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Underestimation of airflow obstruction among young adults using $FEV_1/FVC<70\%$ as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes.

Isa Cerveri[1], Angelo G. Corsico[1], Simone Accordini[2], Rosanna Niniano[1], Elena Ansaldo[1], Josep M. Antó[3,4], Nino Künzli[3,5], Christer Janson[6], Jordi Sunyer[3,4], Deborah Jarvis[7], Cecilie Svanes[8], Thorarinn Gislason[9], Joachim Heinrich[10], Jan P. Schouten[11], Matthias Wjst[10], Peter Burney[7], and Roberto de Marco[2] .

Institutional affiliation of each author:
[1]Division of Respiratory Diseases, IRCCS "San Matteo" Hospital Foundation, University of Pavia, Pavia, Italy; [2]Unit of Epidemiology and Medical Statistics, Department of Medicine and Public Health, University of Verona, Verona, Italy; [3]Center for Research in Environmental Epidemiology (CREAL) at Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain; [4]Department of Experimental Sciences and Health, Universitat Pompeu Fabra (UPF), Barcelona, Spain, and CIBER in Epidemiology and Public Health; [5]Institució Catalana de Recerca i Estudis Avançats (ICREA) Barcelona, Spain; [6]Department of Medical Sciences, Respiratory Medicine and Allergology, University of Uppsala, Uppsala, Sweden; [7]Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College, London, UK; [8]Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway; [9]Department of Allergy, Respiratory Medicine and Sleep, Landspitali University Hospital, Reykjavik, Iceland; [10]Institute of Epidemiology, GSF-National Research Center for Environment and Health, Neuherberg, Germany; [11]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Corresponding author and reprint request: Angelo G. Corsico, Clinica Malattie Apparato Respiratorio, Fondazione IRCCS Policlinico San Matteo, via Taramelli 5, 27100 Pavia, Italy. Phone: (39) 0382 501029. Fax: (39) 0382 503425. E-mail: angelo.corsico@unipv.it

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ABSTRACT

Background: Early detection of airflow obstruction is particularly important among young adults because they are more likely to benefit from intervention. Using the $FEV_1/FVC<70\%$ fixed ratio, airflow obstruction may be under-diagnosed. The lower limit of normal (LLN) which is statistically defined by the lower 5^{th} percentile of a reference population, is physiologically appropriate but it still needs a clinical validation.

Methods: To evaluate the characteristics and longitudinal outcomes of subjects misidentified as normal by the fixed ratio with respect to the LLN, 6,249 participants (aged 20-44 years) in the European Community Respiratory Health Survey (ECRHS) were examined and classified into 3 groups (absence of airflow obstruction by the LLN and the fixed ratio; presence of airflow obstruction only by the LLN; presence of airflow obstruction by the two criteria) in 1991-93. LLN equations were obtained from the normal non-smoking participants. A set of clinical and functional outcomes was evaluated in 1999-2002.

Results: The misidentified subjects were 318 (5.1%); only 45.6% of the subjects with airflow obstruction by the LLN were also identified by the fixed cut-off. At baseline, FEV_1 (107%, 97%, 85%) progressively decreased and bronchial hyperresponsiveness (slope 7.84, 6.32, 5.57) progressively increased across the 3 groups. During the follow-up, misidentified subjects had a significantly higher risk of developing COPD and a significantly higher use of health resources (medicines, ED visits/hospital admissions) because of breathing problems than the subjects without airflow obstruction ($p<0.001$).

Conclusions: Our findings show the importance of using statistically derived spirometric criteria to identify airflow obstruction.

INTRODUCTION

Guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and from the International Consensus Statement sponsored by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) suggest that airflow obstruction is present when the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) is less than 70%.[1,2] This criterion is set regardless of age and gender in an attempt to simplify the diagnosis. However, since the FEV_1/FVC ratio is inversely proportional to age, the use of a fixed cut-off would be expected to "over call" obstruction in old subjects and to "under call" obstruction in young individuals.[3] The trade-off with simplicity and ease of remembrance could come at expense of misclassification. The extent of misclassification of airflow obstruction as related to age using the fixed cut-off has been already quantified in previous studies.[4-8] Even the GOLD guidelines of December 2007 recognize the possible over-diagnoses in the elderly but they do not consider potential under-diagnoses in the younger population.[9] The fixed cut-off lacks of statistical justification while the values below the 5^{th} percentile of the frequency distribution of measures in a healthy population are considered below the “normal” limit for that biological parameter.[10-12] This means that, by convention, an individual's lung function is taken to be "low" if it is below the 5^{th} lung function percentile for "healthy" persons of equivalent sex and age. The recent joint statements on lung function testing from the ATS and the ERS recommend that the statistically derived lower limit of normal (LLN) should be used in lieu of the fixed ratio.[13]

Roberts et al.[5] have recently suggested that confirmatory evidence of which criteria is of greater clinical value is required and the last revision of the GOLD guidelines state that longitudinal studies are urgently needed to validate the use of the LLN.[9] Data on the relationship between the different criteria used to identify airflow obstruction (LLN *vs* fixed cut-off) and outcomes are crucial for recommendations for the clinical use of spirometry. The prognostic implications of the two criteria in the elderly have been evaluated by Mannino et al. in a recent prospective study,[14] but to date younger age groups have not been studied. While in old COPD patients, using poor spirometric criteria may lead to misdirection of resources, unnecessary costs, and individual and societal harm, in young adults this may lead to miss the opportunity of an early diagnosis of the disease.[15,16]

In the present study, data from a large cohort of young adults (20-44 years), followed for 9 years during the 1990’s as part of the European Community Respiratory Health Survey (ECRHS) I, have been used to investigate the clinical and functional characteristics and longitudinal outcomes of the subjects identified as “normal” by the fixed ratio but abnormal by the LLN. For this purpose, LLN equations for young adults were obtained from the normal non-smoking participants in the ECRHS I.

