ORIGINAL ARTICLE

Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction

Surya P Bhatt,[1] Jessica C Sieren,[2] Mark T Dransfield,[1] George R Washko,[3] John D Newell Jr,[2] Douglas S Stinson,[4] Gideon K D Zamba,[5] Eric A Hoffman,[2] for the COPDGene Investigators

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2012-202810).

[1]Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA
[2]Department of Radiology, University of Iowa, Iowa City, Iowa, USA
[3]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[4]Department of Radiology, National Jewish Health, Denver, Colorado, USA
[5]Department of Biostatistics, University of Iowa College of Public Health, Iowa City, Iowa, USA

Correspondence to
Dr Surya P Bhatt, Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, THT 422, 1720, 2nd Avenue South, Birmingham, AL 35294, USA; spbhatt@uab.edu

Received 2 October 2012
Revised 18 February 2013
Accepted 27 February 2013
Published Online First 23 March 2013

ABSTRACT

Background Diagnosis of chronic obstructive pulmonary disease is based on detection of airflow obstruction on spirometry. There is no consensus regarding using a fixed threshold to define airflow obstruction versus using the lower limit of normal (LLN) adjusted for age. We compared the accuracy and discrimination of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommended fixed ratio of forced expiratory volume in the first second/forced vital capacity<0.70 with LLN in diagnosing smoking-related airflow obstruction using CT-defined emphysema and gas trapping as the disease gold standard.

Methods Data from a large multicentre study (COPDGene), which included current and former smokers (age range 45–80 years) with and without airflow obstruction, were analysed. Concordance between spirometric thresholds was measured. The accuracy of the thresholds in diagnosing emphysema and gas trapping was assessed using quantitative CT as gold standard.

Results 7743 subjects were included. There was very good agreement between the two spirometric cutoffs (κ=0.85; 95% CI 0.83 to 0.86, p<0.001). 7.3% were discordant. Subjects with airflow obstruction by fixed ratio only had a greater degree of emphysema (4.1% versus 1.2%, p<0.001) and gas trapping (19.8% vs 7.5%, p<0.001) than those positive by LLN only, and also smoking controls without airflow obstruction (4.1% vs 1.9% and 19.8% vs 10.9%, respectively, p<0.001). On follow-up, the fixed ratio only group had more exacerbations than smoking controls.

Conclusions Compared with the fixed ratio, the use of LLN fails to identify a number of patients with significant pulmonary pathology and respiratory morbidity.

Key messages

What is the key question?
- What is the best spirometric threshold to diagnose airflow obstruction and chronic obstructive pulmonary disease?

What is the bottom line?
- We report that, compared with the fixed ratio, use of the lower limit of normal will fail to identify a number of patients with significant pulmonary pathology and respiratory morbidity.

Why read on?
- There is no consensus regarding the best diagnostic cutoff for detecting smoking-related airflow obstruction. In contrast to previous studies which did not use a gold standard measure of lung pathology, we used CT as gold standard to compare spirometric criteria.

INTRODUCTION

The diagnosis of chronic obstructive pulmonary disease (COPD) is based on detection of airflow obstruction by spirometry. This is defined by a reduction in the ratio of the forced expiratory volume in the first second (FEV_1) to the forced vital capacity (FVC).[1] There is controversy regarding appropriate cutoff values for this ratio as this value changes with age. The Global Initiative for Chronic Obstructive Lung Disease (GOLD COPD) defined airflow obstruction at a fixed post-bronchodilator cutoff at $FEV_1/FVC<0.70$.[2] Questions were raised about the potential for underestimation of airflow obstruction at younger ages and over-diagnosis of COPD in older subjects using a fixed ratio.[3 4] The American Thoracic Society (ATS) and the European Respiratory Society (ERS) proposed using a threshold below the lower limit of normal (LLN) adjusted for age instead of a fixed criterion.[5] They defined the LLN as the fifth percentile of reference values drawn from the National Health and Nutrition Examination Survey (NHANES) III cohort.[6] Calculation of LLN is based on multiple regression calculations and may be subject to considerable variability around the median and is affected by gender and race.[7] While the LLN might be a statistically more sound method of diagnosing airflow obstruction than the fixed ratio, it has not been clinically validated for want of a gold standard. Longitudinal studies of outcomes comparing the two methods of defining cutoffs have been equivocal.[8 9]

CT is increasingly used to quantify emphysema by regions of low attenuation and small airway disease by objective measures of gas trapping on the expiratory scan.[10–12] Measures of emphysema on CT correlate well with histopathological diagnosis of emphysema.[10 12] We compared the fixed ratio and LLN thresholds for the detection of smoking-related airflow obstruction using CT-detected emphysema and airway disease as the gold standard.

Linked

▶ http://dx.doi.org/10.1136/thoraxjnl-2013-203497

To cite: Bhatt SP, Sieren JC, Dransfield MT, *et al*. *Thorax* 2014;**69**:409–414.

METHODS

Study population

Smokers and former smokers enrolled in a large multicentre study (COPDGene) were included in the study. Details of the study protocol have been published previously.[13] Briefly, we included subjects between the ages of 45 and 80 years with at least 10 pack-years of cigarette smoking. Subjects with lung diseases other than asthma and COPD were excluded from the study. For this study, we further excluded patients with physician-diagnosed asthma. Subjects completed a St George's Respiratory Epidemiology questionnaire, a modified ATS Respiratory Epidemiology questionnaire and performed a 6 min walk test according to the ATS guidelines.[13] The BODE (Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity) index was also calculated.[14] The modified Medical Research Council (MMRC) dyspnoea score was used to measure subject-perceived dyspnoea.[15] Pre-bronchodilator and post-bronchodilator spirometry was performed according to the ATS criteria.[5] The COPDGene study was approved by the institutional review boards of all 21 participating centres.

