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Population impact of different definitions of airway obstruction

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ABSTRACT: There is currently no consensus on the criteria for diagnosing chronic obstructive pulmonary disease. This study evaluated the impact of different definitions of airway obstruction on the estimated prevalence of obstruction in a population-based sample.

Using the Third National Health and Nutrition Examination Survey, obstructive airway disease was defined using the following criteria: 1) self-reported diagnosis of chronic bronchitis or emphysema; 2) forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.70 and FEV_1 <80% predicted (Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage IIA); 3) FEV_1/FVC below the lower limit of normal; 4) FEV_1/FVC <88% pred in males and <89% pred in females; 5) FEV_1/FVC <0.70 ("fixed ratio"). Spirometry in this dataset did not include reversibility testing, making it impossible to distinguish reversible from irreversible obstruction.

Rates in adults varied from 77 per 1,000 (self-report) to 168 per 1,000 (fixed ratio). For persons aged >50 yrs, the fixed ratio criteria produced the highest rate estimates. For all subgroups tested, the GOLD Stage II criteria produced lower estimates than other spirometry-based definitions.

Different definitions of obstruction may produce prevalence estimates that vary by >200%. International opinion leaders should agree upon a clear definition of chronic obstructive pulmonary disease that can serve as a population-based measurement criterion as well as a guide to clinicians.

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Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the USA [1]. COPD is the only leading cause of death that is increasing in prevalence worldwide [2], and is widely underdiagnosed in the primary care setting [3]. Since early detection and intervention is currently the best approach to reducing the burden of COPD, there has been a call for global strategies to assess the prevalence of COPD [2]. Unfortunately, there is no consensus on the criteria for diagnosis of COPD. However, all international bodies, as well as a majority of national guidelines, agree that COPD should be defined physiologically using spirometry [4, 5]. The ratio of forced expiratory volume in one second (FEV1) to vital capacity (VC) or forced vital capacity (FVC) is an accepted indicator of the presence of airflow limitation. Using criteria based upon this measure, VIEGI *et al.* [6] demonstrated that the measured prevalence of disease depends upon the criterion used to define obstruction. Thus, the comparison of rates between countries, indeed even between individual published reports, is complicated by the differing criteria used to measure obstruction [7]. For population-based estimates to be comparable across different populations, there should be minimal systematic bias between criteria. In addition, successful widespread implementation of spirometry requires the obtained measurement be simple, reproducible and usable across the spectrum of populations to be evaluated.

Using several widely used definitions of airway obstruction, the impact of these definitions on overall prevalence estimates for the USA was compared using the Third National Health and Nutrition Examination Survey (NHANES III). Their impact on the relationship between obstruction and age, sex, race/ethnicity, and smoking status was then examined. Since the spirometric testing used in NHANES III did not include reversibility testing, it was not possible to distinguish reversible from irreversible obstruction.

Materials and methods

Study subjects

The NHANES III was conducted from 1988–1994 by the US National Center for Health Statistics. Using a stratified multistage clustered probability sample, the survey was designed to identify an unbiased sample that could, using appropriate weights, be extrapolated to the entire civilian noninstitutionalised population in the USA. Study participants completed extensive household and personal health questionnaires, and underwent a comprehensive physical examination, including spirometry. A total of 81 sites were included in the final sample. A complete description of the NHANES III survey methodology has been previously published [8].

Spirometry procedures were based on the 1987 recommendations of the American Thoracic Society (ATS) [9]. A customised Ohio Sensorimed 827 dry rolling seal spirometer (Ohio Medical Instrument Company, Cincinatti, OH, USA) was used. After calibration of the equipment, each subject performed five to eight forced expiratory manoeuvres, with the goal of meeting the ATS acceptability and reproducibility criteria [10]. A more detailed description of the spirometric procedures is available [11].

Among the total NHANES III sampled population, 13,322 patients had a reliable and reproducible spirometry test. This population represented a weighted reference population of 147,438,632 people, which included persons aged ⩾17 yrs of all races. For the analysis, a lower age cut-off of 30 yrs was used in order to reduce the confounding effects of asthma in younger people. Subjects aged >80 yrs, and subjects not of Caucasian, African-American or Mexican-American race/ethnicity were excluded because there were no reliable reference equations for spirometry results. Thus, the study population included non-Hispanic Whites, non-Hispanic Blacks, and Mexican-Americans aged 30–80 yrs with a satisfactory spirometry test. The total final (crude) study population was 9,838, representing a weighted study population of 109,483,437 subjects.

Methods

Four widely used spirometry-based definitions of airway obstruction and one self-reported definition were compared (table 1). Age, sex, and race-specific values for predicted FEV1 and predicted FEV1/FVC were calculated for each patient using reference equations described by HANKINSON *et al.* [10]. Similarly, age, sex, and race-specific lower limits of the normal range for FEV1/FVC were calculated for each person using reference equations from the same source. These were based on the predicted value minus 1.645-times the SE of the estimate.

