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A novel spirometric measure identifies mild chronic obstructive pulmonary disease unidentified by standard criteria

Short Title: A novel spirometric criterion for mild COPD

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This article has an online data supplement.

Abstract

Rationale: In chronic obstructive pulmonary disease both smaller and larger airways are affected. Forced expiratory volume in one second (FEV_1) mainly reflects large airways obstruction, while the later fraction of forced exhalation reflects reduction in terminal expiratory flow.

Objective: To evaluate the relationship between spirometric ratios, including the ratio of forced expiratory volume in 3 and 6 seconds (FEV_3/FEV_6), and small airway measures and gas trapping in quantitative chest computed tomography (CT), and clinical outcomes in the COPDGene cohort.

Methods: 7,853 current and ex-smokers were evaluated for airflow obstruction using recently-defined linear iteratively-derived equations of Hansen et al.[1] to determine lower limits of normal equations for pre-bronchodilator FEV_1/FVC, FEV_1/FEV_6, FEV_3/FEV_6 and FEV_3/FVC. General linear and ordinal regression models were applied to the relation between pre-bronchodilator spirometry and radiologic and clinical data.

Main Results: Of the 10,311 participants included in the COPDGene Phase 1 study, participants with incomplete quantitative CT or relevant spirometric data were excluded, resulting in 7,853 participants in the present study. Of 4,386 participants with ratio of FEV_1 to forced vital capacity (FEV_1/FVC) greater than lower limit of normal, 15.4% had abnormal FEV_3/FEV_6. Compared to participants with normal FEV_3/FEV_6 and FEV_1/FVC, abnormal FEV_3/FEV_6 was associated with significantly greater gas trapping, St. George Respiratory Questionnaire score, mMRC dyspnea score, BODE index, and shorter six-minute walking distance (all $P < 0.0001$), but not CT-evidence of emphysema.

Conclusions: Current and ex-smokers with pre-bronchodilator FEV_3/FEV_6 < lower limit of normal as the sole abnormality identifies a distinct population with evidence of small airway disease in quantitative CT, impaired indices of physical function and quality of life otherwise deemed normal by current spirometric definition.

Key words: airway obstruction, spirometry, thoracic radiology, COPD

Introduction

Expiratory airflow obstruction is the key finding supporting chronic obstructive pulmonary disease (COPD) diagnosis. Airflow obstruction prevalence varies widely by definition used[1-5]. Recently, Hansen et al. defined equations characterizing pre-bronchodilator normal values for several spirometric variables using the Third National Health and Nutrition Examination Survey (NHANES) database[1]. For this analysis, lower limits of normal (LLN) resides at 5th percentile of each decade of age, and results in a more balanced estimation of LLN than previous approaches[6,7]. These new reference ranges were further evaluated here[1].

Small airways are frequently involved early in the course of COPD with significant pathologic changes before symptom onset and spirometry changes[8-10]. Forced expiratory volume in one second (FEV_1) mainly reflects large airways obstruction. Since the later fraction of forced exhalation (e.g. FEV_3) better reflects smaller airway contributions, it may be a more sensitive measure to diagnose early airway obstruction in COPD[11,12]. Spirometric ratios have less variability than timed forced expirations[12,13]. Accumulating evidence suggests many current or former smokers have clinical, radiological and physiological abnormality not identified by currently-used spirometric measures[9,14-16]. The FEV_1 forced vital capacity (FVC) ratio may remain within the “normal” range even after considerable airway damage has occurred. FEV_3/FEV_6 and FEV_3/FVC have been proposed as measures capable of detecting small airways disease hence mild COPD manifestations[11,17]. Supportingly, a greater number of smokers were found below LLN for FEV_3/FEV_6 than for FEV_1/FEV_6[1] and below LLN for FEV_3/FVC than for FEV_1/FVC[1,18]. However, the clinical importance of an isolated low pre-bronchodilator FEV_3/FEV_6 or FEV_3/FVC in smokers remains unknown.

We aimed to determine whether FEV_3/FEV_6<LLN and FEV_3/FVC<LLN were associated with quantitative computed tomography (CT) and other COPD-related clinical outcomes in subjects with normal pre-bronchodilator spirometry by standard criteria (e.g., FEV_1/FVC>LLN) in the COPDGene cohort[19]. Quantitative computed tomography (CT) is useful for *in vivo* assessment of lung morphological changes and provides visual and quantitative assessment of COPD[20,21]. In particular, quantitative CT is useful to quantify emphysema percentage and distribution, airway dimensions changes, and gas trapping severity in COPD[22-24]. We hypothesized that abnormal FEV_3/FEV_6 and FEV_3/FVC would be associated with quantitative CT abnormalities and adverse clinical manifestations.

Materials and Methods

Study population and data collection

We utilized data from COPDGene for participants enrolled between 2007 and 2011[19]. The cohort includes 10,311 non-Hispanic white and African-American men and women, 45-80 years old, with ≥10 pack-years smoking history. COPDGene study excluded those with pregnancy, previous lung resection surgery, active cancer treatment, or history of lung disease other than asthma and COPD[19]. For the present study, excluding those with incomplete CT and spirometric data yielded 7,853 participants (see *online supplement*). As clinical and functional correlates, we used St. George's Respiratory Questionnaire (SGRQ)[25] (permission was obtained for use of this instrument), modified Medical Research Council (mMRC) dyspnea scale[26] and BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) scores[27], and six-minute walking distance (6MWD)[28]. Institutional Review Boards approved the study at 21 participating centers (see *online supplement*). Participants provided written informed consent.

Spirometry and quality control

Spirometry was performed using an ultrasound-based spirometer (EasyOne™, Model 2001, NDD Medizintechnik AG, Zurich, Switzerland) before and after albuterol administration following ERS/ATS recommendations[29]. Positive bronchodilator response was defined as an increase in FEV_1 and/or FVC ≥12% of baseline and 200 ml[29]. *Online supplement* presents quality control assurance details.

In our analysis, we defined LLN criteria abnormality originating from spirometry data of the Third NHANES, in which only pre-bronchodilator responses were collected[1]. For our analysis, values of the pre-bronchodilator FEV_1, FVC, FEV_3, and FEV_6 from the best test were chosen; best test was defined as the maneuver with the largest FVC and FEV_1 sum. % predicted values were calculated from NHANES-III equations[6,30].

Quantitative CT analysis

CT scans were acquired at full inspiration and after tidal expiration (see *online supplement*). Emphysema is defined as morphologically loss of alveolar tissue[31]. Percentage of low attenuation areas below −950 Hounsfield Units (HU) on end-inspiratory CT scan is thought to represent emphysema%[22]. Airway disease was assessed by segmental airway wall area percentage[32]. Two additional measurements assessed small airway disease by means of expiratory scans. Gas trapping% was defined as %lung voxels below −856 HU on expiratory scans[33]. Expiratory/inspiratory ratio of mean lung attenuation (E/I MLA) was defined as the ratio of mean lung attenuation from density histograms on inspiratory and expiratory scans[34].

Statistical analyses

SPSS 22.0 procedures were used (Armonk, NY: IBM Corp.) (also see *online supplement*). Relationships between spirometry (independent variable) and CT, clinical and functional correlates (dependent variables) were assessed by multiple linear regression models using age, sex, race, pack-year smoking, body mass index (BMI) and CT scanner type (only for CT measures) as covariates. Covariates were retained if $P<0.10$. Quantitative CT, SGRQ and 6MWD were log transformed; regression coefficients (β) were then back-transformed to aid interpretation. Compared to a reference category, relative differences for outcome variables were determined by $(e^{\beta}-1)\times100\%$, while holding other predictors constant (see *online supplement*). A proportional odds model was used for ordinal outcomes (BODE and mMRC). Analyses were performed separately for the whole study population and the $FEV_1/FVC\geq LLN$ subgroup. $P<0.05$ was considered statistically significant.

To define impairments in the $FEV_1/FVC\geq LLN$ subgroup, we selected explanatory variables predicting important outcomes and reasonable thresholds in COPD: FEV_1 %predicted <65%, mMRC scale dyspnea ≥2, 6MWD <350 meters, SGRQ >25 and BODE score >2[27,35]. To define clinically meaningful radiologic abnormality, we used newly described cutoffs: 3.5 for emphysema% and 21 for gas trapping%[36].

Results

Spirometric characterization

Subject characteristics for the 7,853 participants are presented in Table 1. Pre-bronchodilator FEV_1/FVC was <LLN in 3,467 (44.1%) participants, thus defining, by standard

criteria, those having airflow obstruction; the remaining 4,386 (55.9%) had no recognizable airflow obstruction.

Abnormality of FEV_1/FVC and FEV_3/FEV_6 in the overall group

In the overall group, participants <LLN for either FEV_1/FVC (3,467; 44.1%) or FEV_3/FEV_6 (3,965; 50.5%) criteria were older, had lower BMI, longer smoking history and were more likely Caucasian. These individuals also had lower spirometric measurements, higher pulmonary structural impairments, dyspnea, SGRQ and BODE scores and shorter 6MWD (Table 1). Correlates of FEV_1/FVC and FEV_3/FEV_6 abnormality in the overall subject group are presented in *online supplement*, e-Table 1.

Correlates of FEV_3/FEV_6 abnormality in participants with FEV_1/FVC ≥LLN

Of subjects with normal FEV_1/FVC, more (677, 15.4%) had FEV_3/FEV_6 <LLN than FEV_3/FVC <LLN (312, 7.1%). Those with FEV_3/FEV_6 <LLN had significantly worse spirometric, clinical outcomes and CT indices (with exception of emphysema %) than those with FEV_3/FEV_6 ≥LLN (Figure 1, Table 2). While individuals with FEV_3/FVC <LLN had significantly worse spirometry and SGRQ, their quantitative CT results (except E/I MLA) were not significantly different from those with FEV_3/FVC ≥LLN (Table 2).

Importantly, association of FEV_3/FEV_6 abnormality with structural and clinical outcomes was significant –though somewhat weaker than in the overall group (e-Table 1)– in non-obstructed participants (FEV_1/FVC ≥LLN) (Table 3): gas trapping% was 27.5% greater, WA% was 1.8% greater and E/I MLA was 2.0% greater than those with FEV_3/FEV_6 ≥LLN. We also observed 40.8% greater SGRQ and 7.2% shorter 6MWD in those with abnormal FEV_3/FEV_6.

They were also more likely to be in higher mMRC category (adjusted OR: 1.6, 95% CI: 1.4 – 1.9, P<0.0001) and BODE index (adjusted OR: 2.8, 95% CI: 2.1 − 3.7, P<0.0001) compared with FEV_3/ FEV_6 ≥LLN subjects (Table 3).

Finally, to better understand if reversible smooth muscle contraction was a significant determinant of these findings, we excluded 1,708 (21.7%) participants with a positive bronchodilator response. Results in those 3,868 with negative bronchodilator response and with FEV_1/FVC ≥LLN showed essentially the same associations of FEV_3/FEV_6 abnormality as in the wider group (e-Table 2).

Multivariable analyses in the subgroup without airflow obstruction but with FEV_3/FVC <LLN (Table 4) showed significant associations with CT parameters reflecting small airways disease (gas trapping% and E/I MLA), SGRQ, mMRC and BODE. Notably, however, strength of these associations was lower than for FEV_3/FEV_6 (Tables 3 and 4).

Impairments in subjects with FEV_3/FEV_6 abnormality and FEV_1/FVC ≥LLN

Among those with normal spirometry by FEV_1/FVC criteria, impairments in radiological and clinical outcomes were significantly more common among those with FEV_3/FEV_6 <LLN compared to FEV_3/FEV_6 ≥LLN participants, except CT evidence of emphysema (Figure 2, e-Table 5). This finding further supports that abnormal FEV_3/FEV_6 in patients with otherwise normal spirometry have worse clinical symptoms, less functional capacity and worse air trapping, but not significantly greater emphysema%.

Discussion

We identified 677 (15.4%) current and former smokers classified as non-obstructed using standard pre-bronchodilator spirometric criteria ($FEV_1/FVC \geq LLN$) in the COPDGene population in whom FEV_3/FEV_6 was abnormal. This group with FEV_3/FEV_6 as the sole abnormality showed impairments in quantitative CT indices (gas trapping%, E/I MLA and segmental wall area, but not emphysema%) as well as shorter 6MWD, increased mMRC, SGRQ and increased BODE scores. We believe that this analysis establishes a criterion that detects mild structural, functional and clinical abnormalities in subjects otherwise deemed normal by standard spirometric definitions.

