRC/TLC, we generated mutually exclusive categories of high TLC *versus* high FRC/TLC, as well as a third category of participants with high TLC and high FRC/TLC (figure 1). The characteristics of these strata are shown in table 1 and supplementary table S4. Among the 2159 participants with preserved spirometry (GOLD-0), 610 had high TLC, but not high FRC/TLC ("hyperexpanded"); 610 had high FRC/TLC, but not high TLC ("air trapped"); and 110 had high TLC and high FRC/TLC ("air trapped and hyperexpanded" or "hyperinflated") (figure 1).

Baseline radiographic mechanisms associated with TLC versus *FRC/TLC categories*

Examination of the CT-measured metrics for emphysema, air trapping and airway disease among the mutually exclusive lung volumes categories of high TLC and high FRC/TLC are shown in figure 6. Compared to air-trapped participants with high FRC/TLC, the hyperexpanded participants with high TLC had higher emphysema scores as measured by PRM^{emph} and $Insp_{-950}$, but lower air trapping scores as measured by $PRM^{airtrapping}$, Exp_{-856} and lower airway disease score as measured by Pi10. Interestingly, the hyperinflated participants with both high TLC and high FRC/TLC had the highest air trapping ($PRM^{airtrapping}$, Exp_{-856}) compared to either high TLC or high FRC/TLC groups, and more emphysema (PRM^{emph} and $Insp_{-950}$) compared to the high FRC/TLC group.

Baseline symptoms and outcomes associated with TLC versus *FRC/TLC categories*

Associations of the respiratory symptoms, physical activity, and exacerbation frequency with lung volume categories are shown in figure 7. Compared to air-trapped participants with high FRC/TLC, the hyperexpanded participants with high TLC had lesser respiratory symptoms by mMRC and SGRQ scores and were able to walk a greater distance on 6-min walk test. The rate of bronchodilator responsiveness and self-reported COPD exacerbation in the previous year at baseline visit seemed to be lower among those with high TLC compared to those with high FRC/TLC, but the comparisons did not reach statistical significance (p=0.070 and p=0.084 for bronchodilator responsiveness by FEV_1 and exacerbation,