Imaging

Volumetric CT scans were obtained at two fixed lung volumes, maximal inspiration (total lung capacity (TLC)) and relaxed maximal exhalation (functional residual capacity (FRC)). Quantitative measures of emphysema and gas trapping were assessed using three-dimensional Slicer software (http://www.airwayinspector.org) and airway dimensions using Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, Iowa, USA).[13] Emphysema was measured using the percentage of lung volume at TLC with attenuation less than −950 Hounsfield units (HU) (low attenuation area, $\%LAA950_{insp}$), and percentage of voxels below the 15th percentile (Perc15).[13] Gas trapping was measured using the percentage of lung volume at FRC with attenuation less than −856 HU ($\%LAA856_{exp}$). Wall area percentage of segmental airways (Wall area pct) was used to quantify airway disease.[13]

Case definition

Subjects were categorised as having smoking-related airflow obstruction by the fixed GOLD COPD criteria if FEV_1/FVC was <0.70 (Fixed+). Post-bronchodilator values were used. TheNHANES III reference equations were used to calculate predicted values and LLN for FEV_1/FVC.[6] Subjects falling below the fifth percentile of FEV_1/FVC for age by ATS/ERS criteria were categorised as having smoking-related airflow obstruction by LLN criteria (LLN+). Those negative by both criteria were deemed 'normal' smokers without airflow obstruction, and those positive by both criteria were designated as having COPD. Discordant cases were further categorised into those positive by the fixed but not the LLN criteria (Fixed+LLN−), and those positive by LLN but not fixed criteria (LLN+Fixed−). As there is no consensus on the cutoff for defining emphysema by quantitative CT, we used 5% $LAA950_{insp}$ based on expert recommendations and previous studies[16 17] and 7% based on a study correlating quantitative CT with pathology. We also assessed emphysema at the 10% and 15% cutoffs for $LAA950_{insp}$. We defined significant gas trapping as >15% $LAA856_{exp}$.[16]

Follow-up

Subjects were contacted every 6 months by an automated telephony system using a validated questionnaire.[18] Information obtained included incidence and frequency of exacerbations, new use of home oxygen, new diagnosis of COPD by a physician and all-cause mortality. Exacerbations were defined as episodes requiring use of either antibiotics or systemic steroids for acute worsening of respiratory symptoms.

Statistical analyses

Concordance between fixed and LLN criteria was assessed using κ statistics. Baseline characteristics of those concordant and discordant for airflow obstruction were compared with smokers concordant for not having airflow obstruction, using analysis of variance. Tukey's test was used for post hoc comparisons between groups. Univariate analyses were performed using the Student t test (for continuous variables) and χ^2 test (for categorical variables) if appropriate. For comparisons between the fixed-only group and smokers without airflow obstruction, logistic regression analyses were used to adjust for confounding variables significant on univariate analyses. Cox proportional hazards were calculated for exacerbations on follow-up. Sensitivity and specificity of fixed and LLN thresholds for diagnosing emphysema using CT as gold standard were calculated, at varying cutoffs for emphysema (5%, 7%, 10% and 15% $LAA950_{insp}$). Positive and negative likelihood ratios were also calculated. Similar calculations were made for gas trapping ($LAA856_{exp}$ >15%). Accuracy of spirometric cutoffs in diagnosing emphysema was calculated by the degree of total agreement ((true positive+true negative)/total). p Value <0.05 was deemed statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS V.11.5).

RESULTS

We included 7743 subjects. There was a high degree of agreement between the two spirometric cutoffs (κ=0.85, p<0.001; Table 1). We identified 566 subjects (7.3%) who were discordant for a diagnosis of smoking-related airflow obstruction by the two criteria. As the fixed ratio is thought to underestimate disease at a younger age and overestimate at an older age, we compared concordance between fixed and LLN across arbitrarily defined age groups (table 1). Our inclusion criteria required subjects to be at least 45 years old to enter the study. In the older deciles, there

Table 1 Degree of agreement between the fixed ratio and LLN for airflow obstruction for an entire cohort and across age deciles

	Overall (n=7743)	45–50 (n=1303)	51–60 (n=2806)	61–80 (n=3638)
Smokers (Fixed−LLN−)	4491	1055	1929	1519
COPD (Fixed+LLN+)	2686	210	759	1712
Fixed+LLN−	548	22	116	407
LLN+Fixed−	18	16	2	0
κ (95% CI)	0.85 (0.83 to 0.86)	0.90 (0.87 to 0.93)	0.90 (0.88 to 0.92)	0.78 (0.76 to 0.80)

LLN, lower limit of normal.

were no subjects who were LLN+ but Fixed−, and hence the highest age deciles were combined. Concordance remained high except in the highest age deciles when it declined (table 1).

