COPD prognosis in relation to diagnostic criteria for airflow obstruction in smokers.

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**What this paper adds:**

*What is already known on this subject:*

- When diagnosing COPD, using the current guideline-recommended fixed 0.70 cut-off point for FEV₁/FVC may not accurately reflect abnormal lung function at all ages, as this ratio declines with age in healthy persons.

- The use of the fixed 0.70 cut-off point to define airway obstruction may lead to a substantial rate of false-positive COPD diagnoses among middle-aged and elderly persons.

*What this study adds:*

- Results from a longitudinal study in smokers with high-quality data, which focuses at the most important marker of COPD prognosis, i.e. accelerated postbronchodilator lung function decline.

- FEV₁ decline in subjects deemed *obstructed* according to a fixed criterion (FEV₁/FVC<0.70), but *non-obstructed* by a sex and age-specific criterion for this ratio closely resembles FEV₁ decline in subjects designated as *non-obstructed* by both criteria.

- Based on this study and other recent studies, guideline recommendations on how to establish the presence of airway obstruction when diagnosing COPD should be reconsidered.
ABSTRACT

Aim

To establish which cut-off point for the FEV1/FVC (i.e. fixed 0.70 or Lower Limit of Normal cut-off point) best predicts accelerated lung function decline and exacerbations in middle-aged smokers.

Methods

We performed secondary analyses on the Lung Health Study dataset. 4,045 smokers aged 35 to 60 years with mild to moderate obstructive pulmonary disease were subdivided into categories based on presence or absence of obstruction according to both FEV1/FVC cut-off points. Postbronchodilator FEV1 decline served as primary outcome to compare subjects between the respective categories.

Results

583 subjects (14.4%) were non-obstructed and 3,230 subjects (79.8%) were obstructed according to both FEV1/FVC cut-off points. 173 (4.3%) subjects were obstructive according to the fixed but not according to the LLN cut-off point (‘discordant’ subjects). Mean postbronchodilator FEV1 decline was 41.8 (SE 2.0) ml/year in non-obstructive subjects, 43.8 (3.8) ml/year in discordant subjects, and 53.5 (0.9) ml/year in obstructive subjects (p<0.001).

Conclusion

Our study showed that FEV1 decline in subjects deemed obstructed according to a fixed criterion (FEV1/FVC<0.70), but non-obstructed by a sex and age-specific criterion (LLN) closely resembles FEV1 decline in subjects designated as non-obstructed by both criteria. Sex and age should be taken into account when assessing airflow obstruction in middle-aged smokers.
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction and progressive decline of lung function. COPD is a major cause of morbidity and mortality. A recent worldwide study indicated an overall prevalence of spirometry-confirmed COPD among middle-aged and elderly persons of approximately 10%. The clinical COPD guidelines issued by the Global Initiative for Obstructive Lung Disease (GOLD) and the National Institute for Clinical Excellence (NICE) recommend that obstruction should be defined as a forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) ratio below a fixed value of 0.70. In contrast, in their lung function guidelines the American Thoracic Society (ATS) and the European Respiratory Society (ERS) advocate the use of a ‘lower limit of normal’ (LLN) approach to define abnormally low FEV₁/FVC values.

The fixed 0.70 cut-off point is probably not an accurate reflection of abnormal lung function at all ages, because it has convincingly been shown that the FEV₁/FVC ratio declines with age in healthy persons. This could imply that by using a fixed cut-off point some middle-aged and elderly people are incorrectly considered to have airflow obstruction while their FEV₁/FVC is actually in the normal range.

A recent review of all published studies concluded that the prevalence of spirometry-confirmed COPD in middle-aged and elderly people is greater when using the fixed 0.70 threshold for the FEV₁/FVC than when using a LLN definition of the ratio. Discordant prevalence rates occurred in 4% up to 20% of cases. However, longitudinal studies are needed to determine which of the two approaches best predicts future COPD-related outcomes. The few studies that have looked at this so far used prebronchodilator FEV₁ and evaluated all-cause mortality as an outcome, rather than COPD-specific mortality.
None of these studies were able to look at the most important marker of COPD prognosis, i.e. accelerated postbronchodilator lung function decline.