Increasing evidence suggests that a large fraction of current or former smokers have clinical, radiological and physiological disease not consistently identified by spirometry[9,14-16]. FEV_3/FEV_6 and FEV_3/FVC identified significantly more subjects below LLN than FEV_1/FVC and FEV_1/FEV_6 in the never-smoker NHANES-III population, but the clinical importance of these abnormalities was unknown[1].

Our study is the first to extensively characterize smokers with FEV_3/FVC or FEV_3/FEV_6 as the sole abnormality with respect to pulmonary structural impairment, functional and patient-reported outcomes. We found abnormality in small airway measures (gas trapping% and E/I MLA), segmental airway wall area, FEV_1%pred, FEV_1/FVC %pred, SGRQ, mMRC, BODE and 6MWD each associated with abnormal FEV_3/FEV_6 (Tables 1-3).

Compared with FEV_1/FVC, FEV_3/FVC more sensitively identified reductions in terminal expiratory flow and, accordingly, is able to diagnose mild airflow obstruction[37]. Morris et al. suggested that isolated reduction in FEV_3/FVC (without other spirometric abnormality) may indicate early injury accompanied by hyperinflation and gas trapping[37,38]. We found that isolated

FEV_3/FVC abnormality was not as diagnostic of either CT abnormalities or of COPD-related patient-reported or functional outcomes (Tables 2 and 4).

Structural features in quantitative CT were correlated with FEV_1/FVC, FEV_1/FEV_6, FEV_3/FEV_6 and FEV_3/FVC (e-Table 8). CT features that had strongest correlation with spirometric ratios were small airway measures. These findings are similar to previous results showing that airflow obstruction correlates with emphysema%, gas trapping% and airway dimensions[22,23,39]. Hersh et al. found that gas trapping%, a prominent indirect sign of small airways disease, had a strong correlation with emphysema% and may fail to distinguish between gas trapping caused by emphysema and by small airways disease[24,34,40]. They described an index, the E/I MLA, utilizing paired inspiratory and expiratory images, as a more reliable small airway disease measure in smokers[34,41]. Indeed, we found strong correlation between E/I MLA and all spirometric airflow obstruction indices, including FEV_3/FEV_6 ($r=-0.65$) and FEV_3 %predicted ($r=-0.51$). It is reasonable to infer that significant correlations of gas trapping and E/I MLA with spirometric measurements are a consequence of hyperinflation due to small airways injury.

Lung elastic recoil loss causing expiratory airflow limitation results from emphysematous lung destruction. However, presence of emphysema does not consistently elicit spirometric airway obstruction. Hoesein et al. presented a longitudinal analysis showing that patients initially exhibiting emphysema on CT but without airflow abnormality (defined as FEV_1/FVC <70%) were prone to develop FEV_1 and FEV_1/FVC decline in follow-up studies[42]. Their results suggest that FEV_1/FVC is not sensitive enough to diagnose mild structural changes until emphysema severity exceeds a certain threshold. Our results indicate indirect CT measures of small airways disease in a subset of subjects with otherwise normal spirometry (Table 2). We observed significantly lower FEV_1 %predicted and FEV_1/FVC in participants with FEV_3/FEV_6 <LLN

compared to $FEV_3/FEV_6 \geq$LLN; however these values do not reach diagnostic criteria for abnormality in FEV_1/FVC LLN (Table 2). This finding supports that there is lung structure and function loss in the subgroup not yet recognized as abnormal by $FEV_1/FVC <$LLN[17]. Targeting this undiagnosed population is of great importance, since functional small airways dysfunction is associated with FEV_1 decline in non-obstructed smokers and small airway function improves starting from the first week of smoking cessation in smokers who do not have airflow obstruction[43,44].

Small airways have been regarded as the lung's "silent zone", because obstruction within them causes little spirometric abnormality until obstruction is far advanced[45]. Microstructural studies in COPD showed that morphological small airways changes begin before emphysematous destruction starts[46,47]. In our study, subjects in whom FEV_3/FEV_6 was the sole abnormality had significantly greater gas trapping%, E/I MLA and segmental airway wall area without significantly greater emphysema% (Table 2, Figure 1). The reason for lack of association between emphysema and FEV_3/FEV_6 abnormality may be that isolated FEV_3/FEV_6 abnormality diagnoses COPD in early stages before emphysematous destruction is detectable. However, to confirm this suggestion further longitudinal analysis is required.

A vigorous physical effort and expiration time as long as 20 seconds are needed to measure FVC accurately - hard to achieve in elderly and severely obstructed patients. A shorter expiratory time causes FVC underestimation and FEV_1/FVC overestimation that may lead to false negative interpretation in patients with mild airway obstruction[12,48,49]. FEV_6 has the advantage over FVC of being independent of forced expiration duration; previous studies have shown that FEV_1/FEV_6 is a valid alternative to FEV_1/FVC to diagnose airflow obstruction[48-54]. The present study supports previous observations showing that FEV_1/FEV_6 abnormality had significantly stronger association with structural impairment (emphysema%, gas trapping%, E/I MLA and increased WA%) and to COPD-related outcomes and 6MWD, compared to using FEV_1/FVC abnormality (e-Tables 6 and 7).

Our results should be considered in light of its limitations and strengths. Distal airway walls are dominantly composed of smooth muscle[55]. Distal airway smooth muscle hypertrophy contributes to bronchodilator reversibility in COPD[56]. Varying degrees of smooth muscle contraction may cause variation in airflow limitation. Smooth muscle contraction can be partially reversed by inhaled bronchodilator administration. For this reason, using pre-bronchodilator spirometry for detection of airflow obstruction may lead to overestimation of airflow obstruction. This is the main reason for using post-bronchodilator spirometry in the current COPD definition[57]. In our analysis, we defined abnormality with regard to pre-bronchodilator LLN criteria. From this perspective, unreversed smooth muscle contraction may be one reason why we detected increased gas trapping and E/I MLA and impaired airway dimensions in $FEV_3/FEV_6 \leq LLN$ individuals. However, these structural differences remained significant after excluding bronchodilator-responsive smokers from our analysis. Whether impairments defined in this study precede full-blown COPD warrants further longitudinal analysis of this cohort. Absence of a LLN criterion for post-bronchodilator FEV_3/FEV_6 prevents us from comparing diagnostic capabilities of FEV_3/FEV_6 between pre- and post-bronchodilator measurements. Studies that have evaluated diagnostic performance of different spirometric criteria have usually made comparisons by accepting FEV_1/FVC (<LLN or <0.70) as "gold standard" in diagnosing airflow obstruction[3,58,59]. Our data demonstrates that this approach may be suboptimal for diagnosing airflow obstruction, especially mild, early or small airways disease. We acknowledge, though, that we have not demonstrated that a finding of isolated abnormality in

FEV_3/FEV_6 has prognostic or therapeutic implications. Further, like all spirometric measures, day-to-day variability in lung function and measurement error can contribute to variability of classification of those patients on the border between "normal" and mild abnormality.

Another point deserving consideration regards COPDGene inclusion strategy, which did not exclude smokers with self-reported asthma history. This inclusion strategy may cause over/misdiagnosis of patients who actually have asthma as having COPD or include those with both asthma and COPD. Such smoking asthmatics may demonstrate all of the impairments in functional, structural and quality of life indices observed in our study. We believe, spirometric monitoring during CT scanning might improve standardization and decrease variability in the quantitative CT measures. However, to our knowledge, this is not routinely done in quantitative CT imaging and was not done in the studies of the COPDGene cohort. CT scans were, however, performed by experienced staff, who coached participants to perform a maximal inspiratory maneuver and a relaxed end-expiratory maneuver. Finally, testing new LLN equations in never-smoker adults with available quantitative CT data would be advantageous to discriminate effects of aging and smoking on structural and functional alterations. Nevertheless, we believe our findings discriminate a subgroup with impairment in physiologic, functional, structural and quality of life dimensions resembling COPD not identified by using $FEV_1/FVC>LLN$ regardless of whether these smokers are called asthma-COPD overlap syndrome, smoking asthmatics or COPD.

In conclusion, increasing evidence supports presence of structural lung changes before airflow obstruction becomes evident by routine spirometric criterion[9,14-16]. Our findings, based on the examination of the largest smoker population with available quantitative CT data, demonstrate presence of structural lung changes before airflow obstruction becomes evident by the FEV_1/FVC ratio. We report for the first time that, in those with normal FEV_1/FVC, low FEV_3/FEV_6 is significantly associated with impaired CT measures, shorter 6-minute walk distance, increased dyspnea perception and lower respiratory quality of life. It seems capable of diagnosing spirometric abnormality at an early stage before marked emphysematous changes start. Whether the FEV_1/FVC normal but FEV_3/FEV_6 abnormal population defined in this study will show more rapid COPD progression is unknown. Longitudinal analysis of COPDGene and other cohorts may provide the answer to this question.

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References

1 Hansen JE, Porszasz J, Casaburi R, et al. Re-defining lower limit of normal for FEV1/FEV6, FEV1/FVC, FEV3/FEV6 and FEV3/FVC to improve detection of airway obstruction. *J COPD F.* 2015;2(2):94-102. DOI:http://dx.doi.org/110.15326/jcopdf.15322.15322.12014.10144.

2 Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax.* 2008;63(12):1046-1051.

3 Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Respir J.* 2009;34(3):588-597.

4 Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013;187(4):347-365.

5 Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005;26(5):948-968.

6 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999;159(1):179-187.

7 Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J.* 2012;40(6):1324-1343.

8 Hogg JC, Macklem PT, Thurlbeck W. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med.* 1968;278(25):1355-1360.

9 Cosio M, Ghezzo H, Hogg J, et al. The relations between structural changes in small airways and pulmonary-function tests. *N Engl J Med.* 1978;298(23):1277-1281.

10 McNulty W, Usmani OS. Techniques of assessing small airways dysfunction. *Eur Clin Respir J.* 2014;1. DOI:http://dx.doi.org/10.3402/ecrj.v3401.25898.

11 Basic Spirometry. In: Hansen JE, ed. *Pulmonary Function Testing & Interpretation.* London: Jaypee Brothers Medical Publishers; 2011:42-87.

12 Hansen JE, Sun XG, Wasserman K. Discriminating measures and normal values for expiratory obstruction. *Chest.* 2006;129(2):369-377.

13 Hansen JE. Cigarette Smoking and the Disadvantages of Using a Fixed Ratio of FEV 1/FVC to Diagnose Airway Obstruction. *Turkish Thoracic Journal*. 2009;10(2):82-85.

14 Lutchmedial SM, Creed WG, Moore AJ, et al. How Common Is Airflow Limitation in Patients With Emphysema on CT Scan of the Chest? *Chest.* 2015;148(1):176-184.

15 Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* . 2015;175(9):1539-1549.

16 Wan ES, Hokanson JE, Murphy JR, et al. Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGene study. *Am J Respir Crit Care Med.* 2011;184(1):57-63.

17 Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. *Lancet.* 2015;385(9979):1778-1788.

18 Miller MR, Pincock AC, Grove DM. Patterns of spirogram abnormality in individual smokers. *Am Rev Respir Dis.* 1985;132(5):1034-1040.

19 Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. *COPD.* 2010;7(1):32-43.

20 Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med.* 1999;159(3):851-856.

21 Lynch DA, Austin JH, Hogg JC, et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. *Radiology*. 2015;277(1):192-205.

22 Gevenois PA, De Vuyst P, De Maertelaer V, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med.* 1996;154(1):187-192.

23 Schroeder JD, McKenzie AS, Zach JA, et al. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. *AJR Am J Roentgenol.* 2013;201(3):460-470.

24 Matsuoka S, Kurihara Y, Yagihashi K, et al. Quantitative assessment of air trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. *AJR Am J Roentgenol.* 2008;190(3):762-769.

25 Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med.* 1991;85(Suppl.B):25-31.

26 Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax.* 1999;54(7):581-586.

27 Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005-1012.

28 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166(1):111-117.

29 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-338.

30 Hankinson JL, Crapo RO, Jensen RL. Spirometric reference values for the 6-s FVC maneuver. *Chest.* 2003;124(5):1805-1811.

31 Snider GL, Kleinerman J, Thurlbeck WM, et al. The Definition of Emphysema: Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases Workshop 1. American Review of Respiratory Disease. 1985;132(1):182-185.

32 Hasegawa M, Nasuhara Y, Onodera Y, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2006;173(12):1309-1315.

33 Zach JA, Newell Jr JD, Schroeder J, et al. Quantitative CT of the Lungs and Airways in Healthy Non-Smoking Adults. *Invest Radiol.* 2012;47(10):596.

