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FEV_1/FVC and FEV_1 for the assessment of chronic airflow obstruction in prevalence studies: Do prediction equations need revision?

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Summary
Little is known on the long-term validity of reference equations used in the calculation of FEV_1 and FEV_1/FVC predicted values.

This survey assessed the prevalence of chronic airflow obstruction in a population-based sample and how it is influenced by: (i) the definition of airflow obstruction; and (ii) equations used to calculate predicted values. Subjects aged 45 or more were recruited in health prevention centers, performed spirometry and fulfilled a standardized ECRHS-derived questionnaire. Previously diagnosed cases and risk factors were identified. Prevalence of airflow obstruction was calculated using: (i) ATS-GOLD definition ($FEV_1/FVC < 0.70$); and (ii) ERS definition ($FEV_1/FVC <$ lower limit of normal) with European Community for Coal and Steel (ECCS) reference equations and with predicted values derived from the presumably normal fraction of the studied population.

A total of 5008 subjects (4764 adequate datasets) were studied. Prevalence of airflow obstruction was 8.71% with ATS-GOLD definition and 6.40% with ERS definition and ECCS predicted values. The ERS definition with predicted values derived from the studied population

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provided a 7.96% prevalence. Severity distribution of airflow obstruction was also influenced by the equation used to calculate predicted values of FEV_1.

Prevalence and severity of chronic airflow obstruction are influenced not only by the definition used but also by equations used to calculate predicted FEV_1/FVC and FEV_1 values. These equations likely need to be periodically revised.
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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality, handicap and health care costs worldwide,[1,2] but remains largely underdiagnosed.[3,4] Recent spirometric studies from industrialized countries found a prevalence of COPD with airflow obstruction (GOLD -global initiative on obstructive lung diseases- stage $\geq$1) between 4 and 10%.[5,6] Such data are lacking in France.[5] Higher figures have been found when airflow obstruction is defined according to the absolute value of the ratio of forced expiratory volume in one second to forced vital capacity ($FEV_1/FVC < 0.70$, ''ATS-GOLD definition'') than when the lower limit of normal of FEV_1/FVC ratio is considered (''ERS definition'').[6–10]

Besides, in their joint guidelines on lung function testing, the European Respiratory Society and American Thoracic Society (ERS and ATS) emphasize the need for developing and updating local reference equations for calculation of predicted values of lung function variables. Indeed, most reference equations currently used in Europe were developed more than 20 years ago.[11]

The present study was designed:

(i) To assess the impact of the definition of airflow obstruction on prevalence: $FEV_1/FVC < 0.70$ or lower limit of normal (LLN) of the ratio.
(ii) To determine how the choice of reference equations (i.e., European Community for Coal and Steel or study-derived equations) for calculation of predicted values of FEV_1 and FEV_1/FVC values influences the prevalence and severity distribution of airflow obstruction.
(iii) To estimate the prevalence of chronic airflow obstruction (CAO) in French subjects visiting prevention centers. The proportion of previously undiagnosed cases and identified risk factors were also described.

Materials and methods

Design of the survey

This was a cross-sectional survey in all consecutive subjects presenting to health centers for routine preventive visits during an 8-month period. In France, these visits are offered by the public health coverage system (''social security'') to all subjects aged 45 years or more. Participating centers were harmoniously distributed on the French territory. The sample was built according to national data on age and sex distribution in the general population of the considered age range. Subjects filled a standardized auto-questionnaire and FEV_1 and FVC were measured by a technician who was not aware of answers to the questionnaire. All subjects received an information note before their participation. The study was approved by the ethics committee of Nancy university hospital, France.

Questionnaire

Data obtained from each individual included usual socio-demographic and anthropometrical description, information on clinical symptoms, associated chronic diseases and presumptive diagnosis, and previous assessment of lung function.

The questionnaire was derived from the European Community Respiratory Health Survey (ECRHS) questionnaire.[12] Three questions were added to this questionnaire: 1. Did a doctor ever measure your breathing capacity? 2. Did a doctor ever tell you that you had chronic bronchitis/chronic bronchial obstruction? 3. Are you currently followed by a doctor for chronic bronchitis? Answers on cough and sputum production allowed to assign each subject to one of four groups: no cough and no expectoration, chronic cough (CC), chronic expectoration (CE) and chronic bronchitis (CB), as defined by chronic productive cough lasting at least 3 months per year during the last 2 consecutive years. These groups were mutually exclusive.