Because the variability of pulmonary function increases with age and normal values for the FEV₁/FVC ratio are highly skewed, a FEV₁/FVC threshold based on the common method for calculating the LLN (i.e., simply calculating the fifth percentile of the distribution of z-scores of healthy never-smokers, assuming a normal distribution) may have limited diagnostic accuracy in an older population. Therefore the so-called ‘LMS’ (lambda, mu, sigma) method, has recently been recommended for calculating the lower limit of normal of the FEV₁/FVC. The aim of the study reported in this paper was to establish whether the fixed 0.70 or a LMS cut-off point for the FEV₁/FVC performs best in predicting accelerated postbronchodilator lung function decline in middle-aged smokers. Prebronchodilator FEV₁ decline and pre- and postbronchodilator FVC decline were secondary outcomes. We also investigated which of the two approaches best predicts risk of exacerbations and respiratory related hospital admissions.

METHODS

Study design and population
We used data from the Lung Health Study (LHS), a 5-yr randomized controlled clinical trial in 5,887 smokers aged 35 to 60 years with mild to moderate obstructive pulmonary disease. A full description of the LHS’ design can be found elsewhere.

Spirometry

Spirometry measurements were obtained during three screening visits and annually for a period of 5 years. Participants were tested before and after two inhalations of the
bronchodilator isoproterenol. All spirometry tests were performed according to American Thoracic Society standards(19) More details about quality assurance of the spirometry tests can be found elsewhere.(17)

Definitions of airflow obstruction and subject selection

We defined the lower limit of normal using the LMS method (see online supplement). The LMS method is a common approach for constructing growth-charts in a biologically plausible way(15;20-22) and is currently considered the best method to define the lower limit of normal.(14) We subdivided the study population into four categories based on the presence of airflow obstruction as defined by the LMS and the fixed 0.70 FEV1/FVC cut-off point definitions:

- ‘LMS–Fixed–’: absence of airflow obstruction according to both definitions (‘non-obstructed’ subjects);
- ‘LMS+Fixed–’: presence of airflow obstruction according to the LMS definition, but absence of airflow obstruction according to the fixed definition (‘discordant young’ subjects).
- ‘LMS–Fixed+’: absence of airflow obstruction according to the LMS definition, but presence of airflow obstruction according to the fixed definition (‘discordant old’ subjects);
- ‘LMS+Fixed+’: presence of airflow obstruction according to both definitions (‘obstructed’ subjects).

>Insert Figure 1 here<
Figure 1 illustrates these categories. We restricted our analysis to 4,045 subjects who were consistently classified in the same category at the screening visits and the follow-up visit one year later (see figure 2).

>Insert Figure 2 here<

**Lung function decline**

Accelerated lung function decline over time as the hallmark of disease progression can be considered the gold standard for obtaining a correct COPD diagnosis.(10) (23) Therefore, our primary outcome was the annual rate of postbronchodilator FEV$_1$ decline. (see online supplement for secondary outcome).

**Study definitions for exacerbations and hospital visits**

Exacerbations were defined based on two items in the annual questionnaire. Respiratory related hospital admissions were used as secondary outcomes (see online supplement).

**Smoking behaviour**

Self reported quit status for smoking cigarettes (yes/no) was recorded annually and validated by either salivary cotinine or carbon monoxide levels.

**Statistical analysis**

SAS® Proprietary Software 9·2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. A random coefficient linear regression model with random intercept and random slope was used to estimate the annual decline (PROC MIXED). Smoking behaviour was
included in the model as a time-dependent binary covariate. The comparison of the ‘discordant old’ and ‘obstructed’ categories (see Figure 1) was the principal part of the analyses, but we also compared lung function decline between all discordant subjects and non-obstructed subjects. Students t-test, analysis of variance (ANOVA) and Pearson’s chi-square test were used to determine if the four categories differed with regard to baseline characteristics, proportions of exacerbations and respiratory related hospital admissions. A value of p<0.05 was considered to be statistically significant.