Table 2 shows the comparison of baseline characteristics and of imaging parameters of subjects with and without airflow obstruction who were concordant and discordant by the two spirometric thresholds. The discordant group was composed of subjects with a lower mean FEV_1/FVC than smokers without airflow obstruction, and with greater CT emphysema and gas trapping. Two subsets of the discordant group were further identified (Fixed+LLN− and LLN+Fixed−) (table 3). The discordant group was composed largely of the fixed-only subset. Fixed-only subjects were more likely to be older, male and Caucasian, and were also more likely to have a greater smoking burden than the LLN-only subset. The fixed-only group had a greater degree of CT-quantified emphysema (4.1% vs 1.2%; p=0.004) and gas trapping (19.8% vs 7.5%; p<0.001) than the LLN-only group. This was also reflected by a higher TLC and FRC by CT. These subjects were also more likely to be on home oxygen at baseline than in the LLN-only group (4.6% vs 0; p<0.001). The fixed-only group also had significantly more emphysema, gas trapping and bronchial wall thickening than smokers without airflow obstruction (table 3). These differences held true after adjusting for age, sex, race, pack-years of smoking and body mass index (adjusted OR for emphysema 1.12, 95% CI 1.09 to 1.15, p<0.001; OR for gas trapping 1.05, 95% C 1.04 to 1.06, p<0.001; OR for wall area% 1.16, 95% CI 1.12 to 1.20, p<0.001). We had follow-up data for 6036 subjects for a median of 592 days (range 9–1335). On follow-up, the fixed-only group had a greater frequency of acute exacerbations than the LLN-only group (0.3 vs 0.07 per year; p=0.01). Compared with those without airflow obstruction, the fixed-only group had a higher risk of exacerbations (unadjusted HR 1.1, 95% CI 1.0 to 1.2, p=0.04) (table 3). The fixed-only group also had higher scores on St George's Respiratory Questionnaire (19.6 (18.9) vs 16.9 (18.1); p<0.01). One-quarter of the fixed-only group were initiated on home oxygen following the baseline visit (26% vs 15%; p=0.01). A small number (1.6%) of smokers without airflow obstruction were also on home oxygen at baseline. Interestingly, the LLN-only group had a higher BODE index than the fixed-only group, an effect driven by a higher MMRC score in the LLN-only group. No subjects in the LLN-only group died on follow-up compared with five subjects in the fixed-only group, though the difference was not statistically significant.

For the entire cohort, when emphysema was defined as $LAA950_{insp}$ >5%, the fixed ratio was more sensitive and the LLN more specific for the detection of this abnormality (table 4 and see online supplementary table S1). The overall agreement for positive and negative cases with CT as gold standard was comparable. This pattern held true when emphysema was defined at increasing levels of severity (see online supplementary

Table 2 Comparison of concordant and discordant groups for airflow obstruction by FEV_1/FVC fixed ratio and LLN†

	Concordant		
Variable	**Smokers (Fixed−LLN−) (n=4491)**	**COPD (Fixed+LLN+) (n=2686)**	**Discordant (n=566)**
Age	57.1 (8.4)	63.2 (8.6)**	64.8 (8.4)**
Sex (% women)	2061 (46)	1162 (43)	178 (31)
BMI	29.2 (6.0)	27.4 (5.8)**	28.7 (5.6)
Race (% black)	1760 (39)	548 (20)	79 (14)
Pack-years	38.4 (20.9)	53.2 (26.9)**	49.5 (27.1)**
Oxygen therapy at baseline (%)	70 (1.6)	698 (26)**	25 (4.4)**
FEV_1 (litres)	2.8 (0.7)	1.6 (0.7)**	2.4 (0.7)**
FEV_1 % predicted	92.5 (15.3)	54.7 (21.8)**	81.1 (14.9)**
FVC (litres)	3.5 (0.9)	3.1 (1.0)**	3.6 (1)
FVC % predicted	91.8 (14.9)	81.9 (20.8)**	90.7 (16.6)
FEV1/FVC	0.78 (0.05)	0.50 (0.13)**	0.68 (0.02)**
Response to bronchodilator (%)	424 (9)	980 (37)**	111 (20)**
TLC	5.2 (1.3)	6.1 (1.5)**	5.9 (1.3)**
FRC	2.7 (0.7)	4.0 (1.2)**	3.3 (0.8)**
6MWD	1469 (360)	1226 (398)**	1433 (381)
MMRC	0.8 (1.2)	1.9 (1.4)**	0.9 (1.3)
BODE	0.5 (1.0)	2.6 (2.1)**	0.7 (1.1)*
SGRQ total	17.2 (18.1)	36.9 (21.8)**	19.7 (19)*
SGRQ symptoms	21.9 (21.6)	42.4 (24.9)**	25.9 (23)**
SGRQ activity	26.4 (26.1)	52.6 (28.2)**	29.1 (26.7)
SGRQ impact	10.5 (15.6)	26.4 (21.0)**	12.5 (16.5)*
LAA950insp	1.9 (2.6)	13.2 (12.8)**	4 (4.2)**
LAA856exp	10.9 (9.7)	38.8 (20.9)**	19.4 (11.1)**
Perc15	−904.4 (25.4)	−939.1 (28.7)**	−919.5 (21.3)**
Wall area (%)	60.3 (3)	62.5 (3.1)**	60.9 (2.9)**

All values expressed as mean (SD).
*p<0.05, **p<0.001.
†Statistical significance expressed in comparison with smokers without airflow obstruction (Fixed−LLN−).
6MWD, 6 min walk distance; BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnea and exercise capacity index; FEV_1, forced expiratory volume in the first second; FRC, forced residual capacity; FVC, forced vital capacity; LAA856exp, percentage low attenuation area<856 Hounsfield units at end expiration; LAA950insp, percentage low attenuation area<950 Hounsfield units at end inspiration; LLN, lower limit of normal; MMRC, Modified Medical Research Council dyspnea scale; Perc15, percentage of voxels below the 15th percentile; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Table 3 Comparison of discordant subsets

