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What defines airflow obstruction in asthma?

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ABSTRACT: **Asthma guidelines from the Global Initiative for Asthma (GINA) and from the National Heart, Lung, and Blood Institute provide conflicting definitions of airflow obstruction, suggesting a fixed forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) cut-off point and the lower limit of normality (LLN), respectively. The LLN was recommended by the recent American Thoracic Society/European Respiratory Society guidelines on lung function testing. The problem in using fixed cut-off points is that they are set regardless of age and sex in an attempt to simplify diagnosis at the expense of misclassification.**

The sensitivity and specificity of fixed FEV_1/FVC ratios of 0.70, 0.75 and 0.80 *versus* the LLN were evaluated in 815 subjects (aged 20–44 yrs) with a diagnosis of asthma within the framework of the European Community Respiratory Health Survey.

In males, the 0.70 ratio showed 76.5% sensitivity and 100.0% specificity, the 0.75 ratio 100.0% sensitivity and 92.4% specificity, and the 0.80 ratio 100.0% sensitivity but 58.1% specificity. In females, the 0.70 ratio showed 57.3% sensitivity and 100.0% specificity, the 0.75 ratio 91.5% sensitivity and 95.9% specificity, and the 0.80 ratio 100.0% sensitivity but 72.9% specificity.

The fixed cut-off points cause a lot of misidentification of airflow obstruction in young adults, with overestimation with the 0.80 ratio and underestimation with the 0.70 ratio. In conclusion, the GINA guidelines should change their criteria for defining airflow obstruction.

KEYWORDS: **Airflow obstruction, asthma, diagnosis**

The latest Global Initiative for Asthma (GINA) executive report states that, although the diagnosis of asthma is usually based on the presence of characteristic symptoms, patients with asthma frequently show poor recognition of their symptoms and poor perception of symptom severity [1]. Thus it is stressed that, for patients aged >5 yrs, measurements of lung function to confirm airflow obstruction greatly enhance diagnostic confidence. Most of all, spirometry is key to monitoring lung function as an outcome of asthma. The importance of objective assessment of pulmonary function has also been stressed in the 2007 full guidelines for the diagnosis and management of asthma report of the National Heart, Lung, and Blood Institute (NHLBI) [2]. However, these two guidelines on asthma provide conflicting definitions of airflow obstruction. Whereas the GINA guidelines state that the forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio is normally >0.75–0.80 in adults and that lower values suggest airflow obstruction [3], the NHLBI states that airflow obstruction is indicated by a reduction in FEV_1/FVC relative to reference or predicted values [2]. Moreover, in several studies, the 0.70 fixed cut-off suggested by guidelines from the Global Initiative for Chronic Obstructive Lung Disease [4] has also been applied to asthmatic subjects [5–8].

In the present study, data from the European Community Respiratory Health Survey (ECRHS) were used to investigate the sensitivity and specificity of various fixed FEV_1/FVC cut-off points in young adults with physician-diagnosed asthma with respect to the lower limit of normal (LLN), *i.e.* the lowest 5th percentile of the frequency distribution of measures in a healthy population, according to the recent American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines on lung function testing [9].

METHODS

Study design

The design of ECRHS I and ECRHS II has been described in detail elsewhere [10, 11]. In ECRHS I, an international multicentric study on respiratory

For editorial comments see page 527.

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diseases carried out during 1991–1993 on random samples of young adults aged 20–44 yrs, each participant was sent a brief screening questionnaire (stage 1), and, from those who responded, a random sample was selected to undergo a more detailed clinical and functional examination (stage 2). In addition, a symptomatic sample, formed by the subjects who had reported waking with shortness of breath, asthma attacks or use of asthma medication during stage 1, was studied.

In ECRHS II, a follow-up study of the participants in stage 2 of ECRHS I, performed during 1999–2002, the subjects were invited to undergo the same examination as in the first survey.