A subject was considered as a never-smoker if he smoked less than 50 cigarettes during his entire life, and as an ex-smoker if he stopped smoking more than 1 year ago. Each subject's mean daily (cigarettes per day) and cumulative consumption (pack-years) were established.

Based on answers to the questionnaire, a history or the presence of bronchiectasis or heart failure was recorded as comorbidities.[8] Patients were classified as asthmatics if they declared having asthma as confirmed by a physician or if they declared having asthma without confirmation by a physician AND reported the occurrence, during the previous year, of exercise-induced paroxysmal dyspnea, dyspnea-induced awakening or breathlessness with wheezing.[13]

Spirometry, predicted values, definition and severity of airflow obstruction

Spirometry

Spirometry was performed by specifically trained technicians using daily calibrated spirometers under BTPS conditions. Three spirometers were used: Spirograph Booster (EMO International, La Rochelle, France), Spirolyser SPL 100 (FIM SA, France) and Spiro analyser 2120 (Vitalograph, UK). All fulfilled ATS and ERS standards and were calibrated daily using 3 L syringes.

Three measures were performed. At least two reproducible (variation <200 ml) measurements of FEV_1 were required. Then the best values of FEV_1 and FVC from technically adequate maneuvers were selected for analysis.

Predicted values

Predicted values for FEV_1/FVC and FEV_1 were first calculated using European Community for Coal and Steel equations (ECCS):[11,14] these equations are (H is height in m and A is age in years): for calculation of predicted values of FEV_1/FVC: in men: $-0.18A + 87.21$ (residual standard deviation: 7.17); in women: $-0.19A + 89.10$ (residual standard deviation: 6.51); for calculation of FEV_1: in men: $4.30H - 0.029A - 2.49$ (residual standard deviation: 0.51); in women: $3.95H - 0.025A - 2.60$ (residual standard deviation: 0.38). In addition, equations for calculation of the predicted values of FEV_1/FVC and FEV_1 were obtained for men and women using multiple linear regression with age and height as independent variables in the presumably normal fraction of the population. Three sets of criteria were used to define this fraction of the population: (i) subjects with no symptoms ($n = 2064$); (ii) subjects with no symptoms and no known respiratory or cardiac disease ($n = 1886$); and (iii) subjects with no symptoms, no known respiratory of cardiac disease and no smoking history ($n = 1046$).[15] Lower limits of normal (LLN = predicted value − 1.64 residual standard deviation) obtained with these three reference population were compared.

Definition of airflow obstruction

Three definitions of airflow obstruction were used: $FEV_1/FVC < 0.70$ (''ATS-GOLD definition''),[1] $FEV_1/FVC <$ LLN with predicted values calculated with ECCS reference equations (''ERS definition'')[11] and $FEV_1/FVC <$ LLN with predicted values calculated using regression equations derived from the presumably normal fraction of the studied population, as defined above (''study definition'').

Severity of airflow obstruction

Severity of airflow obstruction was categorized using the ATS-ERS-GOLD classification:[1,2] stage 1, $FEV_1 \geq 80\%$ of predicted value; stage 2, $50\% \leq FEV_1 < 80\%$; stage 3, $FEV_1 < 50\%$. For subjects with airflow obstruction according to ATS-GOLD and ERS definitions, ECCS predicted values of FEV_1 were used. For those with airflow obstruction according to the study definition, FEV_1 predicted values were calculated using equations derived from the presumably normal fraction of the population (see above).

Statistical analysis

Sample size calculation was performed considering an expected prevalence of airflow obstruction of about 5%, an allowed risk of error of 0.5% of this percentage, and a possible analysis on two strata; 4500 files had to be analyzed. The predicted proportion of files with missing data or technically inadequate spirometry was estimated at about 10%. Thus, 5000 subjects had to be recruited.