34 Hersh CP, Washko GR, Estepar RS, et al. Paired inspiratory-expiratory chest CT scans to assess for small airways disease in COPD. *Respir Res.* 2013;14:42.

35 Jones PW, Tabberer M, Chen W-H. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT™) scores. *BMC Pulm Med.* 2011;11(1):42.

36 Casaburi R, Dilektasli AG, Porszasz J, et al. Establishing clinically meaningful cutoffs for %emphysema and %gas trapping in quantitative chest CT scans. *Eur Respir J.* 2015;46(Suppl.59):OA2944.

37 Morris ZQ, Coz A, Starosta D. An isolated reduction of the FEV3/FVC ratio is an indicator of mild lung injury. *Chest.* 2013;144(4):1117-1123.

38 Zelter M. The Return of FEV3. *Chest.* 2013;144(4):1089-1091.

39 O'Donnell RA, Peebles C, Ward JA, et al. Relationship between peripheral airway dysfunction, airway obstruction, and neutrophilic inflammation in COPD. *Thorax.* 2004;59(10):837-842.

40 Teel GS, Engeler CE, Tashijian JH, et al. Imaging of small airways disease. *Radiographics.* 1996;16(1):27-41.

41 Bommart S, Marin G, Bourdin A, et al. Relationship between CT air trapping criteria and lung function in small airway impairment quantification. *BMC Pulm Med.* 2014;14:29.

42 Mohamed Hoesein FA, de Hoop B, Zanen P, et al. CT-quantified emphysema in male heavy smokers: association with lung function decline. *Thorax.* 2011;66(9):782-787.

43 Bhatt SP, Soler X, Wang X, et al. Association Between Functional Small Airways Disease and FEV1 Decline in COPD. *Am J Respir Crit Care Med.* 2016: DOI:10.1164/rccm.201511-202219OC.

44 Verbanck S, Schuermans D, Paiva M, et al. Small airway function improvement after smoking cessation in smokers without airway obstruction. *Am J Respir Crit Care Med.* 2006;174(8):853-857.

45 Mead J. The lung's "quiet zone". *N Engl J Med.* 1970;282(23):1318-1319.

46 Hogg JC, McDonough JE, Sanchez PG, et al. Micro-computed tomography measurements of peripheral lung pathology in chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2009;6(6):546-549.

47 McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med.* 2011;365(17):1567-1575.

48 Akpinar-Elci M, Fedan K, Enright P. FEV6 as a surrogate for FVC in detecting airways obstruction and restriction in the workplace. *Eur Respir J.* 2006;27(2):374-377.

49 Swanney MP, Jensen RL, Crichton DA, et al. FEV(6) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. *Am J Respir Crit Care Med.* 2000;162(3):917-919.

50 Bhatt SP, Kim YI, Wells JM, et al. FEV(1)/FEV(6) to diagnose airflow obstruction. Comparisons with computed tomography and morbidity indices. *Ann Am Thorac Soc.* 2014;11(3):335-341.

51 Demir T, Ikitimur HD, Koc N, et al. The role of FEV6 in the detection of airway obstruction. *Respir Med.* 2005;99(1):103-106.

52 Jing JY, Huang TC, Cui W, et al. Should FEV1/FEV6 replace FEV1/FVC ratio to detect airway obstruction? A metaanalysis. *Chest.* 2009;135(4):991-998.

53 Perez-Padilla R, Wehrmeister FC, Celli BR, et al. Reliability of FEV 1/FEV 6 to Diagnose Airflow Obstruction Compared with FEV 1/FVC: The PLATINO Longitudinal Study. PLoS One. 2013;8(8):e67960.

54 Vandevoorde J, Verbanck S, Schuermans D, et al. FEV1/FEV6 and FEV6 as an alternative for FEV1/FVC and FVC in the spirometric detection of airway obstruction and restriction. *Chest.* 2005;127(5):1560-1564.

55 Hyde DM, Hamid Q, Irvin CG. Anatomy, pathology, and physiology of the tracheobronchial tree: emphasis on the distal airways. *J Allergy Clin Immunol.* 2009;124(6 Suppl):72-77.

56 Kim V, Pechulis RM, Abuel-Haija M, et al. Small airway pathology and bronchoreversibility in advanced emphysema. *COPD.* 2010;7(2):93-101.

57 Sterk PJ. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. *Eur Respir J.* 2004;23(4):497-498.

58 Hansen JE, Sun XG, Wasserman K. Should forced expiratory volume in six seconds replace forced vital capacity to detect airway obstruction? *Eur Respir J.* 2006;27(6):1244-1250.

59 Lam DC, Fong DY, Yu WC, et al. FEV3, FEV6 and their derivatives for detecting airflow obstruction in adult Chinese. *Int J Tuberc Lung Dis.* 2012;16(5):681-686.

Figure legends

Figure 1. Comparison of functional, structural and COPD-related clinical indices of participants with FEV_3/FEV_6 ≥LLN (n=3,709) *vs.* FEV_3/FEV_6 <LLN (n=677), among those without clinically defined airflow obstruction by pre-bronchodilator FEV_1/FVC ≥LLN (n=4,386). Participants with FEV_3/FEV_6 <LLN had significantly more impairment on quantitative CT (gas trapping %, E/I MLA, segmental wall area), worse FEV_1 %pred and FEV_1/FVC, greater dyspnea perception and SGRQ, and lower 6MWD. The central horizontal line on each box represents the median, the ends of the boxes are 25 and 75 percentiles and the error bars 10 and 90% percentiles. The lower and upper solid circles (•) represent minimum and maximum values in each group, respectively. * denotes $P < 0.0001$; NS denotes $P > 0.05$. P values derived from the two-sample t-test for normally distributed continuous variables, and the Mann-Whitney U test for continuous non-normal data. Definition of abbreviations: LLN, lower limits of normal; FEV_1 %predicted, forced expiratory volume in 1 second expressed as percent predicted; FVC %predicted, forced vital capacity expressed as percent predicted; E/I MLA, expiratory to inspiratory ratio of mean lung attenuation; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance. The BODE index includes body mass index (BMI), post-bronchodilator FEV_1%predicted, mMRC score, and the six-minute walk distance (6MWD).

Figure 2. Comparison of participants with pre-bronchodilator $FEV_1/FVC \geq LLN$ (n=4,386) divided into subgroups of normal (dark grey bars, N=3709) and abnormal FEV_3/FEV_6 (light grey bars, N=677) deemed to be abnormal by functional, structural and clinical outcomes. Bars represent proportion of the population, the error bars lower and upper bounds for 95% confidence interval. Statistical significance was determined by Pearson *chi-square*. * denotes $P < 0.0001$; NS denotes $P > 0.05$. Definition of abbreviations: n, number of subjects; FEV_1 %predicted, forced expiratory volume in 1 seconds expressed as percent predicted; mMRC, modified Medical Research Council Dyspnea Scale; SGRQ, St. George's Respiratory Questionnaire; 6MWD, 6 minute walking distance. The BODE index includes body mass index (BMI), post-bronchodilator FEV_1%predicted, mMRC score, and the six-minute walk distance (6MWD).

Tables

Table 1. Characteristics of the study population with regard to FEV_1/FVC and FEV_3/FEV_6 LLN.

	FEV_1/FVC		**FEV_3/FEV_6**	
	≥ LLN (n=4386)	**< LLN (n=3467)**	**≥ LLN (n=3888)**	**< LLN (n=3965)**
Age, years	56.9 (51 – 64)	62.7 (55 – 69) *	57.1 (51– 64)	61.9 (54.–69)†
Sex, Male %	51.7	55.8*	53.8	53.3
Race, Caucasian; African-American, %	64; 36	79; 21 *	66; 34	76; 24†
Body mass index, kg/m^2	29.4 ± 6.0	27.8 ± 6.1*	29.6 ± 5.9	27.8 ± 6.1†
Smoking history, pack.years§	36 (24 – 48)	45 (34 – 65)*	35 (23 – 48)	45 (33 – 65)†
Spirometry				
Post-BD FEV_1/FVC ≥70,%	86.8	8.6*	87.8	17.5†
Pre-BD FEV_1 %pred	88.7 ± 15.7	52.7 ± 22.2*	89.9 ± 15.3	56.0 ± 23.2†
Pre-BD FEV_3 %pred	95.2 ± 17.6	67.3 ± 23.4*	91.8 ± 15.1	78.7 ± 20.4†
Pre-BD FEV_6 %pred	91.0 ± 15.1	70.1 ± 20.5*	91.6 ± 14.7	72.1 ± 20.8†
Pre-BD FVC %pred	91.1 ± 15.4	77.7 ± 20.7*	91.8 ± 15.1	78.7 ± 20.4†
Post-BD FEV_1 %pred	91.3 ± 15.8	56.9 ± 23.2*	92.4 ± 15.4	60.2 ± 24.0†
Pre-BD FEV_1/FVC, %	75.3 (71.4 – 79.1)	52.8 (39.6 – 62.2)*	76.1 (72.1 – 79.6)	56.2 (41.8 – 65.0)†
Post-BD FEV_1/FVC, %	77.0 (72.8 –81.3)	53.9 (40.6 – 63.9)*	77.7 (73.3 – 81.7)	57.4 (42.5 – 67.2)†
Pre-BD FEV_1/FEV_6, %	78.4 (75.3 –81.5)	59.8 (48.3 – 67.9)*	79.0 (76.1 – 81.9)	62.7 (50.0 – 70.1)†
Pre-BD FEV_3/FVC, %	89.9 (87.4 –92.3)	75.0 (64.9 – 81.6)*	90.4 (87.8 – 92.6)	77.3 (66.6 – 83.9)†
Pre-BD FEV_3/FEV_6, %	93.3 (92.0 –94.5)	85.3 (78.5 – 89.1)*	93.6 (92.5 – 94.6)	86.7 (79.6 – 89.8)†
Quantitative CT indices				
$LAA_{-950insp}$, % (emphysema%)	1.0 (0.4 – 2.5)	7.2 (2.2 – 18.7)*	1.1 (0.4 – 2.6)	5.3 (1.5 – 16.8)†
$LAA_{-856exp}$,% (gas trapping%)	9.0 (4.2 – 15.6)	34.0 (18.0 – 53.6)*	8.9 (4.2 – 15.4)	30.0 (14.4 – 50.8)†
E/I MLA	0.83 (0.80-0.87)	0.91 (0.87-0.95)*	0.83 (0.79 – 0.87)	0.91 (0.86 – 0.94)†
$WA_{segmental}$, %	60.4 ± 3.0	62.5 ± 3.1*	60.3 ± 3.0	62.4 ± 3.2†
HRQL and functional measures				

mMRC[††]	0.9 ± 1.2	1.9 ± 1.5*	0.8 ± 1.2	1.8 ± 1.5[†]
SGRQ, total score	11.3 (3.5-29.5)	36.5 (18.2-54.5)*	10.5 (3.2 – 27.2)	34.8 (16.2 – 53.1)[†]
6MWD, meters[‡]	440 ± 109	376 ± 122*	445 ± 108	379 ± 122[†]
BODE[‡]	0.9 ± 1.2	1.9 ± 1.5*	0.8 ± 1.2	1.8 ± 1.5[†]

Data are mean ± standard deviation or median (IQR 25 – 75), as appropriate. *denotes P value < 0.0001 compared to FEV_1/FVC ≥LLN participants. [†] denotes P value < 0.0001 compared to FEV_3/FEV_6≥LLN participants. [§] Data available for 7755 participants. [††] Data available for 7849 participants. [‡]Data available for 7756 participants. Statistical significance was determined by the two-sample *t*-test for normally distributed continuous variables and the Mann-Whitney *U* test for comparison of continuous non-normal data between FEV_3/FEV_6 ≥LLN *vs*. <LLN groups. Body mass index, post-bronchodilator FEV_1%predicted, mMRC score, and 6MWD were integrated to calculate the 10-point BODE index[27]. Definition of abbreviations: pre-BD, pre-bronchodilator; post-BD, post-bronchodilator; FEV_1 %predicted, forced expiratory volume in 1 second expressed as percent predicted; FVC %predicted, forced vital capacity expressed as percent predicted; FEV_3 %predicted, forced expiratory volume in 3 seconds expressed as percent predicted; FEV_6 %predicted, forced expiratory volume in 6 seconds expressed as percent predicted; $LAA_{-950insp}$, total percentage of all lung voxels less than or equal to −950 Hounsfield Units (HU) on end-inspiratory scans, commonly called Emphysema%; $LAA_{-856exp}$, total percentage of all lung voxels less than or equal to −856 Hounsfield Units (HU) on expiratory scans, commonly called Gas Trapping%; E/I MLA, expiratory to inspiratory ratio of mean lung attenuation; WA, wall area; HRQL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire; 6MWD, 6 minute walking distance; mMRC, modified Medical Research Council Dyspnea Scale; COPD, chronic obstructive pulmonary disease.