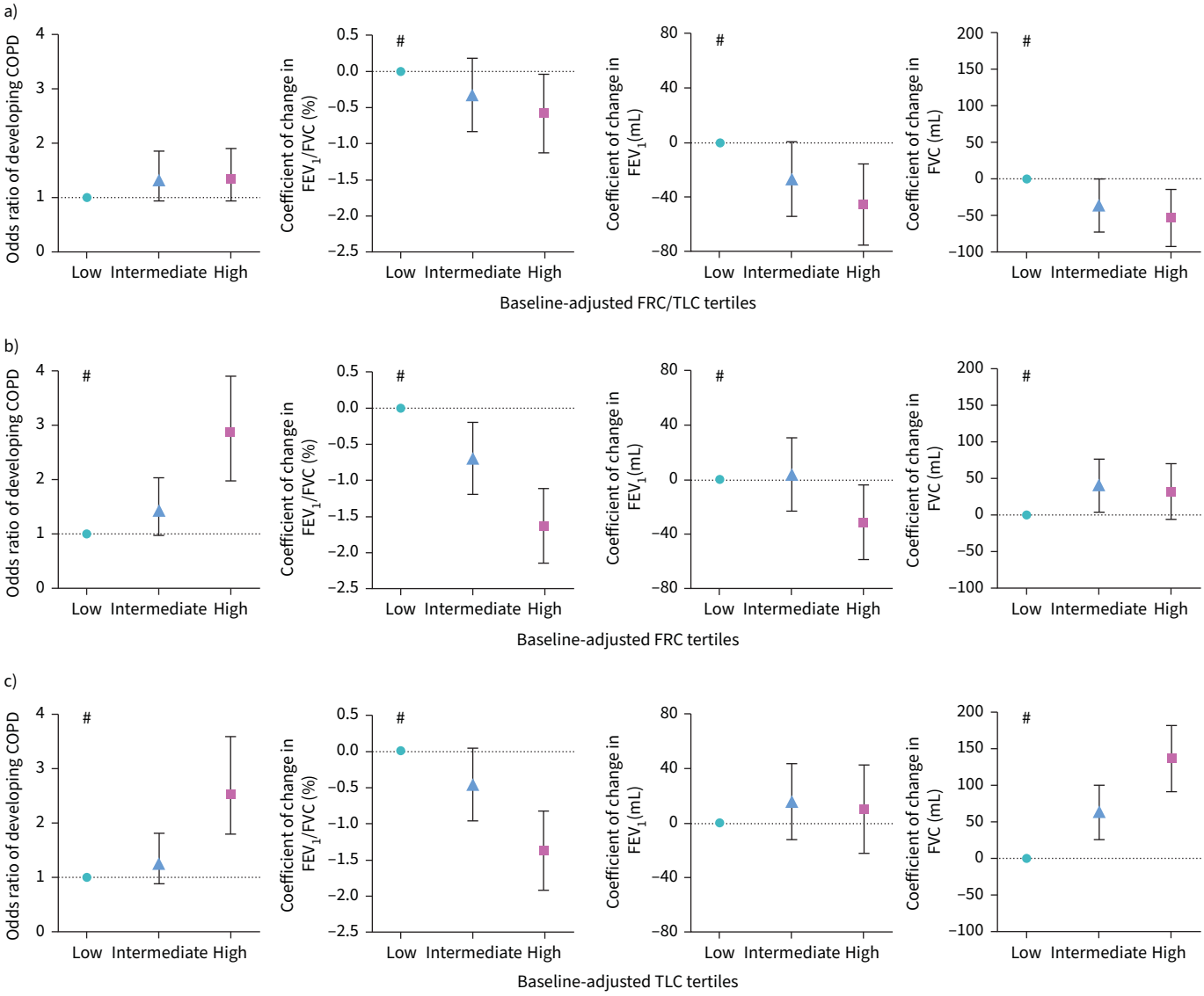

FIGURE 4 Change in spirometry with strata of lung volumes. Development of COPD and change in forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and their ratio across strata of a) functional residual capacity (FRC)/total lung capacity (TLC), b) FRC and c) TLC at 5-year follow-up visit. Coefficients (95% CI) from regression models of spirometric indices *versus* tertiles of lung volumes are shown. #: models of spirometry *versus* lung volumes that were statistically significant in linear modelling in addition to the categorical models.

respectively). Of note, the respiratory symptoms and activity level at baseline in the hyperinflated participants with both high TLC and high FRC/TLC were not significantly different to either high TLC or high FRC/TLC groups.

The severity of spirometric COPD developed (*e.g.* by GOLD stage) was also distinct when participants were categorised by TLC *versus* FRC/TLC: compared to hyperexpanded participants with high TLC, air-trapped participants with high FRC/TLC were less likely to develop GOLD-1 disease (OR 0.44, 95% CI 0.27–0.70); p<0.001) and more likely to develop PRISm (OR 4.76, 95% CI 2.63–8.33; p<0.001) (figure 5). Air trapped participants with high FRC/TLC also had a nonsignificant higher trend towards development of more severe (GOLD-2 to GOLD-4) disease (OR 1.42, 95% CI 0.72–2.78; p=0.309).

Longitudinal changes in radiographic, symptomatic and clinical outcomes findings

The TLC and FRC/TLC categories also showed divergent radiographic findings and clinical outcomes longitudinally at 5-year and 10-year follow-up visits, although fewer datapoints from those visits were