Analysis was performed using Statview 5 and SAS softwares (SAS Institute, Cary, NC, USA). Results are expressed as percentages or means ± one standard deviation. Percentages have been compared by two-way and multiway frequency analysis, and means by analysis of variance and *t*-test.[9]

Results

Characteristics of the studied population (Table 1)

A total of 5008 subjects participated in the survey during an 8-month recruitment period. Adequate data were available in 4764 subjects (95.1%). This population differed slightly from the projected sample (national statistics data) on sex (greater proportion of men: 48.1 *versus* 45.8%) and age (smaller proportion of people aged more than 75 years: 11.6 *versus* 19.2%).

Already known chronic respiratory diseases were reported with the following frequency: asthma in 9.1% of subjects, chronic airflow obstruction in 2.6% and chronic bronchitis in 5.8%.

Predicted values of FEV_1/FVC and FEV_1 derived from the presumably normal fraction of the population

LLN obtained from FEV_1/FVC and FEV_1 regression equations did not significantly differ according to how the presumably normal fraction of the studied population was defined: for example, mean LLN for FEV_1/FVC ratio was the same in the three populations used to derive prediction equations,

Table 1 Description of the studied population

	N (%) unless otherwise indicated
Sex ratio M/F	0.92 (2290/2474)
Age (years)	59.9 ± 10.1
45–54	38.0%
55–64	26.8%
65–74	23.5%
75 & more	11.6%
Cumulative smoking of current and ex-smokers (pack-years category, % of total population)	
1–14	816 (40.9%)
15–24	510 (25.6%)
≥25	669 (33.5%)
Daily cigarette consumption	
≤1	50 (2.4%)
2–20	1722 (81.9%)
≥21	331 (15.7%)
Occupational exposure to dusts, gas, fumes	1423 (30.3%)
Chronic cough and sputum production	
No cough nor expectoration	4142 (86.9%)
Chronic cough only	310 (6.5%)
Chronic expectoration only	127 (2.7%)
Chronic cough + expectoration	185 (3.9%)

Table 2 Subjects with a low FEV_1/FVC ratio according to the definition used and smoking status (whole population)

	All	Never-smokers	Ex-smokers	Current smokers
Whole population, *N*	4764	2297	1473	862
ATS-GOLD definition[a]	415/4764	152/2297	139/1473	108/862
	8.71%	6.62%	9.44%	12.53%
	[7.87—9.47]	[5.65—7.69]	[8.02—11.01]	[10.44—14.87]
ERS definition[a]	305/4764	110/2297	97/1473	95/862
	6.40%	4.79%	6.58%	11.02%
	[5.73—7.12]	[3.97—5.72]	[5.40—7.94]	[9.06—13.24]
Study definition[a]	379/4764	143/2297	129/1473	96/862
	7.96%	6.23%	8.76%	11.14%
	[7.21—8.74]	[5.29—7.27]	[7.39—10.28]	[9.16—13.97]
Patients without known lung or heart disease, N	3794	1834	1164	690
ATS-GOLD definition[a]	266/3794	96/1834	90/1164	73/690
	7.01%	5.23%	7.73%	10.58%
	[6.23 − 7.86]	[4.28—6.33]	[6.30—9.37]	[8.45—13.04]
ERS definition[a]	191/3794	66/1834	59/1164	66/690
	5.03%	3.60%	5.07%	9.57%
	[4.37—5.77]	[2.82 − 4.53]	[3.92 − 6.45]	[7.54—11.93]
Study definition[a]	243/3794	89/1834	85/1164	63/690
	6.40%	4.85%	7.30%	9.13%
	[5.66—7.22]	[3.94—5.91]	[5.91—8.91]	[7.15—11.46]

[a] ATS-GOLD definition: $FEV_1/FVC < 0.70$; ERS definition: $FEV_1/FVC < 88\%$ predicted in men, 89% predicted in women, predicted values from ERS equations; Study definition: $FEV_1/FVC <$ {predicted − 1.64 RSD}, with predicted values and residual standard deviation from the presumably normal fraction of the studied population. Data are numbers (percentage of the corresponding population) [95% confidence interval of the prevalence rate].

i.e. 0.66 in men and 0.69 in women. Thus, the largest sample was selected ($n = 1036$ men, 1028 women with no respiratory symptom). In that sample, equations for calculation of FEV_1/FVC predicted values were: in men, $-0.114A + 86.14$; in women, $-0.080A + 85.15$. Residual standard deviations were 6.00 in men, 5.97 in women. For FEV_1, regression equations were: in men, $3.904H - 0.031A - 2.569$; in women: $2.589H - 0.025A - 0.887$. Residual standard deviations were 0.52 in men and 0.35 in men.