Variable	Smokers (Fixed−LLN−) (n=4491)	Fixed+LLN−(n=548)	LLN+Fixed− (n=18)
Age	57.1 (8.4)	65.3 (7.9)**	47.2 (2.0)
Sex (% women)	2061 (46)	162 (30)**	16 (89)
BMI	29.2 (6.0)	28.7 (5.5)*	28.1 (8.3)
Race (% black)	1760 (39)	64 (12)**	15 (83)
Pack-years	38.4 (20.9)	50.0 (27.2)**	35.7 (20.4)
Oxygen therapy at baseline (%)	70 (1.6)	25 (4.6)**	0 (0)
FEV_1 (litres)	2.8 (0.7)	2.4 (0.7)	2.3 (0.6)
FEV_1 % predicted	92.5 (15.3)	80.9 (14.9)**	86.6 (12.1)
FVC (litres)	3.5 (0.9)	3.6 (1.0)	3.3 (0.9)
FVC % predicted	91.8 (14.9)	90.4 (16.6)*	99.3 (13.8)
FEV_1/FVC	0.78 (0.05)	0.67 (0.02)**	0.70 (0.01)
Response to bronchodilator (%)	424 (9)	105 (19)**	5 (30)
TLC	5.2 (1.3)	5.9 (1.3)**	4.5 (1.2)
FRC	2.7 (0.7)	3.3 (0.8)**	2.5 (0.5)
6MWD	1469 (360)	1433 (383)	1423 (336)
MMRC	0.8 (1.2)	0.9 (1.3)	1.7 (1.4)
BODE	0.5 (1.0)	0.7 (1.1)**	1.4 (1.1)
Exacerbation frequency (per year)	0.25 (1.1)	0.33 (1.2)*	0.08 (0.3)
LAA950insp	1.9 (2.6)	4.1 (4.3)**	1.2 (1.3)
LAA856exp	10.9 (9.7)	19.8 (11.0)**	7.5 (5.2)
Perc15	−904.4 (25.4)	−920.5 (20.3)**	−889.9 (30.2)
Wall area (%)	60.3 (3)	60.8 (2.8)**	62.9 (3.1)

All values expressed as mean (SD).
*p<0.05; **p<0.001 for comparison between smokers (Fixed−LLN−) and fixed-only groups.
6MWD, 6 min walk distance; BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnea and exercise capacity index; FEV_1, forced expiratory volume in the first second; FRC, forced residual capacity; FVC, forced vital capacity; LAA856exp, percentage low attenuation area <856 Hounsfield units at end expiration; LAA950insp, percentage low attenuation area <950 Hounsfield units at end inspiration; MMRC, Modified Medical Research Council dyspnea scale; Perc15, percentage of voxels below the 15th percentile; TLC, total lung capacity.

table S1). The fixed ratio had increasing sensitivity and LLN increasing specificity with older age groups, across the range of emphysema severity. Table 4 and online supplementary table S2 also summarise the accuracy and discrimination of the two spirometric thresholds in diagnosing gas trapping.

DISCUSSION

We have shown that in a cohort of smokers and former smokers at high risk for developing smoking-related airflow obstruction, there is very good concordance between the two spirometric cutoffs, using a fixed cutoff of $FEV_1/FVC < 0.70$ and the LLN. However, concordance was poorer in older age groups. The fixed ratio for FEV_1/FVC identified a group of subjects who had significantly more emphysema and gas trapping defined by CT. These subjects were misclassified as normal by LLN criteria. These subjects were more likely to be older, male and Caucasian, and had a greater smoking burden. They were more likely to be on home oxygen therapy at baseline, a large number of them were initiated on home oxygen on follow-up, and they suffered more frequent exacerbations.

COPD has traditionally been diagnosed by demonstrating airflow obstruction by spirometry, though FEV_1/FVC declines with age, and there is controversy regarding the impact of this change.[5] Using a fixed FEV_1/FVC threshold of <0.70 for diagnosis has been criticised based on multiple studies reporting underestimation of airflow obstruction at younger ages and over-diagnosis at older ages.[3 4 19–22] While using LLN does reduce the prevalence figures for older ages,[4] this had not been validated with a gold standard or with outcomes. Also, comparison studies between the two diagnostic thresholds were done using the LLN as gold standard, a priori declaring that the LLN is a better cutoff for diagnosing disease.[3 5 19–22] In addition, these studies almost uniformly did not include post-bronchodilator values as recommended by GOLD COPD.[2]

Table 4 Discrimination and accuracy of FEV_1/FVC cutoffs in detecting emphysema and gas trapping

			LR (95% CI)		Agreement		
	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive	Negative	Overall	Positive	Negative
Emphysema at least 10% (prevalence=18%)							
Fixed	94 (92.6 to 95.2)	69.6 (68.4 to 70.8)	3.1 (3 to 3.16)	0.09 (0.07 to 0.11)	0.74	0.56	0.81
LLN	89.9 (88.2 to 91.4)	77.1 (76.0 to 78.1)	3.92 (3.79 to 4.04)	0.13 (0.11 to 0.15)	0.79	0.61	0.86
Gas trapping at least 15% (prevalence=48%)							
Fixed	70.2 (68.7 to 71.8)	84.2 (83.0 to 85.4)	4.46 (4.12 to 4.82)	0.35 (0.33 to 0.37)	0.77	0.75	0.79
LLN	61.2 (59.6 to 62.9)	89.0 (87.9 to 90.0)	5.56 (5.05 to 6.13)	0.44 (0.42 to 0.46)	0.76	0.71	0.79

FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; LLN, lower limit of normal; LR, likelihood ratio.