METHODS

Design of the study

The design of the ECRHS I and ECRHS II has been described in details elsewhere.[17,18] In the ECRHS I, an international multicentre study on respiratory diseases, carried out in 1991-1993 on random samples of young adults aged 20-44 years, 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 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 at stage 1, was studied.

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

Subjects

A total of 12,254 subjects out of the 15,705 participants in the ECRHS I stage 2 from 25 European centres, from the random and symptomatic samples, were eligible for the present study; 6,249 of these subjects attended the second survey and had lung function measurements fulfilling the ATS criterion for reproducibility.

LLN equations

The LLN equations for FEV_1/FVC were obtained from 1,227 males and 1,309 females who participated in the ECRHS I (1991-93) and who were defined "normal" according to Johannessen et al. (see the Online Appendix).[19] Two-level linear regression models,[20] with subjects (level 1 units) nested into centres (level 2 units), were used to calculate the LLN equations separately in males and females. Both the models had the FEV_1/FVC ratio as the dependent variable, a random intercept term at level 2, and age as a fixed effect. A Markov chain Monte Carlo method (Gibbs sampling) was used to estimate the model parameters. The LLN equations were computed as predicted FEV_1/FVC (from the fixed part intercept and slope coefficient) – 1.645 * square root of the sum of the level 1 and level 2 variances, in order to identify the 5% of the 'normal' subjects with the lowest values in the reference population.

The resulting equations for males and females are the following (fig 1):

$LLN_{males} = 79.401 – 0.185 * AGE$ and $LLN_{females} = 85.101 – 0.287 * AGE$.

The LLN equations were obtained using MLwiN software (Multilevel Models Project, Institute of Education, London).

Definitions

The subjects considered in the analysis were classified into three groups according to the presence of airflow obstruction at baseline (ECRHS I), as defined by the LLN and the fixed cut-off, that is: absence of airflow obstruction by both criteria; presence of airflow obstruction by the LLN but absence of the condition according to the fixed cut-off ("misidentified subjects"); presence of airflow obstruction by both criteria. No subjects was classified with airflow obstruction by the fixed cut-off but without the condition by the LLN at the ECRHS I. Subjects with presence of airflow obstruction by the LLN but absence of the condition according to the fixed cut-off were defined as "misidentified". The subjects were further classified according to presence of a self-reported diagnosis of asthma during lifetime at the ECRHS II (positive answer to both the questions "Have you ever had asthma?" and "Was this confirmed by a doctor").

A set of biometric, clinical and functional characteristics measured at baseline was taken into account: gender, age, ever smoking during lifetime, FEV_1% predicted and FVC% predicted,[21] bronchial hyperresponsiveness (BHR),[22] high total IgE (>100 kU/l), IgE sensitisation, chronic cough or phlegm (see Online Appendix for a more detailed description of these variables).

A set of clinical and functional outcomes was evaluated at the second survey (ECRHS II): FEV_1<80% predicted (9-year incidence among those with a $FEV_1 \geq 80\%$ at baseline); chronic cough or phlegm (9-year incidence among those without the symptom at baseline); self-reported medication use because of breathing problems in the past 12 months; hospital services utilization (i.e. at least one ED visit and/or one hospital admission) because of

breathing problems during the follow-up (evaluated by the rate of occurrence of the first ED visit/hospital admission).

Statistical analysis

The distribution of the biometric, clinical and functional characteristics considered in the analysis was compared among the misidentified subjects and those identified with or without airflow obstruction by both criteria at baseline (ECRHS I). Pearson's chi-squared test, t test on the equality of means, and Wilcoxon rank-sum test were used when appropriate. No correction for multiple testing was performed.

The outcomes at the ECRHS II were compared among the three groups of subjects using two-level regression models,[20] with subjects (level 1 units) nested into centres (level 2 units). The models had the outcome of interest as the dependant variable, a random intercept term at level 2, and two dichotomous indicators of the presence/absence of airflow obstruction as defined by the two criteria at baseline (misidentification with the fixed cut-off = reference category) as fixed effects.

The statistical analysis was performed using STATA software (StataCorp, College Station, TX, USA).

RESULTS

Out of the 6,249 young adults, 318 (5.1%) individuals were classified as having airflow obstruction only by the LLN and 267 (4.3%) by both the LLN and the 70% fixed cut-off; therefore, only 45.6% of the subjects with airflow obstruction by the LLN were also identified by the fixed cut-off.

The main characteristics of the subjects identified with or without airflow obstruction by both criteria, or misidentified by the fixed cut-off are described in table 1. The misidentified subjects were significantly younger, had a significantly higher percentage of females, a significantly lower FEV_1% predicted, a significantly higher level of BHR, a significantly higher percentage of individuals with high total IgE (>100 kU/l), IgE sensitization, chronic cough or phlegm or self-reported diagnosis of asthma than those without airflow obstruction.

When compared to those with airflow obstruction defined by both criteria the misidentified subjects were significantly younger, had a significantly higher percentage of females, a significantly lower level of exposure to tobacco smoke, a significantly higher FEV_1% predicted, a significantly lower level of BHR and a significantly lower percentage of individuals with IgE sensitization or asthma.

During the follow-up the 9-year incidence of FEV_1<80% predicted and of chronic cough or phlegm were significantly higher among the misidentified subjects at baseline than among those without airflow obstruction by both criteria (table 2). The proportion of subjects who reported medication use because of breathing problems in the past 12 months at the ECRHS II, and the rate of utilization of hospital services because of breathing problems during the follow-up were also significantly higher among the misidentified subjects at baseline than among those without airflow obstruction. The incidence of FEV_1<80% and the rate of utilization of hospital services because of breathing problems during the follow-up were not significantly different between the misidentified subjects and those with airflow obstruction (table 2).