Prevalence and severity of chronic airflow obstruction (Tables 2 and 3)

Symptoms of chronic bronchitis were present in 3.9% of subjects, among whom most subjects did not exhibit airflow obstruction (97%). Prevalence of chronic airflow obstruction was influenced by the definition used. It was of the same magnitude with the ATS-GOLD definition and the ''study definition''. The ERS definition gave a smaller prevalence (Table 2).

In the majority of patients with chronic airflow obstruction, the disease was categorized as stage 1 (Table 3). Depending on the definition used to diagnose airflow obstruction and on the reference equation used to calculate predicted FEV_1, there were small differences in the repartition of patients according to disease severity. These tendencies were observed in the three sub-groups of smoking status (data not shown).

For all subsequent analysis, airflow obstruction was defined by $FEV_1/FVC < 0.7$.

Prevalence *versus* previous diagnosis

In the non-asthmatic population with symptoms of chronic bronchitis ($n = 150$), a previous diagnosis of respiratory disease (named chronic bronchitis of chronic airflow obstruction by the subjects) was reported by three subjects. Among the 295 subjects with airflow obstruction, eight reported such a diagnosis.

Risk factors

Prevalence of chronic airflow obstruction was influenced by smoking status but 17.2% of non-asthmatic subjects with airflow obstruction were never smokers, and the prevalence of $FEV_1/FVC < 0.70$ was 5.3% in never smokers (Table 2). Occupational exposure to dusts, gas, toxic compounds or fumes were reported by about 30% of subjects. In the population without already known chronic respiratory or heart disease, such exposures were associated with a significant increase in chronic bronchitis (2.5% of the non-exposed *versus* 4.0% of the exposed subjects, $p = 0.011$) and chronic airflow obstruction (6.4 *versus* 8.2%, respectively, $p = 0.047$).

Table 3 Distribution of % predicted FEV_1 in subjects with airflow obstruction

Definition of airflow obstruction	FEV_1 (% predicted)	Number in the category/ number of subjects with airflow obstruction according to the considered definition
ATS-GOLD definition[a]	≥80%	245/415 = 59.0%
	[50−80]	150/415 = 36.1%
	[30−50]	18/415 = 4.3%
	<30%	2/415 = 0.5%
ERS definition[a]	≥80%	154/287 = 53.7%
	[50−80]	115/287 = 40.1%
	[30−50]	16/287 = 5.6%
	<30%	2/287 = 0.7%
Study definition[a]	≥80%	232/421 = 55.1%
	[50−80]	150/421 = 35.6%
	[30−50]	37/421 = 8.8%
	<30%	2/421 = 0.5%

Predicted values were calculated using ECCS equations for subjects with airflow obstruction according to ERS and ATS-GOLD definitions and study equations for subjects with airflow obstruction according to the study definition.

[a] ATS-GOLD definition: $FEV_1/FVC < 0.7$; ERS definition: $FEV_1/FVC <$ 88% predicted in men, 89% predicted in women; study definition: $FEV_1/FVC <$ predicted value − 1.64 residual standard definition, with predicted value derived from the presumably normal fraction of the studied population.

Discussion

In this sample of 4764 subjects visiting health prevention centers, the prevalence of airflow obstruction among non-asthmatics differed according to the definition and prediction equation used, ranging between 6 and 9%. Severity distribution also varied depending on the equation used to calculate predicted values. FEV_1 was >50% predicted in most subjects with airflow obstruction. In the vast majority of these subjects, no airway disease had been previously diagnosed. Finally, tobacco smoking and occupational exposures could be identified as risk factors for airflow obstruction in that population.

Limitations of the study

Some limitations of the study have to be addressed.