Using post-bronchodilator values for FEV_1/FVC reduces the prevalence rates for COPD by a third, possibly adjusting for the reported over-diagnosis at older ages. The controversy regarding the appropriate cutoff and whether to adjust for age stems from the unresolved issue of what defines 'normal'. Most diseases such as hypertension, diabetes mellitus and chronic kidney disease are diagnosed based on population data, showing a worse longitudinal outcome beyond a certain threshold. In addition, definitions are not adjusted for age, recognising that some individuals will be misclassified.[23–25] In contrast, COPD is a disease in which age-related adjustments have been proposed, but as our data suggest, this approach underestimates the presence of pathology and the risk of respiratory morbidity.

Our results are supported by longitudinal studies demonstrating poor outcomes in subjects defined as having disease only by the fixed ratio. In a cohort of older patients from the Cardiovascular Health Study who were followed for 11 years, Mannino *et al* showed that subjects who were Fixed+ but LLN − had an increased risk of death (adjusted HR of all-cause mortality 1.3; 95% CI 1.1 to 1.5) and an increased risk of COPD-related hospitalisation (HR 2.6; 95% CI 2.0 to 3.3).[8] Another study using the original NHANES cohort showed that the fixed-only group had an increased risk of death (HR 1.46).[26] Rather than the fixed ratio over-diagnosing the presence of COPD, Izquierdo Alonso *et al* showed in a large study that the LLN criteria possibly detected 26% fewer cases.[27] In their study, the greater number of cases detected by the fixed ratio only did not differ from the LLN group in the number of exacerbations, medication use or comorbidities, suggesting that the LLN group identified far fewer cases with poor respiratory outcomes.[27] Though using the fixed ratio of <0.70 was initially an expert recommendation, subsequent studies support this cutoff. Using longitudinal data from the NHANES III cohort, Vaz Fragoso *et al* assessed different thresholds of FEV_1/FVC below 0.80 in decrements of 0.05 and assessed all-cause mortality on longitudinal follow-up. They found that mortality increased first below a cutoff of 0.70 with a HR of 1.23 (95% CI 1.03 to 1.47).[28]

The relative enrichment of the fixed-only group with men and Caucasians merits comment. Beyond the age of 50 years, the LLN criteria define the FEV_1/FVC cutoff at approximately two to three points lower for men versus women, and one to two points lower for Caucasians versus African Americans.[6] This might result in more stringent criteria for obstruction for men and Caucasians such that they would be excluded by LLN criteria, but be retained by fixed criteria. As African Americans and women are more likely to develop early onset and severe emphysema despite similar smoking exposure,[16] they may also be more likely to meet the more stringent LLN criteria in the older age groups and thus fall within the concordant group, though this cannot be confirmed in our cross-sectional study.[29 30]

A surprisingly high number of subjects in the fixed-only group were initiated on home oxygen therapy after study enrolment. This may be in part due to the presence of non-COPD lung disease (such as obstructive sleep apnoea) or the development of exercise or nocturnal desaturation. The influence of these factors on the prescription of supplemental oxygen may be particularly important in subjects living at altitude as previously reported by Kim *et al*; however, our results suggest that the fixed-only population is at risk for the development of an oxygen requirement.[31]

Our study showed striking disagreement between spirometry and CT defined emphysema (figure 1). While the latter has been validated with pathology, spirometry appears to be more specific than sensitive for the detection of disease. While we do not advocate using CT as the sole method for the diagnosis of COPD or the selection of patients for treatment, it may provide complementary information in some cases.

The argument for the use of either the fixed ratio or LLN threshold depends on the desired performance characteristics of the test, with the latter having more specificity but less sensitivity in older patients. LLN has been proposed to be superior in that it would prevent unnecessary initiation of medication. Though current guidelines do not recommend treating asymptomatic subjects regardless of the threshold used to define airflow obstruction, our data confirm the findings of other studies suggesting fixed-only subjects have significant respiratory morbidity.[8 26 27] There is also evidence that even patients with mild chronic airflow obstruction have dyspnoea, poor quality of life and miss a large number of days at work,[32 33] and even early emphysema is associated with systemic consequences and comorbidities.[34] While it may appear that the fixed ratio only identifies older patients with non-consequential or 'senile'