Table 1: Characteristics of the subjects eligible at the ECRHS I and traced at the ECRHS II, classified into three groups according to the presence of airflow obstruction as defined by the two criteria. All variables are measured at the ECRHS I, unless stated otherwise.

	subjects without AO	misidentified subjects	subjects with AO		
	n = 5,664	n = 318	n = 267		
fixed cut-off (70%)	**AO –**	**AO –**	**AO +**	**p-value (misidentified subjects *vs* those without AO)**	**p-value (misidentifiedsubjects *vs* those with AO)**
LLN	**AO –**	**AO +**	**AO +**		
females	52.8%	64.2%	39.7%	<0.001	<0.001
age (years):				0.007	<0.001
• **<30**	32.9%	39.6%	19.5%		
• **[30-40)**	40.9%	41.2%	37.1%		
• **≥40**	26.2%	19.2%	43.4%		
ever smokers	56.5%	58.4%	65.9%	0.521	0.061
median n° of pack-years * (IQR)	9.5 (4.2-17.7)	9.5 (5.0-18.0)	15.0 (5.0-27.0)	0.303	0.004
mean FEV_1 % pred (sd)	107.1 (12.4)	97.0 (11.2)	84.7 (16.1)	<0.001	<0.001
mean FVC % pred (sd)	108.6 (13.0)	113.8 (13.3)	109.5 (17.3)	<0.001	<0.001
BHR, mean slope (sd) †	7.84 (2.09)	6.32 (2.46)	5.57 (2.25)	<0.001	0.007
high total IgE	22.9%	31.5%	37.0%	0.001	0.178
IgE sensitization	32.5%	42.0%	53.5%	0.001	0.008
chronic cough or phlegm	12.1%	17.4%	23.4%	0.005	0.075
physician-diagnosed asthma ‡	13.8%	27.4%	53.9%	<0.001	<0.001

AO = airflow obstruction
IQR = interquartile range
BHR = bronchial hyperresponsiveness

* among ever smokers.
† a low slope is indicative of a high BHR; the p-values were obtained after adjusting for baseline FEV_1 % predicted.
‡ self-reported diagnosis of asthma during lifetime at the ECRHS II.

Table 2: 9-year incidence of FEV_1<80% predicted and of chronic cough or phlegm, medication use because of breathing problems in the past 12 months at the ECRHS II and hospital services utilization because of breathing problems between the two surveys, according to the presence of airflow obstruction as defined by the two criteria, among the subjects identified at the ECRHS I and traced at the ECRHS II.

		subjects without AO	misidentified subjects	subjects with AO		
	fixed cut-off (70%)	**AO –**	**AO –**	**AO +**	**p-value (misidentified subjects *vs* those without AO)**	**p-value (misidentified subjects *vs* those with AO)**
	LLN	**AO –**	**AO +**	**AO +**		
FEV_1 < 80% pred. *	**N° of subjects at risk**	5,576	295	174	-	-
	crude incidence rate (1,000/yr) [95%CI]	1.89 [1.55 to 2.32]	5.66 [3.41 to 9.40]	15.87 [10.72 to 23.49]	-	-
	incidence rate ratio [95%CI]	0.34 [0.19 to 0.58]	1.00	3.17 [1.66 to 6.05]	<0.001	<0.001
chronic cough or phlegm †	**N° of subjects at risk**	4,865	257	197	-	-
	crude incidence rate (1,000/yr) [95%CI]	8.69 [7.85 to 9.61]	14.31 [10.17 to 20.13]	10.69 [6.82 to 16.76]	-	-
	incidence rate ratio [95%CI]	0.61 [0.42 to 0.87]	1.00	0.78 [0.44 to 1.38]	0.006	0.400
medication use ‡	**N° of subjects**	5,634	316	267	-	-
	crude proportion (%) [95%CI]	13.2 [12.3 to 14.1]	24.1 [19.4 to 29.2]	51.3 [45.1 to 57.4]	-	-
	risk ratio [95%CI]	0.55 [0.45 to 0.67]	1.00	2.08 [1.71 to 2.54]	<0.001	<0.001
hospital services utilization §	**N° of subjects**	5,641	317	267	-	-
	crude rate (1,000/yr) [95%CI]	5.63 [5.00 to 6.34]	13.43 [9.68 to 18.61]	17.53 [12.81 to 24.00]	-	-
	rate ratio [95%CI]	0.45 [0.32 to 0.64]	1.00	1.39 [0.88 to 2.19]	<0.001	0.158

AO = airflow obstruction

* the subjects at risk were those with a $FEV_1 \geq 80\%$ predicted at baseline; the incidence rate ratios were obtained by a two-level Poisson regression model.

† the subjects at risk were those without chronic cough or phlegm at baseline; 84 subjects at risk with missing information on the outcome were not considered in the analysis; the incidence rate ratios were obtained by a two-level Poisson regression model.

‡ 32 subjects with missing information on the outcome were not considered in the analysis; the risk ratios were obtained by a two-level Poisson regression model with a robust error variance and no offset.[23]

§ 24 subjects with missing information on the outcome were not considered in the analysis; the crude rates of occurrence of the first ED visit / hospital admission between the two surveys were calculated setting the person-years for the subjects who reported at least one hospital contact equal to half the length of the follow-up; the rate ratios were obtained by a two-level complementary log-log survival model.[24]

Considering separately the 5,235 subjects without self-reported diagnosis of asthma during lifetime, only 34.7% of the subjects with airflow obstruction by the LNN were also identified by the fixed cut-off. In the Online Appendix tables 1 and 2 were replicated for both subjects with and without asthma (see tables A1-A4). During the follow-up, among subjects without asthma, besides the incidence of FEV_1<80% and the rate of utilization of hospital services because of breathing problems, the proportion of subjects who reported medication use because of breathing problems in the past 12 months at the ECRHS II was not significantly different between the misidentified subjects at baseline and those with airflow obstruction by both criteria.