Subjects and definitions

A total of 13,113 subjects out of 16,638 participants in stage 2 of ECRHS I from 27 European centres, from the random and symptomatic samples, provided lung function measurements fulfilling the ATS criterion for reproducibility [12]. The present analysis was limited to the 815 subjects (355 males and 460 females) aged 20–44 yrs who also attended ECRHS II and who reported a diagnosis of asthma during their lifetime (positive answers to both of the questions ''Have you ever had asthma?'' and ''Was this confirmed by a doctor?'') during both of the surveys (ECRHS I and II), in order to minimise potential misclassification.

The subjects were grouped according to the presence of airflow obstruction during ECRHS I as defined by the LLN and fixed FEV_1/FVC cut-off points. The LLN equations for FEV_1/FVC were obtained from 1,227 males and 1,309 females [13] who participated in stage 2 of ECRHS I and who were defined as normal according to JOHANNESSEN *et al.* [14]. Predicted values and LLN equations for FEV_1 and FVC were also calculated separately in males and females using the same methods as for FEV_1/FVC ratio (table 1).

TABLE 1 Predicted and lower limit of normal (LLN) lung function equations for males and females from the European Community Respiratory Health Survey data

Males	
Predicted equation	
FEV_1	4.976Ht – 0.020A – 3.695
FVC	6.957Ht – 0.010A – 6.610
FEV_1/FVC	89.602 – 0.185A
LLN equation	
FEV_1	4.976Ht – 0.020A – 4.526
FVC	6.957Ht – 0.010A – 7.602
FEV_1/FVC	79.401 – 0.185A
Females	
Predicted equation	
FEV_1	3.872Ht – 0.019A – 2.412
FVC	5.251Ht – 0.009A – 4.425
FEV_1/FVC	94.644 – 0.287A
LLN equation	
FEV_1	3.872Ht – 0.019A – 3.021
FVC	5.251Ht – 0.009A – 5.182
FEV_1/FVC	85.101 – 0.287A

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; Ht: height (in metres); A: age (in years).

Statistical analysis

The sensitivity and specificity of increasing fixed FEV_1/FVC cut-off points were calculated using the LLN as the gold standard for defining airflow obstruction. For each fixed cut-off point, the 95% confidence interval of sensitivity and specificity was computed by logistic regression models with adjusted SEM for intragroup (*i.e.* ECRHS centre) correlation. The exact one-sided 97.5% confidence interval was calculated when the estimate of sensitivity or specificity was equal to 100.0%. Youden's index was used to find the best fixed cut-off point [15]. Logistic regression models with adjusted SEM for intragroup correlation were also used to test the association between age and the percentages of false negatives (for the 0.70 cut-off point) and false positives (for the 0.80 cut-off point).

RESULTS

The demographic, clinical and functional characteristics during ECRHS I of the 815 subjects with physician-diagnosed asthma are reported in table 2. Of these subjects, 236 (29.0%) were classified as having airflow obstruction by the LLN, whereas 158 (19.4%), 258 (31.7%) and 428 (52.5%) were classified as having airflow obstruction using the FEV_1/FVC ratios of 0.70, 0.75 and 0.80, respectively. Using the LLN as the gold standard for defining airflow obstruction, the sensitivity and specificity of the 0.70 ratio were 76.5 and 100.0% for males, and 57.3 and 100.0% for females, respectively; the sensitivity and specificity of the 0.75 ratio were 100.0 and 92.4% for males, and 91.5 and 95.9% for females, respectively; and the sensitivity and

TABLE 2 Demographic, clinical and functional characteristics during European Community Respiratory Health Survey I of the 815 asthmatic subjects considered in the analysis

Females %	56.4
Age %	
<30 yrs	38.8
30–40 yrs	37.7
⩾40 yrs	23.5
Smoking status %	
Nonsmokers	50.8
Past smokers	20.5
Current smokers	28.7
Smoking history# pack-yrs	8.6 (3.5–16.0)
FEV_1 % pred	90.1±15.0
FEV_1 <LLN %	23.2
FVC % pred	97.2±12.8
FVC <LLN %	9.4
FEV_1/FVC	78.1±9.8
FEV_1/FVC <LLN %	29.0
High total IgE¶ %	46.8
IgE sensitisation+ %	70.0