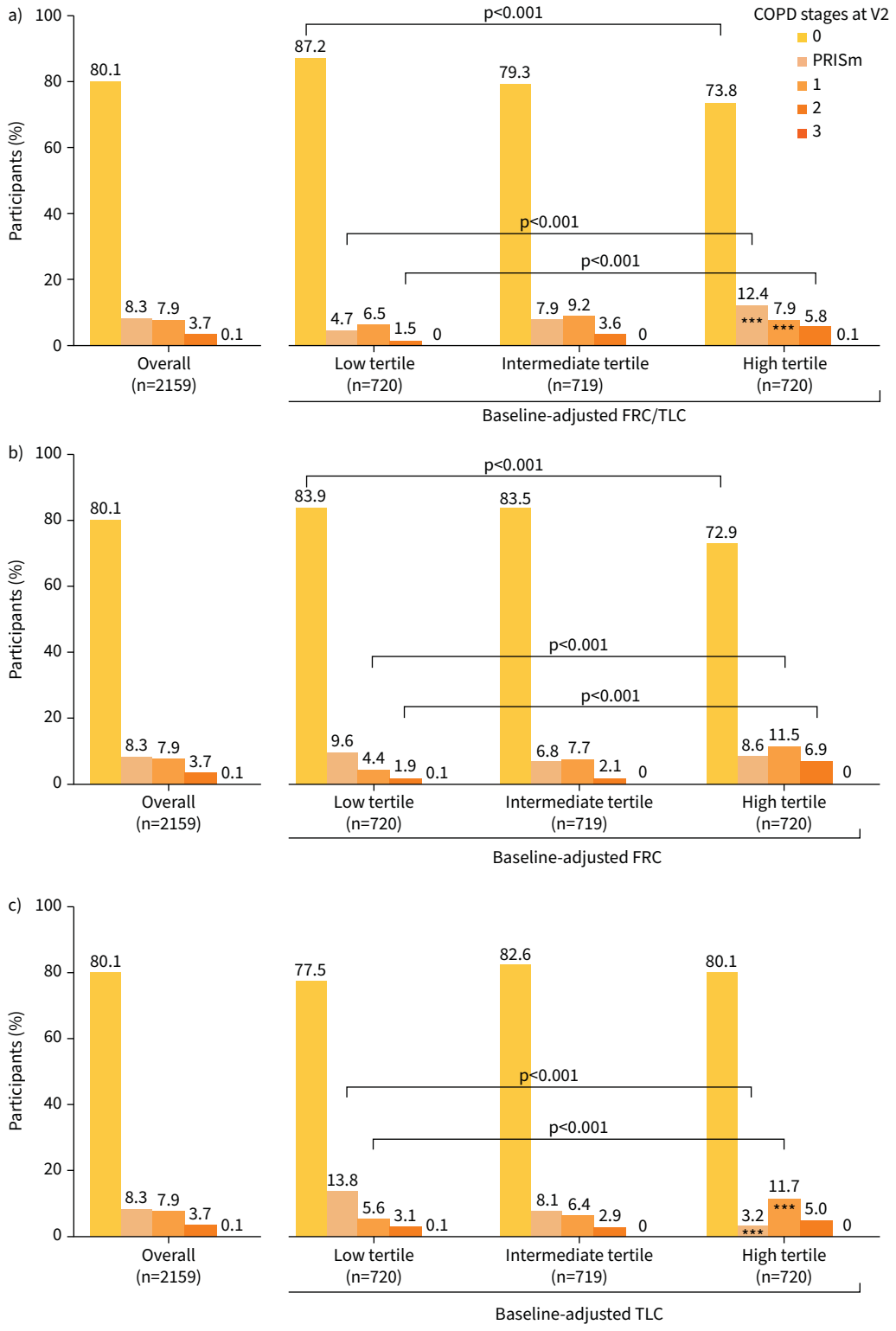

FIGURE 5 Spirometric progression of smokers with preserved spirometry (COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0) at 5-year follow-up visit (V2) stratified by lung volumes. a) Functional residual capacity (FRC)/total lung capacity (TLC), b) FRC and c) TLC. Bar plots show the distribution of COPD GOLD stage at 5-year follow-up visit with strata of baseline lung volumes. The lung volumes were adjusted for age, sex, height and weight. Horizontal bars indicate statistically significant comparisons of the percentages between the high-tertile group in each lung volume stratification with the low-tertile group within that stratification using one-way ANOVA with the Tukey–Kramer *post hoc* test. The symbols on the bars indicate

statistically significant comparisons of the likelihood of progressing to the corresponding GOLD stages between the high tertiles of different lung volume stratifications using mixed-effect logistic modelling with adjustment for age, sex, height, weight, smoking status (current *versus* former) and smoking burden (pack-years). GOLD stage 4 was omitted at 5-year follow-up because no participants developed GOLD stage 4. PRISm: preserved ratio and impaired spirometry. ***: p<0.001.

available compared to baseline, and some comparisons were no longer statistically significant (supplementary table S5 and supplementary figures S3, S4, S5 and S6).