DISCUSSION

Our study shows that the 70% fixed cut-off identifies less than fifty percent of the young subjects who have evidence of airflow obstruction using the LLN criteria. Because self reported lifetime asthma could be a rather arbitrary diagnosis and in young adults asthma and COPD can be exceedingly difficult to distinguish, our primary analysis included all subjects. Considering only the subjects without a self-reported diagnosis of asthma during lifetime, this percentage declines to about one third, showing that the use of the LLN could identify subjects likely to suffer from COPD at an earlier stage than the fixed cut-off.

The use of a statistically derived LLN was being considered as early as the 1980's and it was included in all the subsequent ATS and ERS guidelines on lung function testing.[11] The use of a statistically derived limit below which a value is considered abnormal seems to be necessary because the FEV_1 declines more rapidly with age than the FVC in normal subjects and thus the FEV_1/FVC ratio decreases with age; moreover, it takes the difference of lung function between genders into account. However, in an attempt to simplify the identification of airflow obstruction, the disease specific international guidelines for COPD continue to recommend the fixed cut-off.[9, 25] This has resulted in an ongoing confusion regarding the definition of airflow obstruction. Roberts documented that at the extremes of age and height, a large number of spirometry test results will be interpreted as showing an obstructive defect if a 70% fixed ratio method is used for interpretation compared with the LLN derived from the Third National Health and Nutrition Examination Study data set.[5] Considering the LLN derived from the same data set as "correct" and as the "gold standard", Hansen et al. demonstrate the low sensitivity in the third and fourth decades and the high frequency of misidentified normal subjects and the relatively low specificity and the high percentage of normal subjects misidentified as abnormal individuals, in the seventh and eight decades, with respect to the fixed cut-off.[6]

Our results confirm an unacceptably large under-diagnosis of airflow obstruction in young adults, particularly among females, with using the 70% fixed cut-off. Our large cohort of young adults followed for 9 years allowed us to describe the baseline characteristics and longitudinal outcomes in subjects who were misidentified as normal with the fixed cut-off. Unfortunately, there is a lack of a gold standard for COPD. The hallmark of the disease is the presence of airflow obstruction, but subjects may have obstruction in the absence of COPD. Clinical findings including history and exposure to risk factors (occupational hazards, tobacco smoke and other noxious inhalant) can help the diagnosis of COPD. COPD is generally a progressive disease, especially if a patient's exposure to noxious agents continues. Our results document that, at baseline, subjects misidentified as normal with the fixed cut-off seem to be an intermediate group between normality and COPD. In fact, BHR progressively increased and FEV_1 progressively decreased from subjects without airflow obstruction to those with airflow obstruction by both criteria, through those misidentified as normal. When we considered only misidentified subjects without self-reported asthma, also exposure to tobacco

smoke progressively increases across the three groups. Moreover, in our misidentified subjects the presence of chronic cough and phlegm was similar to that in subjects with airflow obstruction.

Till now, how the different definitions of airflow obstruction relate to outcomes has been studied only in a cohort from an elderly population in which the outcomes were both death and COPD-related hospitalization during the follow-up.[14] Even if outcomes are more difficult to establish and to standardize in young subjects than in the elderly, the prognostic implication of the different criteria is crucial for the practice of medicine. We chose FEV_1<80% predicted which is the cut-point that separates mild COPD from the more severe forms of the disease and the presence of chronic cough or phlegm as the study outcomes;[9] moreover, we considered medication use and hospital services utilization, which are commonly considered in epidemiological studies.[15] With ageing misidentified subjects were at a significantly higher risk of suffering from chronic cough or phlegm and of developing moderate to severe airflow obstruction suggestive of COPD (*i.e.* FEV_1<80% predicted) than subjects without airflow obstruction. Remarkably, the misidentified subjects were at a significantly higher risk of using medication because of breathing problems in the past 12 months at the end of follow-up and of using hospital services because of breathing problems during the follow-up than the subjects without airflow obstruction. Moreover, they presented a similar proportion of subjects with chronic cough and phlegm and a similar rate of utilization of hospital services because of breathing problems during the follow-up to subjects with airflow obstruction by both criteria at ECRHS I. When we considered only the misidentified individuals without self-reported asthma, also the proportion of subjects who reported medication use because breathing problems in the past 12 months at the end of follow-up was similar to that of subjects with airflow obstruction by both criteria.

The currently available opportunities for the management of COPD make an early diagnosis of COPD particularly important. Bronchodilator therapy improves dyspnea, exercise endurance, and health status; at present, the most intriguing question is whether maximal sustained bronchodilation in COPD patients may result also in positive long-term effects.[26] The ongoing results of UPLIFT clinical trial, assessing the long-term functional impact of tiotropium in COPD, will elucidate the role that pharmacological treatment can play in affecting the course of the disease.[27] To date, the only successful intervention shown to conclusively attenuate the loss of lung function over time is smoking cessation. It has been recently well documented that the diagnosis of smoking related airflow obstruction increases the efficacy of smoking cessation advice in affected subjects.[28, 29] Thus, the implementation of LLN in clinical practice may contribute to significant advances in the treatment of the disease and prevention of its complications.