RESULTS

Study subjects
The original LHS study population consisted of 5,887 smokers aged 35 to 60 years. We excluded 1,842 subjects because 1,276 subjects were in different categories based on the fixed and LMS definitions for airflow obstruction during their baseline and first annual visits, and 566 subjects had one missing spirometry result. From the 1,276 subject with unstable classification 681 subjects (56.4 %) lost their obstructed status and 595 subjects (46.6 %) obtained an obstructed status. Ultimately, 4,045 subjects (68.7%) could be included in the analysis (Figure 2). Table 1 shows baseline characteristics for the study population and for the excluded subjects. The latter subjects showed higher spirometry values compared to the study population.
Table 1. Baseline characteristics of the study population and the excluded subjects. Values are mean (SD) unless indicated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Study population</th>
<th>Excluded subjects</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=</strong></td>
<td>4,045</td>
<td>1,276</td>
<td></td>
</tr>
<tr>
<td>Follow-up duration, years</td>
<td>4.9 (0.6)</td>
<td>4.9 (0.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>2513 (62.1)</td>
<td>816 (64.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.71 (0.09)</td>
<td>1.71 (0.09)</td>
<td>0.91</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4 (3.9)</td>
<td>26.0 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>48.5 (6.8)</td>
<td>48.5 (6.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>Cigarettes, no. /day</td>
<td>31.1 (12.6)</td>
<td>31.1 (13.5)</td>
<td>0.88</td>
</tr>
<tr>
<td>Packyears</td>
<td>40.1 (18.3)</td>
<td>40.6 (20.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.7 (2.8)</td>
<td>13.6 (2.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>FEV1 pre-BD, L</td>
<td>2.61 (0.60)</td>
<td>2.73 (0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of predicted</td>
<td>74.4 (9.0)</td>
<td>77.9 (7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 post-BD, L</td>
<td>2.72 (0.63)</td>
<td>2.85 (0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of predicted</td>
<td>77.5 (9.2)</td>
<td>81.1 (8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC pre-BD, L</td>
<td>4.23 (0.96)</td>
<td>4.12 (0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC post-BD, L</td>
<td>4.28 (0.97)</td>
<td>4.13 (0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁/FVC post-bd</td>
<td>0.64 (0.06)</td>
<td>0.69 (0.03)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; pre-BD: prebronchodilator; post-BD: postbronchodilator.

The non-obstructed category comprised 583 (14.4%), the discordant young category 59 (1.5%), the discordant old category 173 (4.3%) and the obstructed category 3,230 subjects (79.8%).
Table 2. Baseline characteristics of the study population. Values are mean (SD) unless indicated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Non-obstructed</th>
<th>Discordant young</th>
<th>Discordant old</th>
<th>Obstructed</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4,045</td>
<td>583</td>
<td>59</td>
<td>173</td>
<td>3,230</td>
<td></td>
</tr>
<tr>
<td>Follow-up duration, years</td>
<td>4.9 (0.6)</td>
<td>4.9 (0.7)</td>
<td>5.1 (0.2)</td>
<td>4.8 (0.8)</td>
<td>4.9 (0.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Males, n (%), Discriminant</td>
<td>2513 (62.1)</td>
<td>378 (64.9)</td>
<td>4 (6.8)</td>
<td>152 (87.9)</td>
<td>1979 (61.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.71 (0.09)</td>
<td>1.72 (0.09)</td>
<td>1.65 (0.07)</td>
<td>1.75 (0.08)</td>
<td>1.71 (0.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4 (3.9)</td>
<td>25.9 (3.9)</td>
<td>24.2 (4.2)</td>
<td>26.3 (3.5)</td>
<td>25.3 (3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>48.5 (6.8)</td>
<td>46.8 (6.6)</td>
<td>38.7 (2.5)</td>
<td>55.5 (3.4)</td>
<td>48.6 (6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarettes, no./day</td>
<td>31.1 (12.6)</td>
<td>29.6 (12.4)</td>
<td>31.2 (16.3)</td>
<td>29.4 (13.2)</td>
<td>31.4 (12.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Packyears</td>
<td>40.1 (18.3)</td>
<td>36.7 (17.4)</td>
<td>25.7 (13.6)</td>
<td>48.0 (17.0)</td>
<td>40.6 (18.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.7 (2.8)</td>
<td>13.9 (2.9)</td>
<td>13.4 (2.2)</td>
<td>13.2 (2.8)</td>
<td>13.6 (2.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>FEV1 pre-BD, L</td>
<td>2.61 (0.60)</td>
<td>2.85 (0.60)</td>
<td>2.47 (0.35)</td>
<td>2.86 (0.48)</td>
<td>2.55 (0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of predicted</td>
<td>74.4 (9.0)</td>
<td>79.6 (7.2)</td>
<td>79.4 (6.8)</td>
<td>78.5 (7.5)</td>
<td>73.1 (8.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 post-BD, L</td>
<td>2.72 (0.63)</td>
<td>2.99 (0.64)</td>
<td>2.61 (0.39)</td>
<td>2.97 (0.50)</td>
<td>2.65 (0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of predicted</td>
<td>77.5 (9.2)</td>
<td>83.5 (7.5)</td>
<td>83.8 (7.2)</td>
<td>81.4 (7.6)</td>
<td>76.1 (9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC pre-BD, L</td>
<td>4.23 (0.96)</td>
<td>4.16 (0.88)</td>
<td>3.68 (0.54)</td>
<td>4.31 (0.75)</td>
<td>4.24 (0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC post-BD, L</td>
<td>4.28 (0.97)</td>
<td>4.12 (0.89)</td>
<td>3.67 (0.56)</td>
<td>4.34 (0.74)</td>
<td>4.31 (0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/FVC post-BD</td>
<td>0.64 (0.06)</td>
<td>0.73 (0.16)</td>
<td>0.71 (0.10)</td>
<td>0.68 (0.10)</td>
<td>0.62 (0.05)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; pre-BD: pre-bronchodilator; post-BD: post-bronchodilator. For descriptions of non-obstructed, discordant young, discordant old and obstructed see figure 1.