Discussion

In this analysis of a large cohort of tobacco-exposed persons with preserved spirometry (GOLD stage 0) from the COPDGene study with 10-year follow-up, we found that lung volume indices in the pre-COPD stage can identify distinct physiological and radiographic phenotypes and predict the future disease severity as spirometric COPD develops. We first established the validity of CT-measured lung volumes, in particular TLC and FRC, as estimates of the plethysmographically measured ones by demonstrating their tight associations. Then, we re-demonstrated the ability of different lung volume indices to identify the susceptible smokers who progress to develop airflow obstruction and spirometric COPD. Next, we showed that different lung volume indices (TLC *versus* FRC/TLC) could identify subgroups of susceptible smokers who are prone to develop diverging severity of spirometric obstruction and symptomatic disease. Finally, we found potential mechanistic radiographic explanations for the diverging lung volume categories that we had identified, specifically the high TLC category representing those tobacco-exposed persons with more radiographic evidence for emphysematous pathology and high FRC/TLC category representing those tobacco-exposed persons with more radiographic evidence of airway disease and airflow obstruction pathology. These findings were independent of the smoking status (current or former) in these tobacco-exposed persons with ⩾10 pack-years of smoking.

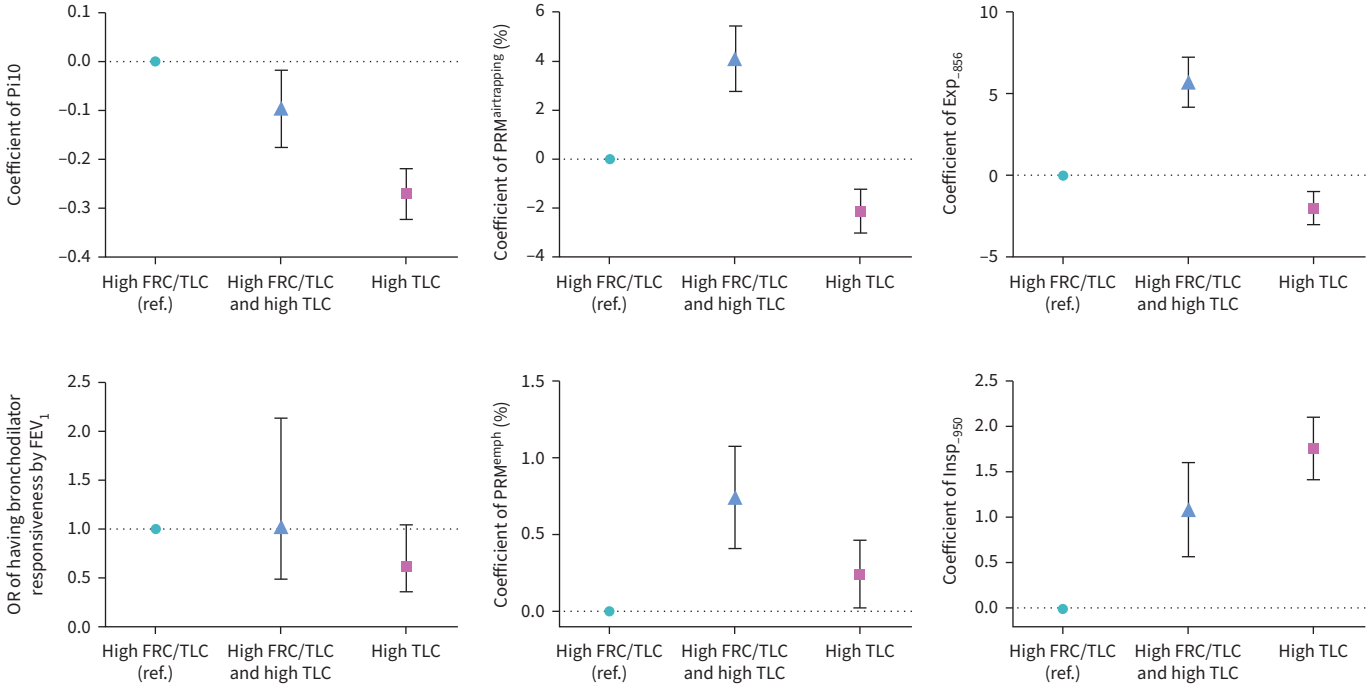

FIGURE 6 Baseline radiographic features among smokers with preserved spirometry (COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0) stratified by lung volumes. Coefficients (95% CI) from regression models of computed-tomographic (CT)-measured indices of high total lung capacity (TLC) tertile relative to high functional residual capacity (FRC)/TLC (reference). Pi10: mean square root of wall area of a hypothetical airway with 10 mm internal perimeter; $PRM^{airtrapping}$: parametric response mapping for air trapping; Exp_{-856}: lung voxels with attenuation <−856 HU on the expiratory CT images; FEV_1: forced expiratory volume in 1 s; PRM^{emph}: parametric response mapping for emphysema; $Insp_{-950}$: lung voxels on inspiratory CT images with attenuation <−950 HU.