The intrinsic limitation of using the LLN criteria is its dependency from the prediction equations and from the reference population from which the prediction equation have been drawn. Ideally, prediction equation should be derived from measurements obtained in a representative sample of healthy subjects from a general population as we have done or, secondly, in a large group of volunteers. Currently, the ATS/ERS committee does not recommend any specific set of equations to be used in Europe but it suggests the need for a new Europe-wide study to derive updated reference equations. At variance, software and hardware have now changed the way of laboratory testing and there is no longer the need for manual, time consuming calculation of predicted values, as even inexpensive spirometers can have predicting equations and statistically derived LLN built in.

A limitation to our study is that the GOLD criteria recommend the use of a post-bronchodilator spirometry test. However, we used pre-bronchodilator values because we have these values only for a very small proportion of subjects. It is possible that post-bronchodilator values would have varied less between the two definitions of airflow

obstruction; how this change could affect outcomes is unclear.[4, 5, 13, 30] Another limitation is that that the LLN equations have been calculated from a group of 'normal' subjects, part of whom were also considered in the analysis (22.5% of the members of the cohort). However, the aim of our analysis was not to define a new LLN for the European general population, but to compare two different criteria for the identification of airflow obstruction.

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

Moreover, we believe that our study intervenes in an lively debate on the definition of airflow obstruction as recently stimulated by Mannino and Buist in their replay to postscript letters on Thorax.[31-34]

In conclusion, our findings show the importance of using statistically derived spirometric criteria to identify airflow obstruction. Thus, we provide powerful support for the view that the criteria for the screening of airflow obstruction should be changed in order to avoid the risk of not identifying a part of the population who is likely to benefit from early intervention.[35] We strongly agree with Falaschetti et al. in recommending that international scientific organizations return to evidence-based medicine and revise their COPD guidelines.[36] The reasons of simplicity and ease of remembrance advanced by many international opinion leaders seem unimportant compared to the objective of being able to properly detect airflow obstruction.

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Co-ordinating Center

Project Leader: P. Burney; Statistician: S. Chinn; Principal Investigator: D. Jarvis; Project Co-ordinator: J. Knox; Principal Investigator: C. Luczynska; Assistant Statistician: J. Potts; Data Manager: S. Arinze.

Steering Committee for ECRHS II

U. Ackermann-Liebrich (University of Basel, Basel, Switzerland); J.M. Antó (Institut Municipal d'Investigació Mèdica (IMIM-IMAS) and Universitat Pompeu Fabra (UPF), Barcelona, Spain); P. Burney (Imperial College, London, UK); I. Cerveri (University of Pavia, Pavia, Italy); S. Chinn (King's College London, London, UK); R. de Marco (University of Verona, Verona, Italy); T. Gislason (Iceland University Hospital, Reykjavik, Iceland); J. Heinrich (GSF – Institute of Epidemiology, Munich, Germany); C. Janson (Uppsala University, Uppsala, Sweden); D. Jarvis (Imperial College); J. Knox (King's College London); N. Künzli (Center for Research in Environmental Epidemiology (CREAL) at Institut Municipal d'Investigació Mèdica (IMIM)); B. Leynaert (Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France); C. Luczynska (King's College London); F. Neukirch (INSERM); J. P. Schouten (University Medical Center Groningen, University of Groningen, Groningen, The Netherlands); J. Sunyer (IMIM-IMAS and UPF); C. Svanes (University of Bergen, Bergen, Norway); P. Vermeire (University of Antwerp, Antwerp, Belgium); M. Wjst (GSF – Institute of Epidemiology).

List of Principal Investigators and Senior Scientific Team

Belgium: South Antwerp & Antwerp City (P Vermeire, J Weyler, M Van Sprundel, V Nelen). **Estonia:** Tartu (R Jogi, A Soon). **France:** Paris (F Neukirch, B Leynaert, R Liard, M Zureik), Grenoble (I Pin, J Ferran-Quentin). **Germany:** Erfurt (J Heinrich, M Wjst, C Frye, I Meyer). **Iceland:** Reykjavik (T Gislason, E Bjornsson, D Gislason, T Blondal, KB Jorundsdottir). **Italy:** Turin (M Bugiani, P Piccioni, E Caria, A Carosso, E Migliore, G Castiglioni), Verona (R de Marco, G Verlato, E Zanolin, S Accordini, A Poli, V Lo Cascio, M Ferrari), Pavia (A Marinoni, S Villani, M Ponzio, F Frigerio, M Comelli, M Grassi, I Cerveri, A Corsico). **Netherlands:** Groningen & Geleen (JP Schouten, M Kerkhof). **Norway:** Bergen (A Gulsvik, E Omenaas, C Svanes, B Laerum). **Spain:** Barcelona (JM Antó, J Sunyer, M Kogevinas, JP Zock, X Basagana, A Jaen, F Burgos), Huelva (J Maldonado, A Pereira, JL Sanchez), Albacete (J Martinez-Moratalla Rovira, E Almar), Galdakao (N Muniozguren, I Urritia), Oviedo (F Payo). **Sweden:** Uppsala (C Janson, G Boman, D Norback, M Gunnbjornsdottir), Goteborg (K Toren, L Lillienberg, AC Olin, B Balder, A Pfeifer-Nilsson, R Sundberg), Umea (E Norrman, M Soderberg, K Franklin, B Lundback, B Forsberg, L Nystrom). **Switzerland:** Basel (N Künzli, B Dibbert, M Hazenkamp, M Brutsche, U Ackermann-Liebrich). **United Kingdom:** Norwich (D Jarvis, B Harrison), Ipswich (D Jarvis, R Hall, D Seaton)

Centers taking part at their own expense

Australia: Melbourne (M. Abramson, R. Woods, E.H. Walters, F. Thien). France: Bordeaux (A. Taytard, C. Raherison), Montpellier (J. Bousquet, P. Demoly). Germany: Hamburg (K. Richter). USA: Portland (M. Osborne, S. Buist, W. Vollmer, L. Johnson).