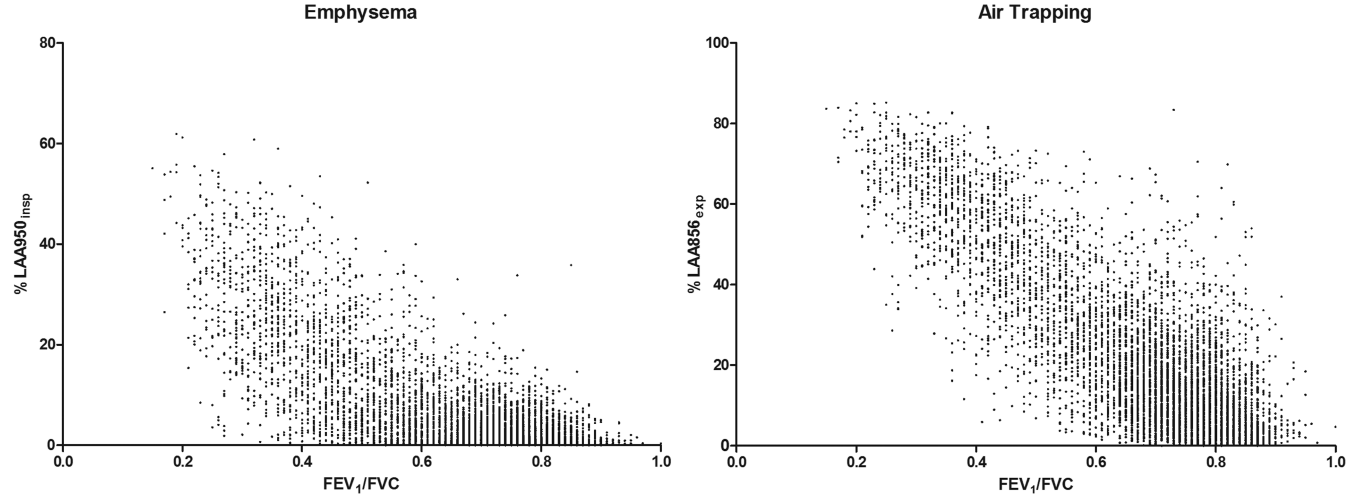

Figure 1 Scatter plot demonstrating that while there is good correlation between FEV_1/FVC and measures of emphysema and gas trapping, there is considerable discordance between spirometry and CT measures for a large number of subjects. FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; LAA950insp, percentage low attenuation area <950 Hounsfield units at end inspiration.

emphysema, this is likely not the case as there is considerably more gas trapping in the Fixed discordant group, arguing for more concurrent airway disease.

Our study has many strengths. This is the first study comparing the two diagnostic thresholds against a validated gold standard. We included a clinically relevant population of smokers and also used post-bronchodilator spirometry. Though we did not compare the diagnostic thresholds in normal controls, these subjects are unlikely to be diagnosed with COPD, and our study was limited to the diagnosis of emphysema and smoking-related airflow obstruction. Our conclusions are not applicable to younger non-smokers under age 45 with airflow obstruction, who we did not include and who are more likely to have asthma. While we excluded subjects with physician-diagnosed asthma, it is possible that there were a few subjects with undiagnosed asthma.

In conclusion, we have shown a high degree of discordance between CT and both spirometric thresholds. Overall, LLN appears to be marginally more specific for disease in older age groups, but will not identify a large number of older patients who have significant respiratory symptoms and CT emphysema. Longitudinal imaging studies are needed to confirm our findings.

Correction notice This article has been corrected since it was published Online First. The author name Douglas A Stinson has been amended to read Douglas S Stinson, and his affiliation amended to read Department of Radiology, National Jewish Health, Denver, Colorado, USA.

Collaborators COPDGene Investigators.

Contributors SPB conceived the study, analysed data and wrote the manuscript. JCS, MTD, GRW, JDN, DAS and EAH contributed to manuscript development, including writing critical components of it. GKDZ contributed to data analyses.

Funding COPDGene is supported by NIH Grant Numbers U01 HL089897 and U01 HL089856.

Competing interests MTD received consultancy fees from Boehringer Ingelheim and GlaxoSmithKline. JDN received consultancy fees from VIDA Diagnostics. EAH is the founder of and owns stocks in VIDA Diagnostics. None of the other authors have any conflicts of interest to declare pertinent to the subject of this manuscript.

Ethics approval Institutional Review Boards of all 21 participating centres.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004;364:709–21.
2 Pauwels RA, Buist AS, Calverley PM, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256–76.
3 Roberts SD, Farber MO, Knox KS, *et al*. FEV1/FVC ratio of 70% misclassifies patients with obstruction at the extremes of age. *Chest* 2006;130:200–6.
4 Hansen JE, Sun XG, Wasserman K. Spirometric criteria for airway obstruction: use percentage of FEV1/FVC ratio below the fifth percentile, not <70%. *Chest* 2007;131:349–55.
5 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
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;159:179–87.
7 Stanojevic S, Wade A, Stocks J, *et al*. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008;177:253–60.
8 Mannino DM, Sonia Buist A, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax* 2007;62:237–41.
9 Vaz Fragoso CA, Concato J, McAvay G, *et al*. Chronic obstructive pulmonary disease in older persons: a comparison of two spirometric definitions. *Respir Med* 2010;104:1189–96.
10 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;159:851–6.
11 Song G, Mortani Barbosa E Jr, Tustison N, *et al*. A comparative study of HRCT image metrics and PFT values for characterization of ILD and COPD. *Acad Radiol* 2012;19:857–64.
12 Madani A, Zanen J, de Maertelaer V, *et al*. Pulmonary emphysema: objective quantification at multi-detector row CT—comparison with macroscopic and microscopic morphometry. *Radiology* 2006;238:1036–43.
13 Regan EA, Hokanson JE, Murphy JR, *et al*. Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010;7:32–43.
14 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;350:1005–12.
15 Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;93:580–6.
16 Foreman MG, Zhang L, Murphy J, *et al*. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. *Am J Respir Crit Care Med* 2011;184:414–20.
17 Patel BD, Coxson HO, Pillai SG, *et al*. Airway wall thickening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;178:500–5.
18 Stewart JI, Moyle S, Criner GJ, *et al*. Automated telecommunication to obtain longitudinal follow-up in a multicenter cross-sectional COPD study. *COPD* 2012;9:466–72.
19 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;34:588–97.
20 Hwang YI, Kim CH, Kang HR, *et al*. Comparison of the prevalence of chronic obstructive pulmonary disease diagnosed by lower limit of normal and fixed ratio criteria. *J Korean Med Sci* 2009;24:621–6.
21 Miller MR, Quanjer PH, Swanney MP, *et al*. Interpreting lung function data using 80% predicted and fixed thresholds misclassifies more than 20% of patients. *Chest* 2011;139:52–9.
22 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;63:1046–51.
23 Chobanian AV, Bakris GL, Black HR, *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.
24 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012;35(Suppl 1):S64–71.
25 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39: S1–266.
26 Mannino DM, Diaz-Guzman E. Interpreting lung function data using 80% predicted and fixed thresholds identifies patients at increased risk of mortality. *Chest* 2012;141:73–80.
27 Izquierdo Alonso JL, De Lucas Ramos P, Rodriguez Glez-Moro JM, *et al*. The use of the lower limit of normal as a criterion for COPD excludes patients with increased morbidity and high consumption of health-care resources. *Arch Bronconeumol* 2012;48:223–8.
28 Vaz Fragoso CA, Concato J, McAvay G, *et al*. Defining chronic obstructive pulmonary disease in older persons. *Respir Med* 2009;103:1468–76.
29 Chatila WM, Hoffman EA, Gaughan J, *et al*. Advanced emphysema in African-American and white patients: do differences exist? *Chest* 2006;130:108–18.
30 Silverman EK, Weiss ST, Drazen JM, *et al*. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:2152–8.
31 Kim DK, Jacobson FL, Washko GR, *et al*. Clinical and radiographic correlates of hypoxemia and oxygen therapy in the COPDGene study. *Respir Med* 2011;105:1211–21.
32 Roche N, Dalmay F, Perez T, *et al*. Impact of chronic airflow obstruction in a working population. *Eur Respir J* 2008;31:1227–33.
33 Garcia-Rio F, Soriano JB, Miravitlles M, *et al*. Overdiagnosing subjects with COPD using the 0.7 fixed ratio: correlation with a poor health-related quality of life. *Chest* 2011;139:1072–80.
34 Decramer M, Rennard S, Troosters T, *et al*. COPD as a lung disease with systemic consequences—clinical impact, mechanisms, and potential for early intervention. *COPD* 2008;5:235–56.