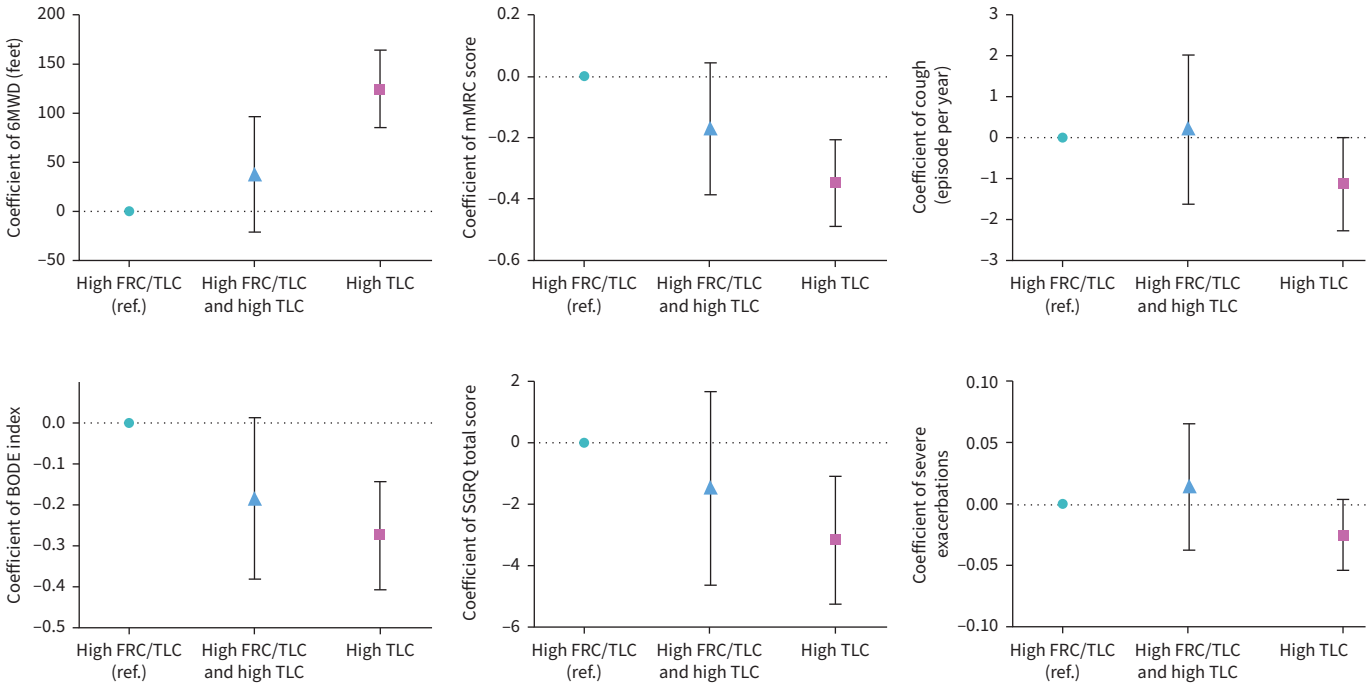

FIGURE 7 Baseline clinical characteristics among smokers with preserved spirometry (COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0) stratified by lung volumes. Coefficients (95% CI) from regression models of clinical characteristics of high total lung capacity (TLC) tertile relative to high functional residual capacity (FRC)/TLC (reference). 6MWD: 6-min walk distance; mMRC: modified Medical Research Council; BODE index: body mass index, airflow obstruction, dyspnoea and exercise index; SGRQ: St George's Respiratory Questionnaire.

These findings also provide mechanistic explanation for our previous observation of the lung volumes biphasic distribution across the severity of airflow obstruction in COPD from three population cohorts of real-world patients and research participants [8]. In those studies, we showed that lung volumes, in particular TLC, VC and IC, have higher values in people with mild COPD (GOLD-1) compared to those with no spirometric obstruction (GOLD-0) or those with moderate disease (GOLD-2), an unexpected finding given the assumption that higher airflow obstruction causes hyperinflation with larger TLC and smaller VC and IC. Longitudinal analysis of those data showed that in fact different subgroups of tobacco-exposed persons with preserved spirometry (GOLD-0) progress to mild (GOLD-1) *versus* moderate (GOLD-2) disease: those with larger baseline TLC, VC and IC went on to develop mild disease (GOLD-1) while those with smaller baseline TLC, VC and IC went on to develop moderate (GOLD-2) disease [8]. Our current study provides a potential mechanistic basis for this observation. Specifically, it seems that the tobacco-exposed persons who progress from GOLD-0 to GOLD-1 disease have differentially more emphysema, but less airway disease, which may potentially cause a decrease in their lung elastance while maintaining airway calibre with resulting larger TLC, but also larger VC and IC. In contrast, the tobacco-exposed persons who progress from GOLD-0 to GOLD-2 disease have differentially more airway disease, but less emphysema, which may cause more severe airflow obstruction and air trapping with resulting smaller VC and IC, and with