Data are presented as median (interquartile range) or mean±SD unless otherwise indicated. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; LLN: lower limit of normal; FVC: forced vital capacity; Ig: immunoglobulin. #: among past and current smokers; ¶: >100 $kU \cdot L^{-1}$; +: at least one specific IgE measurement of ⩾0.35 $kU \cdot L^{-1}$ against five environmental allergens (*Dermatophagoides pteronyssinus*, cat, timothy grass, *Cladosporium herbarum* and a local allergen).

TABLE 3 Sensitivity, specificity and Youden's index of the various forced expiratory volume in 1 s/forced vital capacity fixed cut-off points# by sex

Cut-off	Sensitivity	Specificity	Youden's index
Males			
0.70	76.5 (69.9–82.0)	100.0 (98.4–100.0)¶	0.76
0.71	83.2 (75.5–88.8)	100.0 (98.4–100.0)¶	0.83
0.72	89.9 (82.1–94.6)	99.2 (94.0–99.9)	0.89
0.73	95.8 (90.2–98.3)	97.9 (94.2–99.2)	0.94
0.74	99.2 (94.0–99.9)	95.3 (90.9–97.7)	0.94
0.75	100.0 (96.9–100.0)¶	92.4 (86.5–95.8)	0.92
0.76	100.0 (96.9–100.0)¶	87.7 (81.4–92.1)	0.88
0.77	100.0 (96.9–100.0)¶	80.9 (74.3–86.2)	0.81
0.78	100.0 (96.9–100.0)¶	78.8 (72.8–83.8)	0.79
0.79	100.0 (96.9–100.0)¶	69.5 (63.4–75.0)	0.69
0.80	100.0 (96.9–100.0)¶	58.1 (51.6–64.3)	0.58
Females			
0.70	57.3 (49.5–64.7)	100.0 (98.9–100.0)¶	0.57
0.71	68.4 (58.7–76.7)	100.0 (98.9–100.0)¶	0.68
0.72	72.6 (63.0–80.5)	100.0 (98.9–100.0)¶	0.73
0.73	84.6 (77.7–89.7)	99.4 (97.6–99.9)	0.84
0.74	88.0 (82.4–92.0)	98.0 (96.1–98.9)	0.86
0.75	91.5 (87.4–94.3)	95.9 (93.0–97.7)	0.87
0.76	95.7 (91.3–98.0)	92.1 (88.8–94.5)	0.88
0.77	98.3 (94.0–99.5)	88.3 (84.0–91.6)	0.87
0.78	100.0 (96.9–100.0)¶	84.3 (79.4–88.1)	0.84
0.79	100.0 (96.9–100.0)¶	79.3 (74.0–83.7)	0.79
0.80	100.0 (96.9–100.0)¶	72.9 (67.6–77.6)	0.73

Data are presented as % (95% confidence interval), unless otherwise stated. #: using the lower limit of normal as the gold standard for defining airflow obstruction during European Community Respiratory Health Survey I; ¶: exact one-sided 97.5% confidence interval.

specificity of the 0.80 ratio were 100.0 and 58.1% for males, and 100.0 and 72.9% for females, respectively (table 3; fig. 1). According to Youden's index, the best fixed cut-off point was 0.74 in males and 0.76 in females (table 3). With the 0.70 fixed cut-off point, the percentage of false negatives was significantly higher among younger males ($p=0.015$) and females ($p=0.001$) compared to older subjects (fig. 2), whereas the opposite was observed for the percentage of false positives when the 0.80 fixed cut-off point was used ($p<0.001$ for both males and females) (fig. 3). With the 0.70 fixed cut-off point, the mean FEV_1 was 95.0, 87.0 and 73.5% of the predicted value ($p<0.001$) among subjects with normal lung function, those with misclassification of airflow obstruction and those with a concordant classification, respectively, whereas the mean FEV_1 was 96.8, 91.4 and 78.0% pred ($p<0.001$), respectively, when the 0.80 fixed cut-off point was used.