Supplemental Table 1: Discrimination and accuracy of FEV1/FVC cut offs in detecting emphysema (LAA950insp)

	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	LR (95%CI)		Agreement		
			Positive	Negative	Over all	Positive	Negative
Overall							
Emphysema at least 5% (Prevalence = 29%)							
Fixed	80.4 (78.7-81.9)	74.4 (73.2-75.5)	3.14 (3-3.26)	0.26 (0.24 -0.29)	0.76	0.66	0.81
LLN	74.2 (72.3-75.9)	81.4 (80.4-82.4)	4 (3.79-4.21)	0.32 (0.3-0.34)	0.79	0.68	0.85
Emphysema at least 7% (Prevalence = 23%)							
Fixed	87.7 (86.1-89.2)	72.2 (71.0-73.3)	3.16 (3.05-3.25)	0.17 (0.15 -0.19)	0.76	0.63	0.82
LLN	82.3 (80.5-84.0)	79.5 (78.4-80.4)	4 (3.84-4.18)	0.22 (0.20 -0.25)	0.80	0.66	0.86
Emphysema at least 10% (Prevalence = 18%)							
Fixed	94 (92.6-95.2)	69.6 (68.4-70.8)	3.1 (3-3.16)	0.09 (0.07-0.11)	0.74	0.56	0.81
LLN	89.9 (88.2-91.4)	77.1 (76.0-78.1)	3.92 (3.79-4.04)	0.13 (0.11-0.15)	0.79	0.61	0.86
Emphysema at least 15% (Prevalence = 13%)							
Fixed	98.1 (96.9-98.8)	66.6 (65.4-67.7)	2.93 (2.89-2.97)	0.03 (0.02-0.05)	0.71	0.46	0.80
LLN	96.1 (94.6-97.2)	74.1 (73.1-75.2)	3.72 (3.63 – 3.78)	0.05 (0.04-0.07)	0.77	0.52	0.85
45 to 50 years (n=1303)							
Emphysema at least 5% (Prevalence = 10%)							
Fixed	51.1 (42.3-59.9)	85.9 (83.7-87.8)	3.63 (2.87-4.48)	0.57 (0.47-0.67)	0.82	0.37	0.90
LLN	48.9 (40.1-57.7)	86.2 (84.0-88.1)	3.53 (2.77-4.39)	0.59 (0.5-0.69)	0.82	0.36	0.90
Emphysema at least 7% (Prevalence = 6%)							
Fixed	67.1 (55.7-76.8)	85.5 (83.3-87.4)	4.62 (3.7-5.5)	0.39 (0.27-0.52)	0.84	0.35	0.91
LLN	64.6 (53.2-74.7)	85.8 (83.7-87.7)	4.55 (3.61-5.48)	0.41 (0.3-0.54)	0.85	0.34	0.91
Emphysema at least 10% (Prevalence = 4%)							
Fixed	84 (70.3-92.4)	84.8 (82.7-86.7)	5.54 (4.51-6.23)	0.19 (0.09-0.35)	0.85	0.30	0.91
LLN	82 (68.1-90.9)	85.2 (83.1-87.1)	5.55 (4.48-6.3)	0.21 (0.11-0.37)	0.85	0.30	0.92
Emphysema at least 15% (Prevalence = 3%)							
Fixed	91.7 (76.4-97.8)	84.3 (82.1-86.2)	5.83 (4.75-6.29)	0.10 (0.03-0.28)	0.85	0.25	0.91
LLN	88.9 (73.0-96.4)	84.7 (82.5-86.6)	5.8 (4.65-6.38)	0.13 (0.04-0.32)	0.85	0.24	0.92
51 to 60 years (n=2806)							
Emphysema at least 5% (Prevalence = 19%)							
Fixed	73.4 (69.4-77.0)	78.7 (76.9-80.4)	3.45 (3.16-3.74)	0.34 (0.29-0.39)	0.78	0.56	0.85
LLN	68.7 (64.5-72.6)	82.7 (81.0-84.2)	3.96 (3.58-4.35)	0.38 (0.34-0.43)	0.80	0.57	0.87
Emphysema at least 7% (Prevalence = 14%)							
Fixed	81 (76.7-84.7)	76.9 (75.1-78.5)	3.5 (3.24-3.75)	0.25 (0.2-0.3)	0.78	0.50	0.85