Table 2 shows characteristics of the respective categories. The discordant young category showed a low proportion of men (6.8%), and the discordant old category a high proportion of men (87.9%) compared to the obstructed (61.2%) and non-obstructed categories (64.2%), see also figure 3.

>Insert Figure 3 here<
With a mean age of 55.5 (SD 3.4) years the subjects in the discordant old category were significantly older than those in the obstructed category (48.6 (SD 6.6) years), the non-obstructed category (46.8 (SD 6.6) years), and the discordant young category (38.7 (SD 2.5) years). The mean postbronchodilator FEV1 percentage predicted of 76.1% (SD 9.1) in the obstructed category was lower than in the other three categories. The non-obstructed, discordant young and discordant old categories had mean postbronchodilator FEV1 percentage predicted values of 83.5% (SD 7.5), 83.8% (SD 7.2) and 81.4% (SD 7.6), respectively.

**Lung function decline**

Table 3 shows the adjusted estimates of the mean annual postbronchodilator FEV1 decline and annual decline for the secondary outcomes for each of the categories. Mean postbronchodilator FEV1 decline differed significantly between the categories (p<0.001). Subjects in the young discordant and old discordant categories showed mean postbronchodilator FEV1 decline of 38.7 ml/year and 43.8 ml/year, respectively. This was very similar to the decline in the non-obstructed category of 41.8 ml/year (p=0.634 for the young discordant subjects, p=0.654 for the old discordant subjects), but significantly less than the decline in the obstructed category of 53.5 ml/year (p=0.020 for the young discordant subjects and p=0.012 for the old discordant subjects).
<table>
<thead>
<tr>
<th>Category</th>
<th>Non-obstructed (n=583)</th>
<th>Discordant young (n=59)</th>
<th>Discordant old (n=173)</th>
<th>Obstructed (n=3,230)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(LMS– Fixed–)</td>
<td>(LMS+ Fixed–)</td>
<td>(LMS– Fixed+)</td>
<td>(LMS+ Fixed+)</td>
<td></td>
</tr>
<tr>
<td>(\Delta) FEV1 postbronchodilator, mL/year (SD)</td>
<td>41.8 (48.2)</td>
<td>38.7 (48.4)</td>
<td>43.8 (50.0)</td>
<td>53.5 (51.5)</td>
<td>0.634</td>
</tr>
<tr>
<td>(\Delta) FEV1 prebronchodilator, mL/year (SD)</td>
<td>36.3 (53.1)</td>
<td>33.3 (52.2)</td>
<td>44.1 (53.9)</td>
<td>59.0 (51.5)</td>
<td>0.672</td>
</tr>
<tr>
<td>(\Delta) FVC postbronchodilator, mL/year (SD)</td>
<td>38.2 (57.9)</td>
<td>35.9 (56.8)</td>
<td>41.0 (59.2)</td>
<td>48.5 (56.8)</td>
<td>0.760</td>
</tr>
<tr>
<td>(\Delta) FVC prebronchodilator, mL/year (SD)</td>
<td>48.1 (67.6)</td>
<td>44.6 (66.1)</td>
<td>51.6 (68.4)</td>
<td>62.5 (68.2)</td>
<td>0.696</td>
</tr>
</tbody>
</table>