DISCUSSION

The present study shows that, among young adults with asthma, the use of FEV_1/FVC fixed cut-off points of 0.70 and 0.80 causes a lot of misidentification of airflow obstruction, with overestimation of obstruction with the 0.80 ratio and underestimation with the 0.70 ratio. The extent of the misidentification was particularly high at the extremes of age, and differed between males and females.

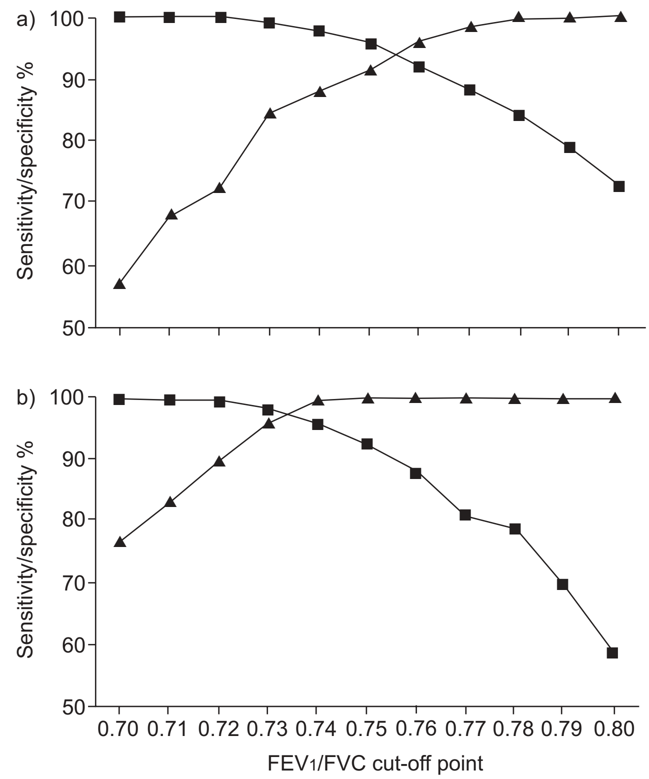

FIGURE 1. Sensitivity (▲) and specificity (■) of increasing forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) cut-off points using the lower limit of normal as the gold standard for defining airflow obstruction during European Community Respiratory Health Survey I in: a) females; and b) males.

Besides airflow obstruction, other important markers of asthma may help in better defining the individual asthma phenotype (IgE and airway inflammation) and its severity/control (symptoms and medications). However, the relevance of pulmonary function, as both a diagnostic tool and an outcome of asthma, is recognised worldwide.

At present, there is lively debate concerning the definition of airflow obstruction specifically focused on COPD [16–22], and many authors have already demonstrated that the trade-off with simplicity and ease of remembrance of the 0.70 fixed cut-off point could come at the expense of misclassification [13, 23–28]. The recommendation of different thresholds for the definition of airflow obstruction in COPD (0.70 ratio) and asthma (0.75–0.80 ratio) is even more difficult to justify and has resulted in ongoing confusion. The higher threshold for asthma than for COPD has probably been chosen because of the different distributions of age and the physiological decline in FEV_1/FVC in the two diseases, even though asthma may also have a late onset. Most of all, the documentation of airflow obstruction is very important for the long-term management of the disease, as recently underlined in the third Expert Panel Report (EPR-3) [2]. The use of a fixed cut-off point in the monitoring of lung function of an asthmatic subject over their lifetime can cause underestimation of airflow obstruction when young and overestimation when old, providing a misleading