hyperinflation and enlarging of TLC only developing with more severe obstruction in GOLD stages 3 and 4. These findings provide a foundation for the biphasic distributions of lung volumes across the spectrum of the spirometric obstruction in COPD, by signifying that increased TLC in mild disease, a hyperexpanded as opposed to hyperinflated state, has different implications to increased TLC in more advanced disease when the presence of severe airway disease and airflow obstruction causes air trapping and hyperinflation.

While it is unclear what the biological mechanisms underlying the distinct pathologies associated with different patterns of lung volumes in pre-COPD are, these observations do suggest that different pathologies may become important in different individuals and at different stages of disease. Moreover, differential lung function growth during childhood due to genetic, environmental or nutritional factors [27–34] may also contribute to the lung volume phenotypes observed here with lower lung growth and thus lower lung volumes being associated with higher risk for development of airflow obstruction and

symptoms [5, 35–39]. Overall, our findings help dissect the heterogeneity of COPD and identify physiological and clinical phenotypes in early and mild disease with important clinical implications. For example, a recent study of the use of inhaled bronchodilators in tobacco-exposed persons with preserved spirometry did not find any improvement in symptoms with the use of those inhaled medications [28]. However, lung volumes were not measured in that study and thus may not have been used to differentiate between tobacco-exposed persons with preserved spirometry with high FRC/TLC (airway disease phenotype) who could potentially be more likely to respond to bronchodilators *versus* tobacco-exposed persons with preserved spirometry with high TLC (emphysema phenotype) who could be less likely to benefit from such therapy. Thus, identifying phenotypes of tobacco-exposed persons in this pre-COPD disease stage using lung volumes would have major implications in terms of discovery of specific biomarkers and design of appropriate therapies for targeting precise stages and phenotypes of disease.