LMS: (lambda, mu, sigma) lower limit of normal; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; \(\Delta\): annual change; * between group differences were analyzed with a random coefficient regression model with random intercept and random slope and were adjusted for differences in validated quit status for cigarettes between the categories. Quit status for cigarettes was statistically significantly associated with lung function at p<0.001 level in all regression models. Fixed: FEV1/FVC<0.70; LMS based on Hankinson prediction equations.
Secondary outcomes

Spirometry

Table 3 shows that the estimated decline of prebronchodilator FEV\textsubscript{1}, prebronchodilator FVC and postbronchodilator FVC follow the same pattern as the postbronchodilator FEV\textsubscript{1} for the different categories. Analysis of prebronchodilator FEV\textsubscript{1} values also indicated similarity in terms of decline between the discordant and non-obstructed categories (table 3; p=0.672 for the young discordant subjects, p=0.091 for the old discordant subjects), but dissimilarity between the discordant and obstructed categories (p<0.001 for the young discordant subjects, p<0.001 for the old discordant subjects). The same results were observed for the prebronchodilator FVC decline. Postbronchodilator FVC decline did not differ significantly between the young discordant (35.9 ml/year) and obstructed (48.5 ml/year) subjects (p<0.092) and between the old discordant (41.0 ml/year) and obstructed (48.5 ml/year) subjects (p<0.102).

Exacerbations

Figure 4 shows the proportion of subjects who experienced one or more exacerbations during the past year, annually measured for a 5-year observation period. At all visits the overall differences in the proportion of subjects with exacerbations between the categories were statistically significant (p<0.001). The obstructed category showed the highest proportion of subjects with exacerbations (26.8%), while the discordant old category showed the lowest proportion (15.7%). During the study period, the proportion of subjects with one or more exacerbations was stable for most categories except for the young discordant category, which started with a proportion of 20.3%, decreased to 15.5% during the following visits and increased to 25.9% at the last annual visit.
Hospital visits

During the 5-year follow-up period 22 respiratory related hospital admissions were registered in the obstructed category and no respiratory related hospital registration in the other three categories.

DISCUSSION

In this study we focused on the rate of lung function decline in subjects identified as obstructive by the fixed 0.70 FEV1/FVC cut-off point but as non-obstructive by a LMS cut-off point for this ratio. In addition we found a small category of younger people, predominantly women, with presence of airflow obstruction according to the LMS definition, but absence of airflow obstruction according to the fixed definition. The mean annual postbronchodilator FEV1 decline in the subjects in both discordant categories was very similar to subjects who were non-obstructive according to both definitions. However, postbronchodilator FEV1 decline was 9.7 ml/year lower than the mean decline in subjects with FEV1/FVC values below both cut-off points (‘obstructed category’).

During the study period, the proportion of subjects with at least one exacerbation was stable for most categories except for the young discordant category, in which we observed an increase to the same level as in the obstructive category at the end of the study period. Although this category (n=59) had the lowest mean annual postbronchodilator FEV1 decline this notable increase in exacerbations in year 5 might be an indication of developing or progression of early COPD. However, this observation should be interpreted with caution:
because of the small number of subjects in this group, a few subjects changing status has a considerable influence on the percentage developing more symptoms. In the old discordant category, the proportion of subjects with at least one exacerbation was consistently lower than in the obstructed category and comparable with the proportion in the non-obstructed category. Together with the finding that the mean lung function decline is similar to the non-obstructed category, this is an indication that subjects in the old discordant category do not suffer from a progressive chronic obstructive condition, i.e. COPD.