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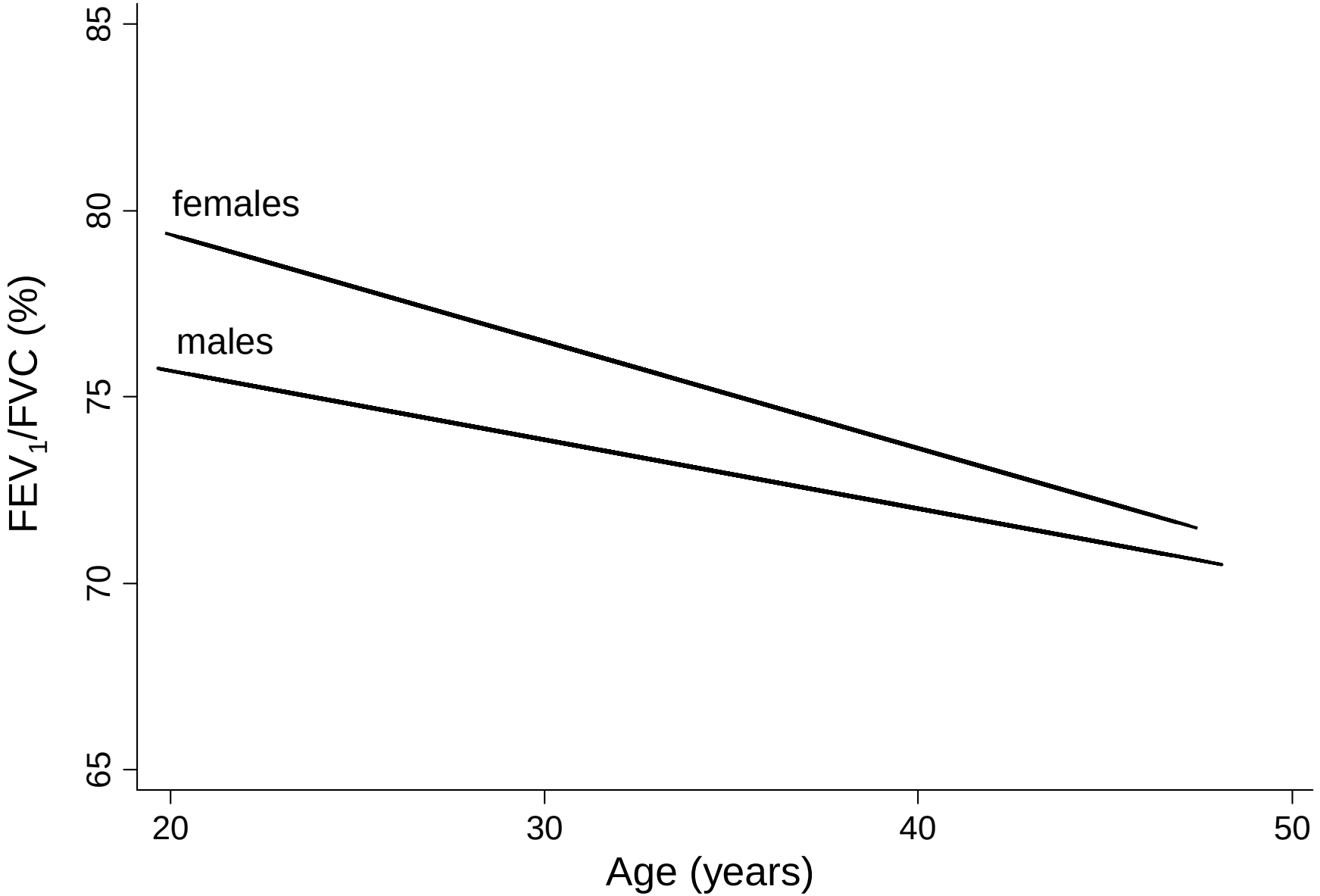
FIGURE LEGEND

Figure 1 The Lower Limit of Normal (LLN) of the ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) normally decreases with age. The downward sloping lines are the LLN equations for the FEV_1/FVC ratio, calculated according to age and gender from the ECRHS I data. The horizontal line indicates the 70% fixed cut-off.



Underestimation of airflow obstruction among young adults using $FEV_1/FVC<70\%$ as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes.

Isa Cerveri, Angelo G. Corsico, Simone Accordini, Rosanna Niniano, Elena Ansaldo, Josep M. Antó, Nino Künzli, Christer Janson, Jordi Sunyer, Deborah Jarvis, Cecilie Svanes, Thorarinn Gislason, Joachim Heinrich, Jan P. Schouten, Matthias Wjst, Peter Burney, and Roberto de Marco.

WEB ONLY APPENDICES

METHODS

Subjects considered for the calculation of the LLN equations

Normal subjects were lifetime non-smokers with a BMI in the range 18.5–30.0 kg/m^2 and with lung function measurements fulfilling the ATS criterion for reproducibility, who did not report asthma-like symptoms (wheezing, nocturnal tightness in the chest, attacks of shortness of breath following strenuous activity, at rest or at night time) in the past 12 months, asthma during lifetime nor chronic cough or phlegm, and who had not used drugs because of breathing problems in the past 12 months.