Table 2. Functional, structural and clinical characteristics of participants with pre-bronchodilator FEV_1/FVC ≥LLN divided into subgroups of normal and abnormal FEV_3/FEV_6 and FEV_3/FVC.

	FEV1/FVC ≥LLN						
	TOTAL	**FEV_3/FEV_6 ≥LLN**	**FEV_3/FEV_6 <LLN**	**P[†]**	**FEV_3/FVC ≥LLN**	**FEV_3/FVC <LLN**	**P[††]**
n, (%)	4386 (100)	3709 (84.6)	677 (15.4)	-	4074 (92.9)	312 (7.1)	-
Age, years	58.0 ± 8.7	58.0 ± 8.7	57.9 ± 8.6	0.78	58.2 ± 8.7	56.2 ± 7.6	< 0.0001
Sex, Male %	51.7	53.0	44.9	< 0.0001	51.2	58.0	0.02
Smoking history, pack.years	35.7 (23.7 – 48.3)	35.1 (23.0 – 48.0)	38.0 (27.7 – 52.8)	< 0.0001	35.5 (23.3 – 48.1)	36.7 (25.9 – 48.8)	0.15
FEV_1, % $_{pred}$	88.7 ± 15.7	90.4 ± 15.1	79.1 ± 15.6	< 0.0001	89.0 ± 15.7	85.0 ± 14.7	< 0.0001
FEV_3, % $_{pred}$	95.2 ± 17.6	96.5 ± 17.2	88.3 ± 18.0	< 0.0001	95.6 ± 17.6	90.7 ± 16.1	< 0.0001
FEV_6, % $_{pred}$	91.0 ± 15.1	91.8 ± 14.6	86.7 ± 16.8	< 0.0001	91.1 ± 15.1	89.8 ± 14.9	< 0.0001
FVC, % $_{pred}$	91.1 ± 15.4	91.8 ± 14.9	87.4 ± 17.1	< 0.0001	90.8 ± 15.3	94.8 ± 16.1	< 0.0001
FEV_1/FVC, %	75.3 (71.4 – 79.1)	76.4 (72.7 – 79.8)	70.2 (68.2 – 72.1)	< 0.0001	75.8 (72.0 – 79.4)	69.5 (67.8 – 71.4)	< 0.0001
FEV_3/FEV_6, %	93.3 (92.0 – 94.5)	93.6 (92.6 – 94.7)	90.6 (89.8 – 91.4)	< 0.0001	93.4 (92.1 – 94.6)	91.7 (90.6 – 92.7)	< 0.0001
FEV_3/FVC, %	89.9 (87.5 – 92.3)	90.6 (88.2 – 92.6)	86.9 (84.9 – 88.4)	< 0.0001	90.2 (88.0 – 92.5)	83.8 (82.3 – 85.4)	< 0.0001
$LAA_{-950insp}$, %	0.98 (0.39 – 2.53)	0.97 (0.40 – 2.47)	1.03 (0.38 – 2.85)	0.18	0.98 (0.39 – 2.48)	1.08 (0.41 – 3.09)	0.12
$LAA_{-856exp}$, %	9.0 (4.2 – 15.6)	8.6 (4.0 – 15.1)	10.8 (5.3 – 19.6)	< 0.0001	9.0 (4.1-15.6)	10.0 (5.2 – 15.4)	0.09
E/I MLA	0.83 (0.80 – 0.87)	0.83 (0.79 – 0.87)	0.85 (0.81 – 0.89)	< 0.0001	0.83 (0.79 – 0.87)	0.84 (0.80 – 0.87)	0.04
WA $_{segmental}$, %	60.4 ± 3.0	60.3 ± 3.0	61.4 ± 3.2	< 0.0001	60.4 ± 3.1	60.4 ± 3.0	0.87
SGRQ total score	11.3 (3.5 ± 29.5)	10.4 (3.0 – 27.0)	19.9 (6.2 – 38.3)	< 0.0001	11.1 (3.5 – 29.1)	15.0 (3.8 – 34.7)	0.01
mMRC*	0.88 ± 1.25	0.8 ± 1.2	1.2 ± 1.4	< 0.0001	0.9 ± 1.2	1.0 ± 1.3	0.05
6MWD,meters[‡]	440 ± 109	444 ± 108	415 ± 116	< 0.0001	439 ± 109	447 ± 118	0.22
BODE index [‡]	0.6 ± 1.0	0.5 ± 0.9	0.9 ± 1.3	< 0.0001	0.6 ± 1.0	0.7 ± 1.1	0.09

Data are expressed as mean ± standard deviation or median (IQR 25 – 75) as appropriate.

[†] Univariate comparison between FEV_3/FEV_6 ≥LLN *vs*. FEV_3/FEV_6 <LLN. [††] Univariate comparison between FEV_3/FVC ≥LLN *vs*. FEV_3/FVC <LLN. * Data available for 4385 participants. [‡] Data available for 4364 participants.

Statistical significance was determined by the two-sample *t*-test for normally distributed continuous variables, the Mann-Whitney *U* test for comparison of continuous non-normal data between FEV_3/FEV_6 ≥LLN *vs*. <LLN and FEV_3/FVC ≥LLN *vs*. <LLN groups.

Definition of abbreviations: n, number of subjects; FEV_1 %predicted, forced expiratory volume in 1 second expressed as percent predicted; FEV_3 %predicted, forced expiratory volume in 3 seconds expressed as percent predicted; FEV_6 %predicted, forced expiratory volume in 6 seconds expressed as percent predicted; FVC %predicted, forced vital capacity expressed as percent predicted; $LAA_{-950insp}$, total percentage of all lung voxels less than or equal to −950 Hounsfield Units (HU) on end-inspiratory scans, commonly called Emphysema%; $LAA_{-856exp}$, total percentage of all lung voxels less than or equal to −856 Hounsfield Units (HU) on expiratory scans, commonly called Gas Trapping%; E/I MLA, expiratory to inspiratory ratio of mean lung attenuation; WA, wall area; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance.

The BODE index includes body mass index, post-bronchodilator FEV_1%predicted, mMRC score, and the 6MWD.

Table 3. General linear regression models of difference in quantitative CT indices, quality of life and 6 minute walk distance in participants with FEV_3/FEV_6 <LLN among those with FEV_1/FVC ≥LLN (n=4386).

	Gas Trapping%[†1]	**Wall area%**[†1]	**E/I MLA%**[†1]	**SGRQ**[†2]	**6MWD**[†2]	**mMRC**[2]	**BODE**[2]
	% difference	**% difference**	**% difference**	**% difference**	**% difference**	**OR**	**OR**
FEV_3/FEV_6 <LLN vs. FEV_3/FEV_6 ≥LLN*	27.5	1.8	2.0	40.8	-7.2	1.6	2.8
95% CI	18.1- 37.8	1.4 - 2.2	1.6 - 2.4	28.0 - 55.0	-9.4 - (-5.0)	1.4 - 1.9	2.1 - 3.7
e^{β}	1.275	1.018	1.020	1.408	0.928	-	-
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

[†] Gas trapping%, E/I MLA, wall area%, SGRQ and 6MWD were natural log transformed. The displayed coefficients (% difference and CI 95%) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. For example, for gas trapping %, the expected mean gas trapping % of FEV3/FEV6 <LLN group is higher than the one of FEV3/FEV6 ≥ LLN by 27.5%. OR indicates the relative odds increase for a higher score of mMRC or BODE between the two groups. For example, the estimated odds of having a one unit higher score of mMRC dyspnea score (worsening from 0 to 4) for FEV_3/FEV_6 <LLN is 1.6 of the odds compared with FEV_3/FEV_6 ≥ LLN. BODE index scores were categorized into four severity stages; BODE stage 1 to 4 with scores of 0-2, 3-4, 5-6 and 7-10, respectively.

* $FEV_3/FEV_6 \geq$ LLN data was used as the reference category. [1] Models controlled for sex, age, race, body mass index, smoking history (pack-years of smoking) and CT scanner type. [2] Models controlled for sex, age, race, body mass index and smoking history (pack-years of smoking).

Definition of abbreviations: E/I MLA, expiratory to inspiratory mean lung attenuation; SGRQ, St. George Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance; OR, odds ratio; CI 95%, exponential (back-transformed) 95% confidence intervals, e^{β}: exponential (back-transformed) regression coefficients.

Table 4. General linear regression models of difference in quantitative CT indices and quality of life in participants with FEV_3/FVC <LLN among those with $FEV_1/FVC \geq$LLN (n=4386).

	Gas Trapping%[†1]	**E/I MLA%**[†1]	**SGRQ**[†2]	**mMRC**[2]	**BODE**[2]
	% difference	**% difference**	**% difference**	**OR**	**OR**
FEV_3/FVC <LLN vs. $FEV_3/FVC \geq$LLN*	18.8	1.2	15.4	1.3	1.8
95% CI	6.6 - 32.3	0.4 - 2.0	0.9 - 32.1	1.03 - 1.61	1.2 - 2.6
e^{β}	1.188	1.012	1.154	-	-
P	0.002	< 0.0001	0.037	0.029	0.004

[†] Gas trapping%, E/I MLA, and SGRQ were natural log transformed. The displayed coefficients (% difference and CI 95%) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. For example, for gas trapping%, the expected mean gas trapping % of FEV3/FEV6 <LLN group is higher than the one of FEV3/FEV6 ≥ LLN by 18.8%. OR indicates the relative odds increase for a higher score of mMRC or BODE between the two groups. For example, the estimated odds of having a one unit higher score of mMRC dyspnea score (worsening from 0 to 4) for FEV_3/FEV_6 <LLN is 1.3 of the odds compared with $FEV_3/FEV_6 \geq$ LLN. BODE index scores were categorized into four severity stages; BODE stage 1 to 4 with scores of 0-2, 3-4, 5-6 and 7-10, respectively.

* $FEV_3/FVC \geq LLN$ data was used as the reference category. [1] Models controlled for sex, age, race, body mass index, smoking history (pack-years of smoking) and CT scanner type. [2] Models controlled for sex, age, race, body mass index and smoking history (pack-years of smoking).

Definition of abbreviations: E/I MLA, expiratory to inspiratory mean lung attenuation; SGRQ, St. George Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance; OR, odds ratio; CI 95%, exponential (back-transformed) 95% confidence intervals, e^{β}: exponential (back-transformed) regression coefficients.