We chose to analyze respiratory related hospital admissions because we consider this a better indicator of prognosis of COPD than all-cause hospitalizations. We are aware of the fact that it is challenging to assign exactly one primary cause for hospitalization. However, in the Lung Health Study all participant-reported hospitalizations were verified by checking the hospital records, coding by an experienced coder, and checking by a panel of three expert physicians. So we believe it is a reliable outcome measure. The number of respiratory related hospital admissions was small (22 during the five years of follow-up), but they all occurred in the obstructed category. The relative young age of the study population (35 to 60 years) and the fact that they were not selected because of a previous diagnosis of COPD and mainly had mild to moderate obstruction are possible explanations for this low number of respiratory related hospital admissions.

**Comparison with existing literature**

In a recent analysis of the LHS cohort, Drummond et al. concluded that individuals with lower baseline FEV1/FVC have more rapid decline and worse mortality, and that it may be necessary to lower the threshold to an FEV1/FVC less than 0.65 or Z-scores less than -2.0 to identify those at increased risk for more rapid fall FEV1 (24). Several studies have shown that lung function decline is accelerated in individuals diagnosed with COPD. (1,25,26) However,
these studies did not focus on the definition of airway obstruction itself, but only used the current GOLD criteria in their final analysis. Other studies have reported high rates of false positive diagnostic interpretations when the fixed and LLN definitions for airflow obstruction are used to classify subjects as obstructive.(27-31) False-positive interpretations may cause erroneous diagnoses in individuals and inflation of COPD population prevalence rates.(32) This proportion of false positives increased with age, as the variance of FEV1/FVC increased with age. Our research group previously showed that as much as 43% of subjects aged older than 80 years were wrongly labelled as having airway obstruction when using the fixed 0.70 cut-off for the ratio in comparison to a LLN definition.(33) While these studies are good examples of how prevalence figures differ when using a cross-sectional design and different cut-off points, they do not provide information regarding the longitudinal course of clinical markers of COPD prognosis or actual disease outcome. In a previous study we have shown that in a primary care cohort of undiagnosed adults lung function below the normal range and early respiratory signs predicted the development and progression of COPD in the next five years.(34)

The use of a fixed cut-off point also seems to cause misclassification of airflow obstruction in younger adults (i.e., aged <45 years), as has recently been reported by Cerveri and colleagues.(35) These misclassified (or ‘underdiagnosed’) subjects were more likely to develop COPD in the following nine years, and had higher respiratory related healthcare than subjects without airflow obstruction according to LLN cut-off points. In our current study the fixed 0.70 FEV1/FVC cutpoint identified 94.1% of subjects with evidence of airflow obstruction according to LLN cutpoints. This misclassification is small compared to the result reported by Cerveri, but our study population was rather different with a higher proportion of obstructed subjects (81.3% versus 9.3%) and a substantial history of cigarette smoking in all study subjects.
Studies which used the LMS method are still scarce as it is a novel way to define airflow obstruction. Stanojevic et al. proposed the use of the LMS method because this method improves the accuracy of reference data for pulmonary function and, as a consequence, results in less misdiagnosis when defining airflow obstruction (15;22).

Some may argue that the use of a statistically derived cut-off point overly complicates the interpretation of spirometry when diagnosing airflow obstruction. However, even simple office spirometers and computer software can calculate the LMS and could easily be reprogrammed to display it. Even when not available, a graphical aid similar to growth charts used in children could be provided to support interpretation of spirometry tests.