Baseline characteristics of the subjects considered in the analysis

The following biometric, functional and clinical variables measured at baseline (ECRHS I) were taken into account: gender, age, ever smoking during lifetime (having reported at least 20 packs of cigarettes or 360 grams of tobacco in a lifetime, or at least one cigarette per day or one cigar a week for one year), FEV_1 % predicted and FVC % predicted (considering the maximum FEV_1 and the maximum FVC from at least two and up to five technically satisfactory manoeuvres; predicted values were from Quanjer),[A1] bronchial hyperresponsiveness (BHR, measured by the regression coefficient of the percentage decline in FEV_1 with the log dose of methacholine – "slope", after transformation),[A2] high total IgE (>100 kU/l), IgE sensitisation (having at least one specific IgE measurement ≥0.35 kU/l among 5 environmental allergens: *Dermatophagoides pteronyssinus*, cat, timothy grass, *Cladosporium herbarum* and a local allergen – *Parietaria judaica* for southern Europe and birch for northern Europe), chronic cough or phlegm (having reported cough and/or phlegm from the chest, usually in winter and on most days for as long as three months each year).

APPENDIX REFERENCES

A1. Quanjer PH, Tammeling GJ, Cotes JE, et al. Symbols, abbreviations and units. Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. *Eur Respir J Suppl*. 1993;**16**:85–100.

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Table A1: Characteristics of the non-asthmatic subjects eligible at the ECRHS I and traced at the ECRHS II, classified into three groups according to the presence of airflow obstruction as defined by the two criteria. All variables are measured at the ECRHS I.

	subjects without AO	misidentified subjects	subjects with AO		
	n = 4,881	n = 231	n = 123		
fixed cut-off (70%)	**AO –**	**AO –**	**AO +**	**p-value (misidentified subjects *vs* those without AO)**	**p-value (misidentified subjects *vs* those with AO)**
LLN	**AO –**	**AO +**	**AO +**		
Females	51.5%	59.7%	38.2%	0.014	<0.001
age (years):				0.018	<0.001
▪ **<30**	32.3%	37.7%	9.7%		
▪ **[30-40)**	41.4%	44.1%	35.0%		
▪ **≥40**	26.3%	18.2%	55.3%		
ever smokers	57.3%	59.1%	70.7%	0.574	0.031
median n° of pack-years * (IQR)	9.6 (4.2-18.0)	11.2 (5.5-19.5)	22.5 (11.5-33.7)	0.098	<0.001
mean FEV_1 % pred (sd)	107.6 (12.3)	97.8 (10.8)	89.7 (13.9)	<0.001	<0.001
mean FVC % pred (sd)	108.9 (13.0)	114.5 (13.1)	113.3 (15.6)	<0.001	0.459
BHR, mean slope (sd) †	8.10 (1.91)	6.94 (2.29)	6.37 (2.07)	<0.001	0.062
high total IgE	20.4%	22.6%	18.3%	0.450	0.379
IgE sensitisation	28.3%	34.6%	27.5%	0.047	0.199
chronic cough or phlegm	10.0%	16.5%	14.9%	0.002	0.689

AO = airflow obstruction
IQR = interquartile range
BHR = bronchial hyperresponsiveness

* among ever smokers.
† a low slope is indicative of a high BHR; the p-values were obtained after adjusting for baseline FEV_1 % predicted.

Table A2: Characteristics of the asthmatic subjects eligible at the ECRHS I and traced at the ECRHS II, classified into three groups according to the presence of airflow obstruction as defined by the two criteria. All variables are measured at the ECRHS I.

	Subjects without AO	misidentified subjects	subjects with AO		
	n = 783	n = 87	n = 144		
fixed cut-off (70%)	**AO –**	**AO –**	**AO +**	**p-value (misidentified subjects *vs* those without AO)**	**p-value (misidentified subjects *vs* those with AO)**
LLN	**AO –**	**AO +**	**AO +**		
Females	61.0%	75.9%	41.0%	0.007	<0.001
age (years):				0.325	0.023
▪ **<30**	36.6%	44.8%	27.8%		
▪ **[30-40)**	37.7%	33.3%	38.9%		
▪ **≥40**	25.7%	21.9%	33.3%		
ever smokers	52.0%	56.3%	61.8%	0.442	0.410
median n° of pack-years * (IQR)	9.0 (3.7-16.5)	7.6 (4.0-15.3)	8.2 (2.7-21.0)	0.595	0.727
mean FEV_1 % pred (sd)	103.8 (12.4)	95.0 (11.8)	80.4 (16.6)	<0.001	<0.001
mean FVC % pred (sd)	106.9 (13.0)	112.1 (13.5)	106.3 (18.0)	0.001	0.006
BHR, mean slope (sd) †	6.13 (2.35)	4.55 (2.04)	4.56 (2.05)	<0.001	0.425
high total IgE	38.3%	55.1%	52.2%	0.004	0.684
IgE sensitisation	59.4%	61.5%	74.6%	0.718	0.045
chronic cough or phlegm	24.7%	19.8%	30.7%	0.313	0.070

AO = airflow obstruction
IQR = interquartile range
BHR = bronchial hyperresponsiveness

* among ever smokers.
† a low slope is indicative of a high BHR; the p-values were obtained after adjusting for baseline FEV_1 % predicted.