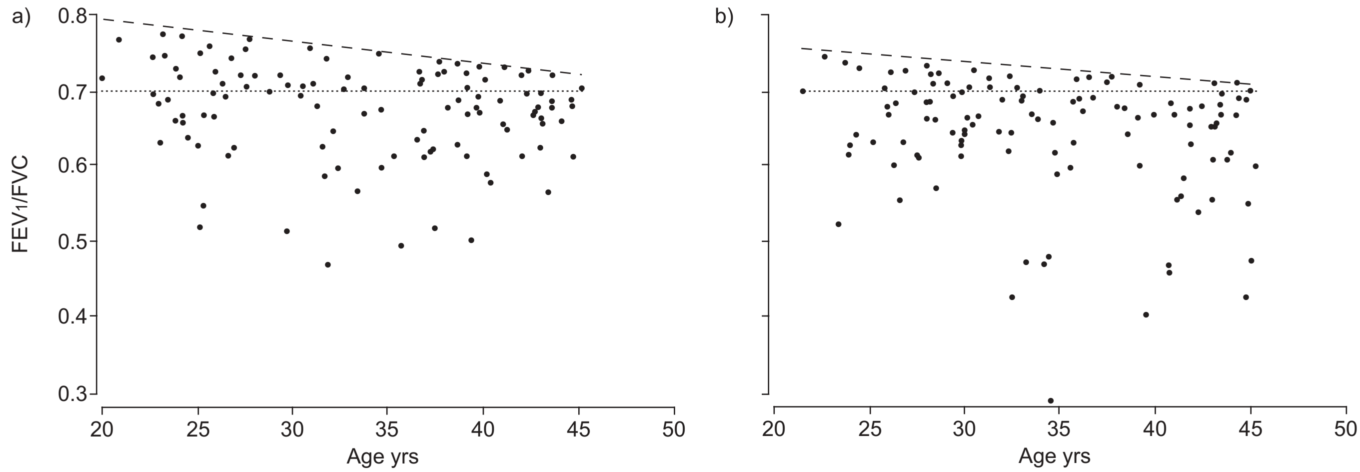

FIGURE 2. Forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of the subjects classified as abnormal by the lower limit of normal (LLN) during European Community Respiratory Health Survey I in: a) females; and b) males. The LLN (– – –) and the 0.70 fixed cut-off point (·········) are shown. Some of the subjects were above the stated age range as there was a lag between sampling frame selection and lung function assessment.

assessment of asthma control. Even the best cut-off points identified in the present study in the age range 20–44 yrs are expected to decrease in accuracy with increasing population age, as already documented for the 0.70 cut-off point in COPD [23–26].

According to the EPR-3 and American College of Physicians educational resources, the present results support the view that airflow obstruction is indicated by a reduction in FEV_1/FVC relative to reference or predicted values [2, 29]. This is physiologically appropriate since FEV_1 declines more rapidly with age in normal subjects than does FVC; thus the FEV_1/FVC ratio decreases with age. Moreover, at variance with any fixed cut-off point, it takes into account the difference in lung function between males and females. However, even the most careful and rigorous scientific investigation could not yield an exact measurement. Rather, repeating an investigation would yield a scatter of measurements that are caused not only by error, but also by natural variability. In other words, measurements themselves, independent of any human or instrumental inaccuracies, exhibit scatter. Since all measurements contain inherent error, the exact or correct value of a measurement can never be identified. A natural consequence of this idea is that the approximation may occasionally be incorrect. Thus, a statistically derived level below which a value is considered abnormal was used since statistics help in the quantification of errors. As recommended by the ATS/ERS guidelines on lung function testing, an individual's lung function is, by convention, considered to be low if it is below the 5th percentile of the frequency distribution of values measured in healthy persons of equivalent sex and age [9]. Obviously, the choice of the 5th percentile is arbitrary, but it corresponds to the typical biostatistical level of the probability threshold that the result has occurred by statistical accident. It is important to realise