Abbreviations list

BMI	body mass index
BODE	BODE index includes body mass index, post-bronchodilator FEV_1%predicted, mMRC score, and 6MWD.
CI	confidence intervals
COPD	chronic obstructive pulmonary disease
CT	computed tomography
E/I MLA	expiratory to inspiratory ratio of mean lung attenuation on quantitative CT scan
FEV_1 %predicted	forced expiratory volume in 1 second expressed as percent predicted
FEV_3 %predicted	forced expiratory volume in 3 seconds expressed as percent predicted
FEV_6 %predicted	forced expiratory volume in 6 seconds expressed as percent predicted
FVC %predicted	forced vital capacity expressed as percent predicted
HRQL	health-related quality of life
HU	Hounsfield Units
$LAA_{–950insp}$	total percentage of all lung voxels less than or equal to –950 Hounsfield Units (HU) on end-inspiratory scans, commonly called emphysema %
$LAA_{–856exp}$	total percentage of all lung voxels less than or equal to –856 Hounsfield Units (HU) on expiratory scans, commonly called gas trapping %
LLN	Lower limits of normal
mMRC	modified Medical Research Council Dyspnea Scale
NHANES-III	Third National Health and Nutrition Examination Survey
OR	odds ratio
SGRQ	St. George's Respiratory Questionnaire

6MWD	Six-minute walking distance
WA %:	wall area %

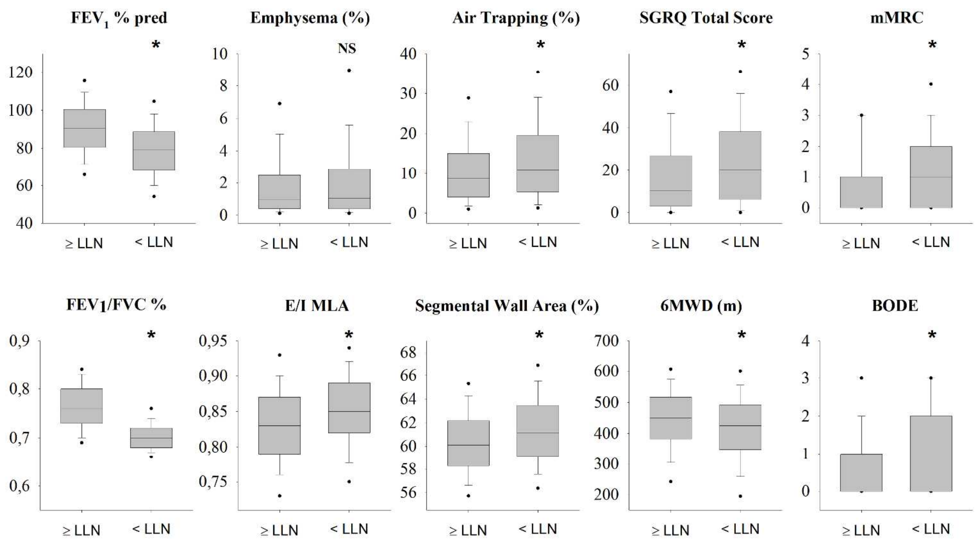

Figure 1. Comparison of functional, structural and COPD-related clinical indices of participants with FEV3/FEV6 ≥LLN (n=3,709) vs. FEV3/FEV6 <LLN (n=677), among those without clinically defined airflow obstruction by pre-bronchodilator FEV1/FVC ≥LLN (n=4,386). Participants with FEV3/FEV6 <LLN had significantly more impairment on quantitative CT (gas trapping %, E/I MLA, segmental wall area), worse FEV1 %pred and FEV1/FVC, greater dyspnea perception and SGRQ, and lower 6MWD. The central horizontal line on each box represents the median, the ends of the boxes are 25 and 75 percentiles and the error bars 10 and 90% percentiles. The lower and upper solid circles (•) represent minimum and maximum values in each group, respectively. * denotes $P < 0.0001$; NS denotes $P > 0.05$. P values derived from the two-sample t-test for normally distributed continuous variables, and the Mann-Whitney U test for continuous non-normal data. Definition of abbreviations: LLN, lower limits of normal; FEV1 %predicted, forced expiratory volume in 1 second expressed as percent predicted; FVC %predicted, forced vital capacity expressed as percent predicted; E/I MLA, expiratory to inspiratory ratio of mean lung attenuation; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance. The BODE index includes body mass index (BMI), post-bronchodilator FEV1%predicted, mMRC score, and the six-minute walk distance (6MWD).

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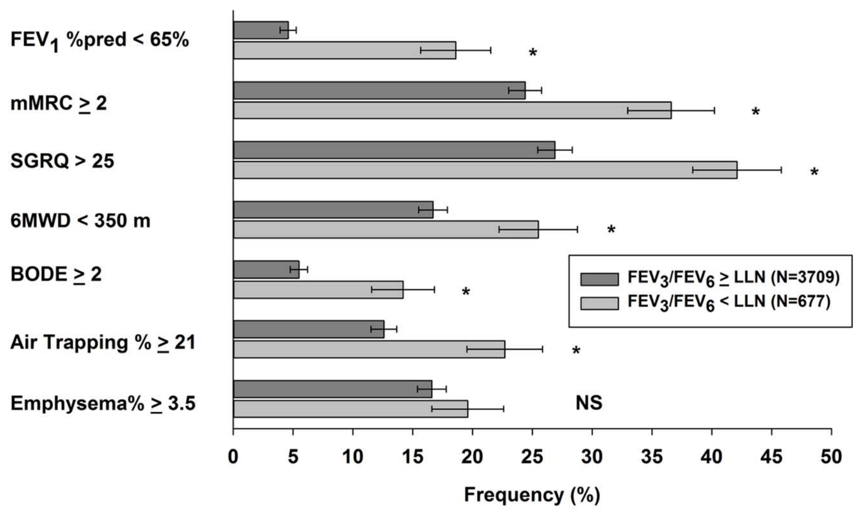

Figure 2. Comparison of participants with pre-bronchodilator FEV1/FVC ≥LLN (n=4,386) divided into subgroups of normal (dark grey bars, N=3709) and abnormal FEV3/FEV6 (light grey bars, N=677) deemed to be abnormal by functional, structural and clinical outcomes. Bars represent proportion of the population, the error bars lower and upper bounds for 95% confidence interval. Statistical significance was determined by Pearson chi-square. * denotes $P < 0.0001$; NS denotes $P > 0.05$. Definition of abbreviations: n, number of subjects; FEV1 %predicted, forced expiratory volume in 1 seconds expressed as percent predicted; mMRC, modified Medical Research Council Dyspnea Scale; SGRQ, St. George's Respiratory Questionnaire; 6MWD, 6 minute walking distance. The BODE index includes body mass index (BMI), post-bronchodilator FEV1%predicted, mMRC score, and the six-minute walk distance (6MWD).

126x74mm (300 x 300 DPI)

A novel spirometric measure identifies mild chronic obstructive pulmonary disease unidentified by standard criteria

-- Online Data Supplement --

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Methods

Inclusion and exclusion criteria

10,311 male and female non-Hispanic White and African-American participants, 45 to 80 years old, with at least 10 pack-years of smoking history were included in the study. Participants with incomplete quantitative CT data (n=1,704), or with incomplete measurements in any of the relevant spirometric data (n=591), and with incomplete measurements in both spirometry and CT (n=163) were excluded, reducing the study population to 7,853 in the present study[1].

Patient-reported outcomes and 6 minute walk distance

Participants' overall health-related quality of life, symptoms and impact of disease were assessed by: St. George's Respiratory Questionnaire (SGRQ, scores ranging from 0-100; where a higher score indicates worse health status)[2]; the modified Medical Research Council Dyspnea Scale (mMRC, ranging from 0 to 4[3]; the multidimensional BODE index (ranging from 0 to 10, higher score indicating worse outcome)[4]. The BODE index uses body mass index (BMI), post-bronchodilator FEV_1%predicted, mMRC score, and the six-minute walk distance (6MWD). BODE index scores were categorized into four severity stages; BODE stage 1 to 4 with scores of 0-2, 3-4, 5-6 and 7-10, respectively. Six-minute walking test was performed according to ATS standards[5].

Spirometry, quality control and definition of normality

Spirometry tests were performed by using an ultrasound-based spirometer (NDD, EasyOne Spirometer Medizintechnik AG, Zurich, Switzerland) before and after administration of 180 mcg of short-acting β_2-agonist (albuterol) in accordance with the ATS recommendations[6].

Spirometric measurements were reviewed and graded (ranging from 0 – 4) by an automated quality assessment software package and by a centralized quality control process established for the COPDGene project (Grade 4: fully met ATS criteria, reproducible to within 50 ml, Grade 3: fully met ATS criteria, reproducible to between 50-100 ml, Grade 2: fully met ATS criteria, reproducible between 100 and 150 ml; Grade 1: partly meeting ATS criteria and/or reproducible between 150-200 ml; Grade 0: failure to meet ATS criteria and/or reproducible greater than 200 ml)[7]. Mean primary quality control grades for pre-bronchodilator FEV_1 and FVC measurements were 3.44 ± 0.90 and 3.21 ± 1.03, respectively in the selected group for the present study.

Best "test" was defined as the maneuver with the largest sum of FVC and FEV_1. For our analysis, values of the best pre-bronchodilator FEV_1, FVC, FEV_3, and FEV_6 were chosen; percent predicted values were calculated from the NHANES-III reference equations (n=5,880)[8,9]. The linear iteratively-derived equations of Hansen et al.[10] were used to determine LLN (lowest 5th percentile) for pre-bronchodilator FEV_1/FVC, FEV_1/FEV_6, FEV_3/FEV_6 and FEV_3/FVC.

Quantitative CT analysis and definition of indices

CT scans were acquired by using a 16- or 64-detector CT scanner at full inspiration and after tidal expiration according to a standardized protocol[1]; image acquisition and analysis procedures have been previously described[11,12]. Emphysema% was assessed by using 3D Slicer (http://www.slicer.org). Airway disease was assessed by wall area percentage of segmental airways WA% = (bronchus outer area - airway luminal area) / (bronchus outer area)) using 'Pulmonary Workstation Plus' software (VIDA Diagnostics, Coralville, IA, U.S.A.)[13]. The CT scans were planned in the COPDGene protocol to be done last on the visit day, after all pulmonary function and other functional tests and symptom assessment questionnaires.

Statistical Analyses

Means and standard deviations were used to describe continuous variables and proportions were used for categorical variables. For non-normal data, medians and interquartile ranges were reported (25^{th} and 75^{th} percentiles) (Tables 1, 2, e-Tables 3 and 6). A chi-square test was used to compare proportions between two groups and a two-sample t-test or one-way ANOVA were used for continuous outcome variables. For non-normal data, the Kruskal-Wallis test was used (Tables 1, 2, and e-Tables 3 and 6). Pairwise comparisons were followed by Tukey's *post hoc* test, to adjust for an overall type I error rate of 5%. Pearson and Spearman coefficients were used to estimate the linear relationships among spirometry, quantitative CT parameters and disease-related outcomes (e-Table 8). In order to assess the relationship between spirometric measurements (independent variable), and quantitative CT measures, SGRQ and 6MWD (outcome variables), a multiple general linear regression model was used for each outcome variable, using age, sex, race, smoking history, BMI and CT scanner type (only for CT measures) as covariates. Other covariates were included in the model where the P-value was less than 0.10. The natural log transformation was used for quantitative CT measures, SGRQ and 6MWD to ensure validity of model assumptions. The consequent regression coefficients (β) were back transformed for easier interpretation. Various reference categories were used for comparisons of spirometric variables. Compared to a reference category, the relative difference for dependent outcome variables was determined by $(e^{\beta} - 1) \times 100$ (%), while holding all other predictors constant. For example, an exponentiated β coefficient (e^{β}) of 1.43 for the outcome $LAA_{-950insp}$ corresponds to a 43% greater mean of $LAA_{-950insp}$ in patients with FEV_1/FEV_6 <LLN compared with the reference group (in this case, those with both FEV_1/FEV_6 ≥LLN and FEV_1/FVC ≥LLN). For ordinal outcomes (BODE and mMRC), the proportional odds model

was used (Tables 3, 4, and e-Tables 1, 2, 4, 7). P-values less than 0.05 were considered statistically significant. For all statistical models, residual analyses were conducted to check the model assumptions. Statistical analyses were performed with SPSS v22.0 (Armonk, NY: IBM Corp.).

Spirometric, demographic, radiologic and clinical characteristics were compared in three ways. Firstly, participants were characterized by FEV_3/FEV_6 above and below LLN (Tables 1-3, e-Tables 1 and 2). Secondly, participants with FEV_3/FVC <LLN were compared with those in whom FEV_3/FVC ≥LLN (Tables 2 and 4). These analyses were performed separately for the total study population (7,853) and the subgroup in whom FEV_1/FVC ≥LLN (4,386). Finally, demographic, spirometric, radiologic and clinical characteristics were compared in a) FEV_1/FVC and FEV_3/FEV_6 concordant and discordant groups (e-Tables 3 and 4), and b) FEV_1/FVC and FEV_1/FEV_6 concordant and discordant groups (e-Tables 6 and 7).

Results

Correlates of FEV_1/FVC and FEV_3/FEV_6 abnormality in the overall group

After adjustment for sex, age, race, body mass index, smoking history and CT scanner type (only for quantitative CT parameters), with the exception of higher contribution of FEV_1/FVC abnormality to predict extent of emphysema and gas trapping, FEV_3/FEV_6 and FEV_1/FVC abnormality had significant and similar associations with E/I MLA, segmental airway dimensions in quantitative CT, SGRQ, mMRC, 6MWD and BODE in the entire study population (e-Table 1). In participants with FEV_3/FEV_6 abnormality (independent of obstruction determined by FEV_1/FVC), emphysema% was 228.0% greater, gas trapping% was 152.3% greater, WA% was 3.9% greater and E/I MLA was 6.6% greater, compared to those with FEV_3/FEV_6 >LLN.