**Strengths and limitations**

The main strength of our study is that we were able to look at postbronchodilator FEV₁ values instead of prebronchodilator FEV₁ as used by all previous studies that have looked at detection of airflow obstruction.(14;36) This ensures that subjects with reversible obstruction were correctly considered as being obstructive, as there is a general consensus among COPD experts and guidelines that postbronchodilator measurement of the ratio should be used when diagnosing COPD and assessing the severity of airflow obstruction. The quality of the spirometry tests in the Lung Health Study was very high, resulting in accurate estimates of lung function decline for the different categories. (17)

Another strength is the availability of longitudinal data of 4,045 subjects, allowing us to follow lung function decline in different categories of obstruction for several years. This enabled us to subdivide our study cohort into four categories, while each category still contained a substantial number of subjects. We used the novel LMS method which describes the relation between lung function, height and age for both sexes more precisely than the LLN method does.
Because the goal of our study was to compare clearly defined and consistent groups of subjects based on fixed and LMS definitions for airflow obstruction, we only included those subjects who did not shift between categories during their baseline and first annual follow-up visit. As a consequence 1,276 subjects (24%) were excluded from the analysis. This finding shows that one-off spirometry test does not seem to be sufficient to determine airflow obstruction in a substantial proportion of subjects, and suggests that a COPD diagnosis should not be based on a single spirometry test. On the other hand, excluding these subjects clearly comes at the cost of generalizability. Therefore, our analysis should be seen as a ‘proof of concept’ study regarding the presumption that when diagnosing COPD, it is more appropriate to use sex and age specific cut-off points for the FEV$_1$/FVC than it is to use a ‘one size fits all’ fixed (0.70) cut-off point.

**Conclusion**

In conclusion, our study shows that when looking at the cross-sectional description of the study population, the prevalence of airflow obstruction in 35 to 60 years old smokers with mild to moderate obstructive pulmonary diseases greatly differs when different cut-off points for the FEV$_1$/FVC are used. In addition, the discordant categories seem to be comprised of subjects who have a less accelerated decline in postbronchodilator FEV$_1$ than those in the obstructed category. We recommend the use of the LMS approach when defining airflow obstruction in the process of diagnosing COPD. Recently, the ERS Global Lung Function Initiative (GLI) has published new spirometric lung function reference values, which were also based on the LMS method (37).

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AUTHORS' CONTRIBUTIONS

- Reinier Akkermans has been involved in the conception and design of the study, has conducted the statistical analyses, has contributed to the interpretation of the data, and has written the draft version of the article.

- Marion Biermans has been involved in the conception and design of the study, has contributed to the interpretation of the data, and has critically revised the article for important intellectual content.

- Bas Robberts has been involved in the conception and design of the study, has contributed to the interpretation of the data, and assisted in the preparation of the draft version of the article.

- Gerben ter Riet has been involved in the conception and design of the study, has contributed to the interpretation of the data, and has critically revised the article for important intellectual content.

- Annelies Jacobs has been involved in the conception and design of the study, has contributed to the interpretation of the data, and has critically revised the article for important intellectual content.
- Michel Wensing has been involved in the conception and design of the study, has contributed to the interpretation of the data, and has critically revised the article for important intellectual content.

- C van Weel has been involved in the conception and design of the study, has contributed to the interpretation of the data, and has critically revised the article for important intellectual content.

- Tjard RJ Schermer initiated and designed the study, has contributed to the interpretation of the data, has critically revised the article for important intellectual content, and had the overall supervision of the study.
Title figures

**Figure 1.** Graphical representation of the different cut-off points and categories when defining airflow obstruction for a population sample.

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Footnote figure 1

In reality, the curved LLN line for each sex which will show how in females it is right shifted compared to the men which explains why 'discordant young' subjects are predominantly female and 'discordant old' predominantly male.
**Figure 2.** Selection of study subjects from the Lung Health Study dataset

**Figure 3.** Plotting age against baseline postbronchodilator FEV₁/FVC for male (n=2,513, **PANEL A**) and female (n=1,532, **PANEL B**) subjects in the study population.
Footnote panel 3b.

Non-obstructed: not obstructed to any cut-off point; Discordant young: Obstructed according to LMS cut-off point, but not the fixed; Discordant old: Obstructed according to the fixed cut-off point, but not the LMS; Obstructed: obstructed according to both cut-off points; LMS: lambda-mu-sigma method.
Figure 4. Proportion of subjects who experienced one or more exacerbations during the past year.

Reference List