Further research for validation and characterisation of the lung volume phenotypes in pre-COPD is necessary. However, our current study, in combination with other relevant publications [6–8, 40], could provide adequate guidance to generate preliminary recommendations for management of tobacco-exposed persons at risk for COPD. In particular, given that air trapping, as suggested by abnormal (or high-normal) RV/TLC or FRC/TLC, can identify susceptible smokers [6, 7, 40], lung volume measurements should be considered for all people at risk for COPD who are referred for screening spirometry, especially if their test shows that they do not meet the spirometric criteria for COPD (that is, those who have GOLD-0). Furthermore, because of the higher prevalence of symptoms and airway disease in those with high FRC/TLC, management strategies such as bronchodilator therapy should be reserved for tobacco-exposed persons with preserved spirometry who have airway-predominant phenotype (high FRC/TLC); however, evidence for effectiveness of bronchodilator treatment in tobacco-exposed persons with preserved spirometry, but with air trapping is currently lacking, a knowledge gap that demands further investigation. Finally, given that over a third of people with combination of high FRC/TLC and high TLC develop spirometric COPD (table 1), preventative strategies such as smoking cessation should be prioritised towards people with pre-COPD who have both high emphysema and high airway disease burden.

Our study has several limitations. First, the lung volume measures used in this analysis were computed from CT scanning images obtained in the supine position, and did not include spirometry gating; therefore, CT-measured lung volumes may have underestimated the actual TLC and/or overestimated the actual FRC measurements. However, at least in the subgroup of participants who also had plethysmography, the corresponding measurements were closely correlated with each other, providing confidence in accuracy of the CT-measured values. Furthermore, CT imaging is an emerging modality for evaluation of lung physiology and pathology in COPD with merits of its own. Second, the categorisation of lung volume indices by tertiles is an arbitrary approach, as reference values for CT-measured lung volumes are unavailable. However, analysis using lung volumes as continuous variables showed similar associations, validating the overall concept studied here with evaluation of “high” *versus* “low” values for comparison. Finally, although the findings of the study were concluded from well-adjusted regression analysis, the longitudinal evaluation of spirometric data included a limited number of observations at 5- and 10-year follow-up visits with decreasing number of participants at the 10-year visit to increase our confidence in the spirometric trends we witnessed. Although, it has been reported that the spirometric indices may fluctuate over time, there is no clear rationale to support that such fluctuations could result in finding the trend that we observed, including considerations such as presence of asthma. In addition, sensitivity analysis with exclusion of those participants with history of asthma did not significantly affect the trends that were observed.

In conclusion, different lung volume indices can identify divergent physiological and radiographic phenotypes in early disease among tobacco-exposed persons with preserved spirometry and can help to predict the rate of spirometric disease progression and the severity of symptoms in early COPD. These findings further corroborate our previous reports on the utility of lung volumes as an additional dimension in evaluation of COPD, and emphasises their utility for dissection of its heterogeneity. Future research should focus on the biological pathways underlying these lung volumes-based phenotypes in pre-COPD.

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The COPDGene study is registered at www.ClinicalTrials.gov with identifier number NCT00608764. The Department of Veterans Affairs (VA) EHR dataset generated and analysed during the current study were created through the VA Informatics and Computing Infrastructure (VINCI) resource and are available on VINCI digital platform to the VA. Clinical and research data along with the definition of variables are available on NIH dbGaP for the COPDGene study (phs000179.v6.p2).

Ethics approval: The University of California San Francisco Institutional Review Board and the San Francisco Veterans Affairs Health Care System Committee on Research and Development approved the study protocols. The study was also approved by the COPDGene Ancillary Studies and Publications Committee.

Author contributions: M. Arjomandi and S. Zeng conceived and designed the study. S. Zeng, R.P. Bowler and M. Arjomandi developed study protocols. S. Zeng, G. Luo, R.P. Bowler and M. Arjomandi analysed and interpreted data. S. Zeng, G. Luo, D.A. Lynch, R.P. Bowler and M. Arjomandi prepared and edited the manuscript. S. Zeng, G. Luo, D.A. Lynch, R.P. Bowler and M. Arjomandi obtained funding.

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