FEV_3/FEV_6 abnormality was also associated with worse clinical outcomes: 136.0% greater SGRQ score and 16.5% shorter 6MWD (e-Table 1) in the entire study population. These subjects were also more likely to be in a higher mMRC category (adjusted OR: 3,9, P<0.0001) and BODE index (adjusted OR: 10.5, P<0.0001) compared to those with normal FEV_3/FEV_6.

FEV_3/FEV_6 is more sensitive in detecting structural, functional and patient-reported outcomes than FEV_1/FVC

Demographic, radiological, functional and patient-reported outcomes were compared among patients with one or more abnormality in FEV_3/FEV_6 and FEV_1/FVC and those with normal spirometry (e-Table 3). Significant differences were detected among these 4 groups. 47.2% of participants were normal in both FEV_3/FEV_6 and FEV_1/FVC, while 41.9% had abnormality in both FEV_3/FEV_6 and FEV_1/FVC. Importantly, a substantial fraction of the study population (n=677 participants, 8.6%) were abnormal only in FEV_3/FEV_6. These participants had lower FEV_1% pred, FEV_3% pred, FEV_1/FVC %, FEV_3/FEV_6 %, higher gas trapping%, E/I MLA, segmental WA%, as well as worse 6MWD, mMRC, SGRQ and BODE indices compared with those normal in both FEV_3/FEV_6 and FEV_1/FVC. Notably, the extent of emphysema was not statistically different from those normal in both FEV_3/FEV_6 and FEV_1/FVC. Fewer subjects were abnormal in only FEV_1/FVC (n=179, 2.3%). These 179 participants had lower spirometric values and significantly impaired quantitative CT indices including emphysema, however the mMRC, SGRQ, 6MWD and BODE indices were not statistically different from those normal in both FEV_3/FEV_6 and FEV_1/FVC. Participants with isolated FEV_1/FVC abnormality had significantly greater emphysema and gas trapping, smaller segmental WA% and shorter 6MWD compared to those abnormal with FEV_3/FEV_6. Participants with abnormality in both FEV_3/FEV_6 and

FEV_1/FVC had significant impairments in all of the spirometric, structural, functional and quality of life indices compared to patients with either one abnormality in FEV_3/FEV_6 or FEV_1/FVC (e-Table 3).

After adjustment for sex, age, race, body mass index, smoking history and CT scanner type , in participants with isolated FEV_3/FEV_6 abnormality, emphysema% was 11.3% greater, gas trapping % was 24.1% greater, WA% was 1.8% greater and E/I MLA was 2.3% greater compared to those normal in both FEV_3/FEV_6 and FEV_1/FVC. Isolated FEV_3/FEV_6 abnormality was also associated with worse clinical outcomes: 40.1% greater SGRQ score and 6.9% shorter 6MWD (e-Table 4). These participants were also more likely to be in a higher mMRC dyspnea category (adjusted OR:1.6, $P<0.0001$) and BODE index category (adjusted OR:2.5, $P<0.0001$) compared to those with normal FEV_3/FEV_6 and FEV_1/FVC (e-Table 4). Participants with only FEV_1/FVC abnormality had significant associations with all of the radiologic and patient-reported indices except 6MWD. Although isolated FEV_1/FVC abnormality subjects had stronger associations for emphysema and gas trapping extent compared to those with isolated FEV_3/FEV_6 abnormality, those with isolated FEV_3/FEV_6 abnormality had stronger associations with E/I MLA –the more sensitive CT parameter related to small airways dysfunction, as well as with functional exercise capacity, quality of life and mMRC compared to those with isolated FEV_1/FVC abnormality. Expectedly, participants with airflow obstruction assessed by both FEV_3/FEV_6 and FEV_1/FVC had the highest increase in means of all quantitative CT parameters, SGRQ scores and impairment in 6MWD. They also had the highest risk to be in a higher category for mMRC score and BODE index (e-Table 4).

Impairments in subjects with FEV_3/FEV_6 abnormality and $FEV_1/FVC \geq LLN$ with regard to sex

When sex was analyzed to assess whether it was a significant determinant for functional, structural and clinical impairments impairments seen in Figure 2, the only sex-related difference was in the more frequent presence of pathologically important emphysema in males (e-Table 5). Recent results demonstrated that men display greater radiographic emphysema extent than women in the overall COPDGene population[14]. Our results establish that there is also a sex-specific emphysema pattern in the FEV_1/FVC normal smoker population.

FEV_1/FEV_6 is more sensitive in detecting structural, functional and patient-reported outcomes than FEV_1/FVC.

Radiological, functional and patient-reported outcomes were compared among patients with one or more abnormality in FEV_1/FEV_6 and FEV_1/FVC and those with normal spirometry (e-Table 6). 52.7% of participants were normal in both FEV_1/FEV_6 and FEV_1/FVC, while 40.5% had abnormality in both FEV_1/FEV_6 and FEV_1/FVC. 244 participants (3.1%) were abnormal in only FEV_1/FEV_6, and 283 participants (3.6%) were abnormal in only FEV_1/FVC. Spirometric, functional and quality of life indices were significantly different among these 4 groups (e-Table 6).

The presence of only FEV_1/FVC <LLN was associated with lower FEV_1 %pred, emphysema% and gas trapping%, but E/I MLA, segmental wall area %, SGRQ, mMRC, 6MWD, and BODE were not different compared with those in whom both FEV_1/FVC and FEV_1/FEV_6 were normal (e-Table 6). After adjustment for sex, age, race, body mass index, smoking history and CT scanner type (for only quantitative CT parameters), general linear regression models showed that those with abnormality in both FEV_1/FEV_6 and FEV_1/FVC had the most impaired quantitative CT, SGRQ scores and 6MWD. They also had the highest risk for

greater mMRC and BODE index categories (e-Table 7). In addition, participants with isolated FEV_1/FEV_6 abnormality compared with those normal in both FEV_1/FEV_6 and FEV_1/FVC were associated with poorer spirometric measurements (FEV_1 %pred, FEV_1/FVC, FEV_1/FEV_6), increased abnormality in quantitative CT (emphysema%, gas trapping%, E/I MLA, and WA%), poorer functional and patient reported (SGRQ, mMRC, 6MWD, BODE) outcomes (e-Table 6). The general linear regression models showed that, compared to participants normal in both FEV_1/FEV_6 and FEV_1/FVC spirometry, participants with FEV_1/FEV_6 as the sole abnormality had a 43.0% greater emphysema extent, 62.5% greater gas trapping%, 50.3% greater SGRQ score, and 8.3% shorter 6MWD (e-Table 7). Participants with FEV_1/FEV_6 as the sole abnormality had an increased risk to be in the higher mMRC and BODE category.

Participants in whom only FEV_1/FEV_6 was abnormal had lower FEV_1 %pred, FEV_1/FVC, FEV_1/FEV_6 and 6MWD, greater BODE score, wall area% and E/I MLA compared with the sole abnormality based on FEV_1/FVC (e-Table 6). Importantly, in general linear regression models individuals with FEV_1/FEV_6 <LLN had worse emphysema%, gas trapping%, WA%, E/I MLA, SGRQ, 6MWD, mMRC and BODE than those with only FEV_1/FVC <LLN (e-Table 7). Therefore, FEV_1/FEV_6 <LLN is better able to define clinically-relevant abnormality than FEV_1/FVC <LLN.

Spirometric indices are correlated with quantitative CT and COPD-related outcomes

In univariate correlation analysis, measures of structural abnormality in quantitative CT were inversely related to each of the spirometric indices investigated: FEV_1/FVC, FEV_1/FEV_6, FEV_3/FEV_6 and FEV_3/FVC (e-Table 8). Among CT indices, gas trapping% showed the strongest inverse correlations with spirometric measurements (correlation coefficient of gas trapping % with FEV_1/FVC %, FEV_1/FEV_6 %, FEV_3/FEV_6 %, FEV_3/FVC % ranges from - 0.68 to -0.72, P<0.0001). E/I MLA had moderate inverse correlations with spirometry (correlation coefficient of E/I MLA with spirometric ratios range from -0.60 to -0.67, P<0.0001), while segmental WA% had weak-to-moderate inverse correlations with spirometric measures (r ranges from -0.27 to -0.36, P<0.0001). Among disease-related outcomes, BODE had the highest correlation with the spirometry, likely because it includes FEV_1 %predicted.

References

1 Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. *COPD*. 2010;7(1):32-43.

2 Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med*. 1991;85(Suppl.B):25-31.

3 Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581-586.

4 Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005-1012.

5 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.

6 Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948-968.

7 Bhatt SP, Kim YI, Wells JM, et al. FEV(1)/FEV(6) to diagnose airflow obstruction. Comparisons with computed tomography and morbidity indices. *Ann Am Thorac Soc*. 2014;11(3):335-341.

8 Hankinson JL, Crapo RO, Jensen RL. Spirometric reference values for the 6-s FVC maneuver. *Chest*. 2003;124(5):1805-1811.

9 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159(1):179-187.

10 Hansen JE, Porszasz J, Casaburi R, et al. Re-defining lower limit of normal for FEV1/FEV6, FEV1/FVC, FEV3/FEV6 and FEV3/FVC to improve detection of airway obstruction. *J COPD F*. 2015;2(2):94-102. DOI:http://dx.doi.org/110.15326/jcopdf.15322.15322.12014.10144.

11 Group COCW, Barr RG, Berkowitz EA, et al. A combined pulmonary-radiology workshop for visual evaluation of COPD: study design, chest CT findings and concordance with quantitative evaluation. *COPD*. 2012;9(2):151-159.

12 Hoffman EA, Simon BA, McLennan G. State of the Art. A structural and functional assessment of the lung via multidetector-row computed tomography: phenotyping chronic obstructive pulmonary disease. *Proc Am Thor Soc*. 2006;3(6):519-532.

13 Hasegawa M, Nasuhara Y, Onodera Y, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2006;173(12):1309-1315.

14 Hardin M, Foreman M, Dransfield MT, et al. Sex-specific features of emphysema among current and former smokers with COPD. *Eur Respir J*. 2016;47(1):104-112.

15 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.

e-Table 1. General linear regression models of difference in quantitative CT indices, quality of life and 6 minute walk distance in participants with FEV_3/FEV_6 <LLN and FEV1/FVC<LLN groups for the entire cohort (n=7853).

	Emphysema%[†1]	Gas trapping% [†1]	Wall area %[†1]	E/I MLA %[†1]	SGRQ[†2]	6MWD[†2]	mMRC[2]	BODE[2]
	% difference	**% difference**	**% difference**	**% difference**	**% difference**	**% difference**	**OR**	**OR**
FEV_1/FVC <LLN vs. FEV_1/FVC ≥ LLN[*]	321.0	184.0	4.0	7.1	146.0	-16.8	4.2	11.4
95% CI	297 - 346	172 - 196	3.8 – 4.2	6.8 – 7.4	134 - 159	-18.3–(-15.32)	3.9 – 4.6	9.9 – 13.1
e^{β}	4.21	2.84	1.040	1.071	2.46	0.832	-	-
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
FEV_3/FEV_6 <LLN vs. FEV_3/FEV_6 ≥ LLN[‡]	228.0	152.3	3.9	6.6	136.0	-16.5	3.9	10.5
95% CI	208.8 - 248.3	141.9 - 163.0	3.6 - 4.1	6.3 - 6.9	124.4 - 148.1	-17.9 - (-15.0)	3.5 - 4.2	9.0- 12.2
e^{β}	3.28	2.523	1.039	1.066	2.360	0.835	-	-
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Definition of abbreviations: E/I MLA, expiratory to inspiratory mean lung attenuation; SGRQ, St. George Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance; OR, odds ratio; CI 95%, exponential (back-transformed) 95% confidence intervals, e^{β}: exponential (back-transformed) regression coefficients. BODE index scores were categorized into four severity stages; BODE stage 1 to 4 with scores of 0-2, 3-4, 5-6 and 7-10, respectively.

† The emphysema%, gas trapping%, E/I MLA, wall area %, SGRQ and 6MWD were natural log transformed. The displayed coefficients (% difference and CI 95%) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. For example, for emphysema%, the expected mean emphysema% of FEV_3/FEV_6 <LLN group is higher than the one of $FEV_3/FEV_6 \geq$ LLN by 228.0%. OR indicates the relative odds increase for a higher score of mMRC or BODE between the two groups. For example, the estimated odds of having a one unit higher score of mMRC dyspnea score (worsening from 0 to 4) for FEV_3/FEV_6 <LLN is 3.9 of the odds compared with $FEV_3/FEV_6 \geq$ LLN.