Firstly, the study population should not be considered as representative of the French general population: the proportion of subjects with respiratory symptoms and/or a known diagnosis of COPD and/or moderate-to-severe airflow obstruction was probably underestimated, since these patients are usually symptomatic and followed by a physician and, thus, do not visit prevention centers (healthy worker effect). However, the high prevalence of chronic airflow obstruction is in line with other studies using spirometry in developed countries, although we observed a marked under-representation of severe cases.[3,4,9,16] As in these studies, a significant proportion of non-asthmatic subjects with airflow obstruction were never smokers, and reported occupational exposures.[17,18]

Secondly, as in many prevalence studies in the population, we used pre-bronchodilator spirometry to assess the prevalence and severity of airflow obstruction, which does not conform to recent guidelines on COPD. Indeed, it has been shown that pre-bronchodilator spirometry may overestimate the prevalence of COPD by about 20−35%,[19] and post-bronchodilator reference values have been recently developed in Norway.[20] However, French health prevention centers are not allowed to deliver any kind of medication. In addition, the use of pre-bronchodilator values is in line with several recent epidemiological studies such as those by De Marco et al.[12,21] In their most recent paper, these authors conclude that the use of pre-bronchodilator values exposes to a risk of overestimating the prevalence of COPD. They also show that this risk is minimized by exclusion of asthmatic subjects. For this reason, all analyses were performed in the whole population, in non-asthmatics only and in subjects with no known heart or respiratory disease. Finally, it must be outlined that the use of pre *versus* post-bronchodilator values does not alter the value of comparisons between reference equations or definitions of airflow obstruction, which correspond to the main purpose of the paper.

Influence of the definition of airflow obstruction

Prevalence of airflow obstruction was greater with ATS-GOLD definition ($FEV_1/FVC < 0.70$) than with ERS definition based on predicted values calculated using ECCS equations. Surprisingly, the ATS-GOLD definition provided results similar to those obtained with the study definition, which was based on predicted values calculated using equations derived from the presumably normal fraction of the studied population.

Previous studies also found higher numbers of patients with airflow obstruction with ATS-GOLD than with ERS definition.[7−10] It was suggested that these discrepancies were related to an overestimation of the proportion of older subjects with mild airflow obstruction when the 0.70 cut-off is used, since FEV_1/FVC normal values decrease with age. Data reported here also suggest that ERS reference equations may not be applicable in all European populations and may need local or regional validation and periodical revision, which confirms ERS/ATS guidelines. Other reference equations could have been tested, but we chose to limit the analysis to ECCS equations since: (i) they still represent the most frequently used equations in Europe; and (ii) they have been derived from a European rather than a north-American population.

Underdiagnosis of airflow obstruction

A vast majority of detected cases of chronic airflow obstruction previously ignored that they suffered from this illness. This high figure may be at least in part explained by the mode of recruitment, symptomatic and severe subjects with known respiratory disease being less likely to visit prevention centers. Nevertheless, a marked underdiagnosis of COPD was also reported by several

authors[3–5,9,16,22] and may be due to the poor predictive values of symptoms.[23,24]

A major issue is the significance of a low FEV_1/FVC ratio (corresponding to ''stage 1'' COPD) in asymptomatic subjects: are these subjects at risk of developing marked airflow obstruction and respiratory handicap? Or is this low ratio just a statistical artifact? As recently published, clinical data from the present study show that even mild undiagnosed airflow obstruction is associated to increased dyspnea, work loss and altered quality of life.[25] Only a few studies assessed the rate of decline in FEV_1 according to the value of the FEV_1/FVC ratio in subjects with an initially normal FEV_1. In the OLIN longitudinal studies, FEV_1 decline was 33 ml/year in the whole study population and 43 ml/year in incident cases of mild COPD.[26] In the study by Burrows et al., FEV_1/FVC ratio was a strong predictor of subsequent lung function decline.[27] More recently, Enright et al. found similar results with the FEV_1/FEV_6 ratio.[28] However, further longitudinal studies, or analysis of data from existing studies clearly remains to be performed to assess disease progression in patients with stage 1 COPD.

In conclusion, this study found a high prevalence of previously undiagnosed airflow obstruction in subjects visiting prevention centers, despite a low proportion of subjects with symptoms and severe lung function impairment. Differences in prevalence and severity distribution with the definition of airflow obstruction and reference equations used confirm the need for: (i) homogenizing the definitions of airflow obstruction used for teaching, communication, clinical practice or research purposes; and (ii) revisiting equations used to determine predicted normal values of spirometry variables.

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Conflicts of interest statement

Nicolas Roche received fees for speaking, organizing education or consulting from Almirall, Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer.

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