Table A3: 9-year incidence of FEV_1<80% predicted and of chronic cough or phlegm, medication use because of breathing problems in the past 12 months at the ECRHS II and hospital services utilization because of breathing problems between the two surveys, according to the presence of airflow obstruction as defined by the two criteria, among the non-asthmatic subjects identified at the ECRHS I and traced at the ECRHS II.

		subjects without AO	misidentified subjects	subjects with AO		
	fixed cut-off (70%)	**AO –**	**AO –**	**AO +**	**p-value (misidentified subjects *vs* those without AO)**	**p-value (misidentified subjects *vs* those with AO)**
	LLN	**AO –**	**AO +**	**AO +**		
FEV_1 < 80% pred. *	**N° of subjects at risk**	4,811	218	95	-	-
	crude incidence rate (1,000/yr) [95%CI]	1.40 [1.09 to 1.80]	4.05 [2.03 to 8.11]	13.68 [7.77 to 24.09]	-	-
	incidence rate ratio [95%CI]	0.35 [0.16 to 0.72]	1.00	4.25 [1.72 to 10.51]	0.005	0.002
chronic cough or phlegm †	**N° of subjects at risk**	4,293	190	102	-	-
	crude incidence rate (1,000/yr) [95%CI]	8.03 [7.18 to 8.98]	12.25 [7.98 to 18.78]	4.25 [1.60 to 11.33]	-	-
	incidence rate ratio [95%CI]	0.65 [0.42 to 1.01]	1.00	0.36 [0.12 to 1.04]	0.057	0.060
medication use ‡	**N° of subjects**	4,852	229	123	-	-
	crude proportion (%) [95%CI]	6.0 [5.4 to 6.7]	8.3 [5.1 to 12.7]	13.8 [8.3 to 21.2]	-	-
	risk ratio [95%CI]	0.70 [0.50 to 0.98]	1.00	1.59 [0.92 to 2.74]	0.039	0.097
hospital services utilization §	**N° of subjects**	4,861	231	123	-	-
	crude rate (1,000/yr) [95%CI]	3.39 [2.88 to 3.99]	7.43 [4.48 to 12.32]	7.34 [3.67 to 14.68]	-	-
	rate ratio [95%CI]	0.50 [0.29 to 0.85]	1.00	1.06 [0.45 to 2.51]	0.010	0.891

AO = airflow obstruction

* the subjects at risk were those with a FEV_1 ≥ 80% predicted at baseline; the incidence rate ratios were obtained by a two-level Poisson regression model.

† the subjects at risk were those without chronic cough or phlegm at baseline; 66 subjects at risk with missing information on the outcome were not considered in the analysis; the incidence rate ratios were obtained by a two-level Poisson regression model.

‡ 31 subjects with missing information on the outcome were not considered in the analysis; the risk ratios were obtained by a two-level Poisson regression model with a robust error variance and no offset.[A3]

§ 20 subjects with missing information on the outcome were not considered in the analysis; the crude rates of the occurrence of the first ED visit / hospital admission between the two surveys were calculated setting the person-years for the subjects who reported at least one hospital contact equal to half the length of the follow-up; the rate ratios were obtained by a two-level complementary log-log survival model.[A4]

Table A4: 9-year incidence of FEV_1<80% predicted and of chronic cough or phlegm, medication use because of breathing problems in the past 12 months at the ECRHS II and hospital services utilization because of breathing problems between the two surveys, according to the presence of airflow obstruction as defined by the two criteria, among the asthmatic subjects identified at the ECRHS I and traced at the ECRHS II.

		subjects without AO	misidentified subjects	subjects with AO		
	fixed cut-off (70%)	**AO –**	**AO –**	**AO +**	**p-value (misidentified subjects *vs* those without AO)**	**p-value (misidentified subjects *vs* those with AO)**
	LLN	**AO –**	**AO +**	**AO +**		
FEV_1 < 80% pred. *	**N° of subjects at risk**	765	77	79	-	-
	crude incidence rate (1,000/yr) [95%CI]	5.04 [3.60 to 7.06]	10.38 [4.95 to 21.77]	18.62 [10.81 to 32.06]	-	-
	incidence rate ratio [95%CI]	0.49 [0.21 to 1.10]	1.00	1.78 [0.71 to 4.48]	0.082	0.222
chronic cough or phlegm †	**N° of subjects at risk**	572	67	95	-	-
	crude incidence rate (1,000/yr) [95%CI]	13.64 [10.77 to 17.27]	20.29 [11.52 to 35.73]	17.92 [10.80 to 29.72]	-	-
	incidence rate ratio [95%CI]	0.68 [0.37 to 1.25]	1.00	0.91 [0.42 to 1.95]	0.215	0.804
medication use ‡	**N° of subjects**	782	87	144	-	-
	crude proportion (%) [95%CI]	57.4 [53.9 to 60.9]	65.5 [54.6 to 75.4]	83.3 [76.2 to 89.0]	-	-
	risk ratio [95%CI]	0.87 [0.74 to 1.03]	1.00	1.28 [1.12 to 1.46]	0.102	<0.001
hospital services utilization §	**N° of subjects**	780	86	144	-	-
	crude rate (1,000/yr) [95%CI]	20.80 [17.53 to 24.69]	31.69 [20.66 to 48.61]	27.33 [19.22 to 38.86]	-	-
	rate ratio [95%CI]	0.66 [0.41 to 1.05]	1.00	0.91 [0.52 to 1.59]	0.081	0.730

AO = airflow obstruction

* the subjects at risk were those with a $FEV_1 \geq 80\%$ predicted at baseline; the incidence rate ratios were obtained by a two-level Poisson regression model.

† the subjects at risk were those without chronic cough or phlegm at baseline; 18 subjects at risk with missing information on the outcome were not considered in the analysis; the incidence rate ratios were obtained by a two-level Poisson regression model.

‡ 1 subject with missing information on the outcome was not considered in the analysis; the risk ratios were obtained by a two-level Poisson regression model with a robust error variance and no offset.[A3]

§ 4 subjects with missing information on the outcome were not considered in the analysis; the crude rates of the occurrence of the first ED visit / hospital admission between the two surveys were calculated setting the person-years for the subjects who reported at least one hospital contact equal to half the length of the follow-up; the rate ratios were obtained by a two-level complementary log-log survival model.[A4]