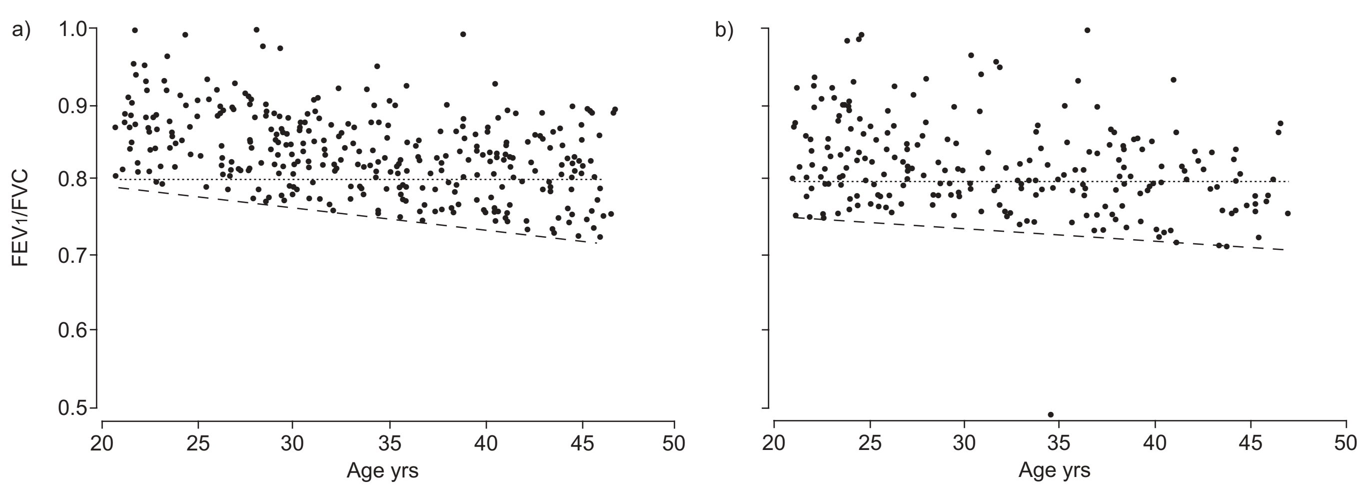

FIGURE 3. Forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of the subjects classified as normal by the lower limit of normal (LLN) during European Community Respiratory Health Survey I in: a) females; and b) males. The LLN (– – –) and the 0.80 fixed cut-off point (·········) are shown. Some of the subjects were above the stated age range as there was a lag between sampling frame selection and lung function assessment.

that there is always a finite chance that the result is a pure accident. In the present case it means that, by definition, 5% of the normal population (and only 5%) exhibit values below than the LLN. The 5th percentile of healthy subjects was applied to the asthmatic subjects even though patients with asthma do not show the same distribution of their FEV1/ FVC as healthy subjects because the aim was to identify airflow obstruction in a group of persons who differ from the norm in a way that is biologically disadvantageous.

The intrinsic limitation of using the LLN criterion is its dependency on the prediction equations and the reference population from which the prediction equations have been drawn. Ideally, prediction equations should be derived from measurements observed in a representative sample of healthy subjects from a general population, as in the present case, or, alternatively, in a large group of volunteers. Currently, the ATS/ERS committee does not recommend any specific set of equations for use in Europe, but suggests the need for a new Europe-wide study to derive updated reference equations [12]. Conversely, software and hardware have now changed the way in which laboratory testing is undertaken and there is no longer need for manual time-consuming calculation of predicted values, as even inexpensive spirometers can have built-in prediction equations and statistically derived LLNs.

The main strength of the present study is that it relies on a large international cohort of subjects from the general population. The ECRHS permitted derivation of the reference equations from measurements obtained in a representative sample of healthy subjects, using the same instruments and lung function protocol as in the followed-up cohort.

In conclusion, the present findings show the importance of using statistically valid spirometric criteria for the identification of airflow obstruction. Support is provided for the view that criteria for defining airflow obstruction in GINA guidelines should be changed.

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A statement of interest for J.M. Antó can be found at www.erj.ersjournals.com/misc/statements.dtl

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