* $FEV_1/FVC \geq$ LLN data was used as the reference category. ‡ $FEV_3/FEV_6 \geq$ LLN data was used as the reference category.

[1] Models controlled for sex, age, race, body mass index, smoking history (pack-years of smoking) and CT scanner type

[2] Models controlled for sex, age, race, body mass index and smoking history (pack-years of smoking)

e-Table 2. General linear regression models of difference in quantitative CT indices, quality of life and 6 minute walk distance in participants with FEV_3/FEV_6 <LLN among those with FEV_1/FVC ≥LLN and a negative bronchodilator response (n=3868).

	Gas Trapping%[†1]	**Wall area%[†1]**	**E/I MLA%[†1]**	**SGRQ[†2]**	**6MWD[†2]**	**mMRC[2]**	**BODE[2]**
	% difference	**% difference**	**% difference**	**% difference**	**% difference**	**OR**	**OR**
FEV_3/FEV_6 <LLN vs. FEV_3/FEV_6 ≥LLN*	28.8	1.7	2.2	37.2	-7.3	1.6	2.9
95% CI	18.3 - 40.3	1.3 - 2.1	1.6 - 2.8	23.5 - 52.5	-9.6 - (-4.8)	1.4 - 1.9	2.1 - 3.9
e^{β}	1.288	1.017	1.022	1.372	0.927	-	-
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

[†] Gas trapping%, E/I MLA, wall area%, SGRQ and 6MWD were natural log transformed. The displayed coefficients (% difference and CI 95%) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. OR indicates the relative odds increase for a higher score of mMRC or BODE between the two groups. * FEV_3/FEV_6 ≥ LLN data was used as the reference category. [1] Models controlled for sex, age, race, body mass index, smoking history (pack-years of smoking) and CT scanner type. [2] Models controlled for sex, age, race, body mass index and smoking history (pack-years of smoking). Positive bronchodilator response was defined as an increase in FEV_1 and/or FVC ≥12% of baseline and 200 ml[15].

Definition of abbreviations: E/I MLA, expiratory to inspiratory mean lung attenuation; SGRQ, St. George Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance; OR, odds ratio; CI 95%, exponential (back-transformed) 95% confidence intervals, e^{β}: exponential (back-transformed) regression coefficients.

e-Table 3. Comparison of spirometric, quantitative CT, quality of life, 6 minute walk distance, and clinical variables among subjects stratified by pre-bronchodilator FEV_1/FVC and FEV_3/FEV_6 normalcy.

	Both ≥LLN[1]	Only FEV_3/FEV_6 <LLN[2]	Only FEV_1/FVC <LLN[3]	Both <LLN[4]	*P*					
					1vs2	*1vs 3*	*1vs 4*	*2vs 3*	*2vs 4*	*3vs 4*
n, (%)	3709 (47.2)	677 (8.6)	179 (2.3)	3288 (41.9)						
Age, years	57 (51 – 64)	59 (52 – 67)	61 (53 – 67)	63 (56 – 69)	*NS*	*	*	*NS*	*	*NS*
BMI	29.6 ± 5.9	28.4 ± 6.3	29.8 ± 6.4	27.7 ± 6.0	*	*NS*	*	*NS*	*NS*	*
Sex, Male %	1964 (53.0)	304 (44.9)	127 (70.9)	1808 (55.0)	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*
Race, Caucasian %	2414 (65.1)	403 (59.5)	147 (82.1)	2610 (79.4)	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*
Duration of smoking, pack.years^{-1} (n=7,755)	35 (23 – 48)	38 (28 – 53)	38 (26 – 53)	46 (34 – 66)	*	*NS*	*	*NS*	*	*
FEV_1 %pred	90.4 ± 15.1	79.1 ± 15.6	78.4 ± 15.5	51.3 ± 21.7	*	*	*	*NS*	*	*
FEV_3 %pred	96.5 ± 17.2	88.3 ± 18.0	89.7 ± 17.8	66.0 ± 23.1	*	*	*	*NS*	*	*
FEV_6 %pred	91.8 ± 14.6	86.7 ± 16.8	87.9 ± 16.2	69.1 ± 20.3	*	*NS*	*	*NS*	*	*
FVC %pred	91.8 ± 14.9	87.4 ± 17.1	92.6 ± 18.1	76.8 ± 20.6	*	*NS*	*	*	*	*
FEV_1/FVC, %	76.4 (72.7–79.8)	70.2 (68.2 – 72.1)	65.1 (63.6 – 66.6)	51.5 (38.8 – 61.1)	*	*	*	*	*	*
FEV_3/ FEV_6, %	93.6 (92.6 – 94.7)	90.1 (89.8 – 91.4)	91.9 (91.1– 92.5)	84.7 (78.1 – 88.7)	*	*	*	*	*	*

$LAA_{-950insp}$, %	0.97 (0.4 – 2.5)	1.03 (0.4 –2.8)	2.5 (0.8 – 5.9)	7.8 (2.4 –19.3)	*NS*	*	*	*	*	*
$LAA_{-856exp}$, %	8.6 (4.0 – 15.1)	10.8 (5.3 –19.6)	15.2 (8.3 – 24.7)	35.6 (19.3 – 54.7)	*	*	*	*	*	*
E/I MLA	0.83 (0.79 – 0.87)	0.85 (0.82 – 0.89)	0.85 (0.82 – 0.88)	0.92 (0.88 – 0.95)	*	*	*	*NS*	*	*
Wall Area, %	60.2 ± 3.0	61.4 ± 3.2	61.1 ± 2.9	62.6 ± 3.1	*	*	*	*NS*	*	*
SGRQ	10.4 (3.0 – 27.0)	19.9 (6.2 – 38.3)	13.4 (5.8 – 31.1)	37.5 (19.8 – 55.0)	*	*NS*	*	*NS*	*	*
mMRC (n=7,849)	0.8 ± 1.2	1.2 ± 1.4	1.0 ± 1.4	2.0 ± 1.4	*	*NS*	*	*NS*	*	*
6MWD, meters (n=7,756)	444 ± 108	415 ± 116	451 ± 109	372 ± 122	*	*NS*	*	*	*	*
BODE (n=7,756)	0.5 ± 0.9	0.9 ± 1.3	0.8 ± 1.3	2.6 ± 2.1	*	*NS*	*	*NS*	*	*

Data are mean ± standard deviation, median (IQR 25-75), or median (min, max). All of the comparisons across four groups $P < 0.0001$. Statistically significant in post-hoc comparisons if $P < 0.0083$. *NS* represents non-significant. * represents $P < 0.0001$. Statistical significance was determined by one-way analysis of variance with Tukey *post-hoc* tests for continuous normal data, Kruskal-Wallis test followed by Mann-Whitney *U* test for pairwise comparisons for continuous non-normal data, and Pearson *chi-square* test for comparison of proportions. Definition of abbreviations: n, number of subjects; BMI, body mass index; FEV_1 %predicted, forced expiratory volume in 1 seconds expressed as percent predicted; FEV_3 %predicted, forced expiratory volume in 3 seconds expressed as percent predicted; FEV_6 %predicted, forced expiratory volume in 6 seconds expressed as percent predicted; FVC %predicted, forced vital capacity expressed as percent predicted; $LAA_{-950insp}$, total percentage of all lung voxels less than or equal to –950 Hounsfield Units (HU) on end-inspiratory scans, commonly called emphysema%; $LAA_{-856exp}$, total percentage of all lung voxels less than or equal to –856 Hounsfield Units (HU) on expiratory scans, commonly called gas trapping%gas trapping%; E/I MLA, expiratory to inspiratory ratio of mean lung attenuation; WA, wall area; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance; LLN, lower limit of normal.

e-Table 4. General linear regression models of the difference in quantitative CT, quality of life, 6 minute walk distance, dyspnea perception and BODE index in models comparing abnormality in FEV_3/FEV_6 and/or FEV_1/FVC in the entire study population (n=7,853).

	Emphysema% [1]	**Gas trapping%** [1]	**Wall Area %** [1]	**E/I MLA %**[1]	**SGRQ**[2]	**6MWD**[2]	**mMRC**[2]	**BODE**[2]
	%difference **95% CI**	**% difference** **95% CI**	**% difference** **95% CI**	**% difference** **95% CI**	**% difference** **95% CI**	**% difference** **95% CI**	**OR** **95% CI**	**OR** **95% CI**
Only FEV_3/FEV_6 <LLN‡ (n=677)	11.3† (1 – 23)	24.1* (16 – 33)	1.8* (1.4 – 2.2)	2.3* (1.7 – 2.8)	40.1* (28 – 53)	- 6.9* (-10 – (-4))	1.6* (1.38 – 1.89)	2.5* (1.90 – 3.22)
Only FEV_1/FVC <LLN‡ (n=179)	78.1* (48 – 114)	47.5* (30 – 68)	1.8* (1.0 – 2.5)	1.9* (1.0 – 2.9)	32.4† (13 – 55)	-1.1 (-6 – 4)	1.5* (1.10 – 1.97)	2.6* (1.63 – 4.16)
Both FEV_3/FEV_6 and FEV_1/FVC‡ <LLN (n=3,288)	350.5* (324 – 378)	206.2* (193 – 220)	4.5* (4.2 – 4.7)	8.0* (7.6 – 8.3)	172.1* (158 – 187)	- 18.8* (-20 – (-17))	4.9* (4.49 – 5.46)	15.2* (12.87 – 17.81)

Emphysema%, gas trapping %, wall area %, E/I MLA, SGRQ and 6MWD were natural log transformed. The displayed coefficients (% difference and CI 95%) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. For example, for emphysema%, the expected mean emphysema% of only FEV_3/FEV_6 <LLN group is higher than the both FEV_3/FEV_6

≥LLN and FEV_1/FVC ≥LLN by 11%. OR indicates the relative odds increase for a higher score of mMRC or BODE between the two groups. For example, the estimated odds of having a one unit higher score of mMRC dyspnea score (worsening from 0 to 4) for only FEV_3/FEV_6 <LLN is 1.61 of the odds compared with both FEV_3/FEV_6 ≥LLN and FEV_1/FVC ≥LLN. [‡] Participants with both FEV_3/FEV_6 ≥LLN and FEV_1/FVC ≥LLN were used as the reference category. * $P < 0.0001$; [†] $P < 0.05$. [1] Models controlled for sex, age, race, body mass index, smoking history and CT scanner type. [2] Models controlled for sex, age, race, body mass index and smoking history. Definition of abbreviations: FEV_1, forced expiratory volume in 1 second; FEV_3, forced expiratory volume in 3 seconds; FEV_6, forced expiratory volume in 6 seconds; FVC, forced vital capacity; E/I MLA, expiratory to inspiratory mean lung attenuation; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walk distance (meters); OR, odds ratio; 95% CI, exponential (back-transformed) 95% confidence intervals. The BODE index includes body mass index (BMI), post-bronchodilator FEV1% predicted, mMRC score, and the 6MWD.

e-Table 5. Comparison of functional, structural and clinical impairments in $FEV_1/FVC \geq LLN$ female and males divided into subgroups of normal and abnormal FEV_3/FEV_6 (n=4386).

FEMALES, N = 2118			
	$FEV_3/FEV_6 \geq$ LLN n = 1962 (%)	$FEV_3/FEV_6 <$ LLN n = 304 (%)	*P*
FEV_1 %pred < 65	5.0	18.0	< 0.0001
mMRC ≥ 2	28.9	40.2	< 0.0001
SGRQ > 25	29.5	43.2	< 0.0001
6MWD < 350 m	18.7	28.1	< 0.0001
BODE ≥ 2	18.3	27.8	< 0.0001
Gas trapping% ≥ 21	9.5	16.9	< 0.0001
Emphysema% ≥ 3.5	12.3	13.7	NS
MALES , N = 2268			
	$FEV_3/FEV_6 \geq$ LLN n= 1745 (%)	$FEV_3/FEV_6 <$ LLN n= 373 (%)	*P*
FEV1 %pred < 65	4.2	19.4	< 0.0001
mMRC ≥ 2	20.3	32.2	< 0.0001
SGRQ > 25	24.7	40.8	< 0.0001
6MWD < 350 m	14.9	22.4	0.001
BODE ≥ 2	13.7	25.3	< 0.0001
Gas trapping% ≥ 21	15.4	29.9	< 0.0001
Emphysema% ≥ 3.5	20.5	27.0	0.01

Data are column percentages representing proportion of the population, (lower and upper bounds for 95% confidence interval). Statistical significance was determined by Pearson *chi-square*. Definition of abbreviations: n, number of subjects; FEV_1 %predicted, forced expiratory volume in 1 seconds expressed as percent predicted; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance; NS: non-significant.

e-Table 6. Comparison of spirometric, quantitative CT, quality of life, 6 minute walk distance, and clinical variables among subjects stratified by pre-bronchodilator FEV_1/FVC and FEV_1/FEV_6 normalcy.