LLN	76.4 (71.8-80.5)	80.9 (79.2-82.3)	3.99 (3.64-4.33)	0.29 (0.24-0.35)	0.80	0.52	0.88
Emphysema at least 10% (Prevalence = 9.6%)							
Fixed	90.7 (86.4-93.8)	75.1 (73.4-76.8)	3.65 (3.42-3.82)	0.12 (0.08-0.18)	0.77	0.43	0.85
LLN	87 (82.2-90.7)	79.3 (77.6-80.8)	4.19 (3.88-4.45)	0.16 (0.12-0.22)	0.80	0.45	0.88
Emphysema at least 15% (Prevalence = 7%)							
Fixed	96.8 (92.8-98.7)	73.5 (71.8-75.2)	3.66 (3.47-3.75)	0.04 (0.02-0.10)	0.75	0.34	0.85
LLN	95.2 (90.8-97.6)	77.8 (76.1-79.3)	4.28 (4.2-4.65)	0.06 (0.03-0.12)	0.79	0.38	0.87
61 to 80 years (n=3638)							
Emphysema at least 5% (Prevalence = 44%)							
Fixed	84.8 (82.9-86.5)	62.9 (60.8-65.0)	2.29 (2.18-2.4)	0.24 (0.21-0.27)	0.73	0.73	0.72
LLN	77.9 (75.7-79.9)	77.5 (75.6-79.3)	3.46 (3.21-3.72)	0.29 (0.26-0.31)	0.78	0.76	0.79
Emphysema at least 7% (Prevalence = 37%)							
Fixed	90.8 (89.1-92.3)	60.5 (58.4-62.5)	2.29 (2.21-2.38)	0.15 (0.13-0.18)	0.72	0.70	0.73
LLN	85.1 (83.0-86.9)	74.8 (72.9-76.6)	3.38 (3.18-3.57)	0.2 (0.18-0.23)	0.79	0.74	0.82
Emphysema at least 10% (Prevalence = 29%)							
Fixed	95.3 (93.8-96.5)	57.1 (55.1-59.0)	2.22 (2.16-2.27)	0.08 (0.06-0.11)	0.68	0.64	0.72
LLN	91.1 (89.2-92.8)	71.2 (69.4-72.9)	3.16 (3.03-3.29)	0.12 (0.1-0.15)	0.77	0.70	0.81
Emphysema at least 15% (Prevalence = 21%)							
Fixed	98.7 (97.6-99.3)	52.7 (50.8-54.5)	2.09 (2.05-2.11)	0.03 (0.01-0.05)	0.63	0.53	0.69
LLN	96.8 (95.2-97.9)	66.4 (64.6-68.1)	2.88 (2.8-2.93)	0.05 (0.03-0.07)	0.73	0.60	0.79

LAA = Lower attenuation area. CI = Confidence Interval. LLN = Lower Limit of Normal.

Supplemental Table 2: Discrimination and accuracy of FEV_1/FVC cut offs in detecting air trapping ($LAA856_{exp}$)

	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	LR (95%CI)		Agreement		
			Positive	Negative	Overall	Positive	Negative
Overall							
Overall (Prevalence = 48%)							
Fixed	70.2 (68.7-71.8)	84.2 (83.0-85.4)	4.46 (4.12-4.82)	0.35 (0.33-0.37)	0.77	0.75	0.79
LLN	61.2 (59.6-62.9)	89.0 (87.9-90.0)	5.56 (5.05-6.13)	0.44 (0.42-0.46)	0.76	0.71	0.79
45-50 years (Prevalence = 22%)							
Fixed	45.3 (39.1-51.6)	90.0 (87.8-91.8)	4.52 (3.57-5.72)	0.61 (0.54-0.68)	0.80	0.50	0.88
LLN	43.8 (37.6-50.1)	90.2 (88.0-91.0)	4.46 (3.51-5.67)	0.62 (0.56-0.70)	0.80	0.49	0.88
51-60 years (Prevalence = 37%)							
Fixed	60.6 (57.3-63.7)	85.1 (83.2-86.8)	4.05 (3.57-4.61)	0.46 (0.43-0.50)	0.76	0.65	0.82
LLN	55.5 (52.2-58.7)	88.5 (86.8-90.0)	4.83 (4.16-5.59)	0.50 0.47-0.54)	0.76	0.63	0.83
61-80 years (Prevalence = 66%)							
Fixed	77.1 (75.2-78.8)	78.7 (76.1-81.0)	3.61 (3.22-4.05)	0.29 (0.27-0.32)	0.78	0.82	0.70
LLN	65.6 (63.6-67.6)	88.9 (86.9-90.6)	5.9 (5.0-7.0)	0.39 (0.36-0.41)	0.73	0.77	0.70

LAA = Lower attenuation area. CI = Confidence Interval. LLN = Lower Limit of Normal.