	Both ≥LLN[1]	Only FEV_1/FEV_6 <LLN[2]	Only FEV_1/FVC <LLN[3]	Both <LLN[4]	*P*					
					1vs2	*1vs 3*	*1vs 4*	*2vs 3*	*2vs 4*	*3vs 4*
n, (%)	4142 (52.7)	244 (3.1)	283 (3.6)	3184 (40.5)						
Age, years	57 (51 – 64)	59 (52 – 67)	60 (53 – 67)	63 (56 – 69)	†	*	*	*NS*	*	*
BMI	29.5 ± 5.9	27.9 ± 6.3	29.2 ± 5.5	27.7 ± 6.1	*	*NS*	*	*NS*	*NS*	*
Sex, Male %	52.1	44.7	67.5	54.8	§	*	§	*	†	*
Race, Caucasian %	65.0	51.6	84.8	79.1	*	*	*	*	*	§
Duration of smoking, pack.years^{-1} (n=7,755)	35 (23 – 48)	39 (25 – 54)	40 (29 – 58)	46 (34 – 65)	*NS*	*	*	*NS*	*	*
FEV_1 %pred	89.5 ± 15.4	74.8 ± 15.2	80.2 ± 14.3	50.2 ± 21.1	*	§	*	*	*	*
FEV_6 %pred	91.3 ± 14.9	85.5 ± 17.3	87.1 ± 15.1	68.6 ± 20.2	*	*NS*	*	*	*	*
FVC %pred	91.5 ± 15.2	84.8 ± 18.9	94.4 ± 17.5	76.2 ± 20.3	*	*	*	*	*NS*	*
FEV_1/FVC, %	75.7 (72.0 – 79.4)	68.3 (67.0 – 70.0)	65.4 (63.7 – 66.7)	50.8 (38.5 – 60.5)	*	*	*	†	*	*
FEV_1/ FEV_6, %	78.7 (75.8 – 81.7)	70.3 (69.5 – 71.5)	73.0 (71.9 – 74.3)	58.0 (47.2 – 66.4)	*	*	*	*	*	*
$LAA_{–950insp}$, %	0.96 (0.4 – 2.4)	1.8 (0.6 – 3.9)	2.0 (0.8 – 3.9)	8.4 (2.6 – 20.1)	*	*	*	*NS*	*	*

LAA$_{-856exp}$, %	8.6 (4.0 – 15.1)	16.1 (9.7 – 26.0)	13.0 (7.1 – 20.8)	36.8 (20.6 – 55.5)	*	*	*	*NS*	*	*
E/I MLA	0.83 (0.79 – 0.87)	0.88 (0.84 – 0.91)	0.84 (0.79 – 0.88)	0.92 (0.88 – 0.96)	*	*NS*	*	*	*	*
Wall Area, %	60.3 ± 3	61.9 ± 3.5	60.7 ± 2.7	62.7 ± 3.1	*	*NS*	*	*	†	*
SGRQ	10.9 (3.3 – 28.6)	21.2 (7.7 – 41.5)	12.9 (5.6 – 28.8)	38.4 (21.2 – 55.5)	*	*NS*	*	†	*	*
mMRC (n=7,849)	0.9 ± 1.2	1.3 ± 1.4	1.0 ± 1.3	2.0 ± 1.4	*	*NS*	*	*NS*	*	*
6MWD, meters (n=7,756)	442 ± 108	397 ± 118	452 ± 103	369 ± 121	*	*NS*	*	*	†	*
BODE (n=7,756)	0.5 ± 1.0	1.1 ± 1.4	0.6 ± 1.0	2.7 ± 1.4	*	*NS*	*	*NS*	*	*

Data are mean ± standard deviation, median (IQR 25-75), or median (min, max). * $P < 0.0001$, † $P < 0.01$, § $P < 0.05$. Statistical significance was determined by one-way analysis of variance with Tukey *post-hoc* tests for continuous normal data, Kruskal-Wallis test followed by Mann-Whitney *U* test for pairwise comparisons for continuous non-normal data, and Pearson *chi-square* test for comparison of proportions. Definition of abbreviations: n, number of subjects; BMI, body mass index; FEV_1 %predicted, forced expiratory volume in 1 seconds expressed as percent predicted; FEV_6 %predicted, forced expiratory volume in 6 seconds expressed as percent predicted; FVC %predicted, forced vital capacity expressed as percent predicted; LAA$_{-950insp}$, total percentage of all lung voxels less than or equal to –950 Hounsfield Units (HU) on end-inspiratory scans; LAA$_{-856exp}$, total percentage of all lung voxels less than or equal to –856 Hounsfield Units (HU) on expiratory scans; E/I MLA, expiratory to inspiratory ratio of mean lung attenuation; WA, wall area; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walking distance; LLN, lower limit of normal.

e-Table 7. General linear regression models of the difference in quantitative CT, quality of life, 6 minute walk distance, dyspnea perception and BODE index in models comparing abnormality in FEV_1/FEV_6 and/or FEV_1/FVC in the entire study population (n=7,853).

	Emphysema% [1]	**Gas trapping%** [1]	**Wall Area %** [1]	**E/I MLA %**[1]	**SGRQ**[2]	**6MWD**[2]	**mMRC**[2]	**BODE**[2]
	%difference 95% CI	**% difference 95% CI**	**% difference 95% CI**	**% difference 95% CI**	**% difference 95% CI**	**% difference 95% CI**	**OR 95% CI**	**OR 95% CI**
Only FEV_1/FEV_6 <LLN‡ (n=244)	43.0* (22 – 68)	62.5* (46 – 81)	2.7* (2.1 – 3.3)	3.6* (2.8 – 4.4)	50.3* (31 – 72)	- 8.3* (-13 – -4)	1.7* (1.35 – 2.20)	2.6* (1.79 – 3.71)
Only FEV_1/FVC <LLN‡ (n=283)	42.2* (23 – 64)	28.6* (16 – 42)	0.9* (0.4 – 1.5)	0.9† (0.2 – 1.7)	21.9† (0.7 – 39)	0.0 (-0.4 – 0.5)	1.4† (1.08 – 1.73)	1.2 (0.78 – 1.96)
Both FEV_1/FEV_6 and FEV_1/FVC‡ <LLN (n=3,184)	373.0* (346 – 402)	217.1* (204 – 231)	4.5* (4.2 – 4.7)	8.0* (7.7 – 8.3)	171.1* (157 – 185)	- 18.9* (-20 – -17)	5.0* (4.50 – 5.47)	14.5* (12.46 – 16.86)

Emphysema%, gas trapping%, E/I MLA, wall area %, SGRQ and 6MWD were natural log transformed. The displayed coefficients (% difference and CI 95%) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. * $P < 0.0001$; † $P < 0.05$. ‡ Participants with both $FEV_1/FEV_6 \geq$LLN and $FEV_1/FVC \geq$LLN were used as the reference category. [1] Models controlled for sex, age, race, body mass index, smoking history and CT scanner type. [2] Models controlled for sex, age, race, body mass index and smoking history. Definition of abbreviations: FEV_1, forced expiratory volume in 1 second; FEV_6, forced expiratory volume in 6 seconds; FVC, forced vital capacity; E/I MLA, expiratory to inspiratory mean lung attenuation; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walk distance (meters); OR, odds ratio; 95% CI, exponential (back-transformed) 95% confidence intervals.

e-Table 8. Univariate correlations (*r*) between spirometric measurements quantitative CT, quality of life, 6 minute walk distance, dyspnea perception and BODE index in the whole study population (n=7,853).

Spirometry	$LAA_{-950insp}$ %	$LAA_{-856exp}$%	E/I MLA	Wall Area %	SGRQ	6MWD	mMRC	BODE
FEV_1, %pred	- 0.46	- 0.58	-0.60	- 0.47*	- 0.55	0.46*	- 0.49	- 0.68
FEV_3 %pred	- 0.38	-0.49	-0.51	-0.46*	-0.53	0.44*	-0.47	-0.65
FEV_6 %pred	- 0.32	-0.45	-0.49	-0.45*	-0.50	0.44*	-0.46	-0.62
FVC, % pred	- 0.21	- 0.33	-0.40	- 0.44*	- 0.44	0.42*	- 0.41	- 0.55
FEV_1/FVC, %	- 0.64	- 0.72	-0.65	- 0.31	- 0.44	0.31	- 0.39	- 0.58
FEV_1/FEV_6, %	- 0.63	- 0.73	-0.67	- 0.36	- 0.46	0.33	- 0.41	- 0.60
FEV_3/FEV_6, %	- 0.61	- 0.71	-0.65	- 0.33	- 0.45	0.33	- 0.41	- 0.59
FEV_3/FVC, %	- 0.62	- 0.68	-0.60	- 0.27	- 0.40	0.31	- 0.37	- 0.53
$LAA_{-950insp}$, %	-	0.80	0.48	NS	0.25	- 0.16	0.25	0.38
$LAA_{-856exp}$, %	0.80	-	0.85	0.18	0.34	- 0.30	0.32	0.49
E/I MLA	0.48	0.85	-	0.32	0.37	- 0.36	0. 34	0.51
Wall Area %	NS	0.18	0.32	-	0.38	- 0.35*	0.32	0.39

All reported correlations are $P < 0.0001$. The listed values are Spearman correlation coefficients unless stated otherwise. * Pearson correlation coefficients. Definition of abbreviations: $LAA_{-950insp}$, total percentage of all lung voxels less than or equal to −950 Hounsfield Units (HU) on end-inspiratory scans; $LAA_{-856exp}$, total percentage of all lung voxels less than or equal to −856 Hounsfield Units (HU) on expiratory scans; E/I MLA, expiratory to inspiratory ratio of mean lung attenuation; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Dyspnea Scale; 6MWD, 6 minute walk distance (meters); FEV_1 %pred, forced expiratory volume in 1 second expressed as percent predicted; FEV_3 %pred, forced expiratory volume in 3 seconds expressed as percent predicted; FEV_6 %pred, forced expiratory volume in 6 seconds expressed as percent predicted; FVC %pred, forced vital capacity expressed as percent predicted; NS, non-significant.

Institutional Review Board Committee name and project approval number for 21 study centers.

Clinical Center	Institution Title	Protocol Number
National Jewish Health	National Jewish IRB	HS-1883a
Brigham and Women's Hospital	Partners Human Research Committee	2007-P-000554/2; BWH
Baylor College of Medicine	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22209
Michael E. DeBakey VAMC	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22202
Columbia University Medical Center	Columbia University Medical Center IRB	IRB-AAAC9324
Duke University Medical Center	The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB)	Pro00004464
Johns Hopkins University	Johns Hopkins Medicine Institutional Review Boards (JHM IRB)	NA_00011524
Los Angeles Biomedical Research Institute	The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center	12756-01
Morehouse School of Medicine	Morehouse School of Medicine Institutional Review Board	07-1029
Temple University	Temple University Office for Human Subjects Protections Institutional Review Board	11369

University of Alabama at Birmingham	The University of Alabama at Birmingham Institutional Review Board for Human Use	FO70712014
University of California, San Diego	University of California, San Diego Human Research Protections Program	070876
University of Iowa	The University of Iowa Human Subjects Office	200710717
Ann Arbor VA	VA Ann Arbor Healthcare System IRB	PCC 2008-110732
University of Minnesota	University of Minnesota Research Subjects' Protection Programs (RSPP)	0801M24949
University of Pittsburgh	University of Pittsburgh Institutional Review Board	PRO07120059
University of Texas Health Sciences Center at San Antonio	UT Health Science Center San Antonio Institutional Review Board	HSC20070644H
Health Partners Research Foundation	Health Partners Research Foundation Institutional Review Board	07-127
University of Michigan	Medical School Institutional Review Board (IRBMED)	HUM00014973
Minneapolis VA Medical Center	Minneapolis VAMC IRB	4128-A
Fallon Clinic	Institutional Review Board/Research Review Committee Saint Vincent Hospital – Fallon Clinic – Fallon Community Health Plan	1143