Subjects who answered "yes" to the questions, "Has a doctor ever told you that you had chronic bronchitis?" or "Has a doctor ever told you that you had emphysema?" were considered to have self-reported COPD. Subjects were defined as smokers if they answered "yes" to the question, "Do you smoke cigarettes now?". Subjects who answered "no" to the question, "Do you smoke cigarettes now?" but "yes" to the question, "Have you smoked at least 100 cigarettes during your entire life?" were classified as former smokers. Persons answering "no" to both questions were labeled never-smokers. These questions were part of the NHANES III Household Adult Questionnaire.

Analysis

For all five possible definitions of airway obstruction, prevalence rates were calculated for the entire study population, and by subgroups defined by age, sex, race/ethnicity, and smoking status. Rates were weighted to the general USA population using the "total Mobile Examination Center and Home-Examined Final weight" (WTPFHX6) defined by NHANES III. Since the goal of this study was to evaluate the impact of different scenarios using a single dataset, the authors did not perform statistical testing.

Results

Table 2 describes the characteristics of the study population. For the entire sample, the mean±SD age was 48.3±13.6 yrs, height was 169.2±7 cm, and weight was 77.6±18.1 kg. FEV1 was 2.9±0.87 L, with a FEV1/FVC of 77.0±9.0%. For the FEV1/FVC% predicted, mean±SD was 96.6±10.2. The values for the mean FEV1/FVC% pred minus 1.64 residual SD were 79.9% for the entire sample, 78.1% for males, and 81.7% for females.

As shown in table 3, the four spirometry-based definitions yielded estimates of total prevalent airway obstruction varying from 8.6 million (Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage IIA) to >18 million (fixed ratio), as compared with 8.5 million with a patient-reported history of COPD. Rate estimates varied from 79 per 1,000 population (GOLD Stage IIA) to 168 per 1,000 with the fixed ratio definition.

For persons aged <50 yrs, the "per cent predicted" and "lower limit of normal" definitions produced the highest rate estimates. For persons aged ⩾55 yrs, the "fixed ratio" definition produced the highest rate estimates. For all age groups, the GOLD Stage IIA definition produced lower estimates than other spirometry-based definitions. Overall, the GOLD Stage IIA definition was more similar to self-reported COPD than were other spirometry-based definitions. The age relationships are presented in figure 1.

For subgroups defined by sex, race/ethnicity and smoking status, rate estimates tended to cluster into two groups, with self-report and GOLD IIA definitions generally producing lower estimates, and the other definitions generally producing higher estimates.

Discussion

By comparing commonly used methods, it is possible to quantify the impact of different measurement approaches on population estimates of obstructive airway disease. As shown by the results from this study, these differences may be large, altering population prevalence estimates of COPD by >200%. This affects public health decisions, such as priority setting, resource allocation, and planning. In some regions, the estimated prevalence of a disease may determine the availability of additional resources or better access for patients.

These differences are also important when comparing published studies using different COPD definitions, or in comparing COPD prevalence rates between populations with

Table 1. – Definitions of airway obstruction

Definition	Reference
Self-reported diagnosis of chronic bronchitis or emphysema "self report"	See text for description of variables used
FEV1/FVC <0.70 and FEV1 <80% pred[#]	GOLD Stage IIA [12]
FEV1/FVC < lower limit of normal[¶]	See text for comparability to ATS guidelines [13]
FEV1/FVC <88% pred in males and <89% pred in females "per cent predicted"	See text for comparability to ERS guidelines [14]
FEV1/FVC <0.70 "fixed ratio" [#]	"Clinical" definition [6], equivalent to GOLD Stage I [12]

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: % predicted; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ATS; American Thoracic Society; ERS: European Respiratory Society. [#]: GOLD specifies that all FEV1 values should refer to postbronchodilator FEV1. The third National Health and Nutrition Examination Survey (NHANES III) did not include reversibility testing [12]. [¶]: the ATS specifies that spirometry should be performed pre- and postbronchodilator. NHANES III did not include reversibility testing [13].

Table 2. – Population characteristics

	Crude	Weighted[#]	FEV1 mL	FEV1% pred	FVC mL	FVC% pred	FEV1/FVC%	FEV1/FVC% pred
Total study population	9838	109483437	2900±866	95.7±16.7	3762±1038	99.6±15.1	77.0±9.0	96.6±10.2
Age yrs								
30–34	1542	18978806	3484±777	100.0±12.6	4254±979	102.8±12.3	82.3±6.2	98.2±7.2
35–39	1400	17419936	3307±755	98.7±12.7	4083±970	101.2±12.9	81.4±6.0	98.3±7.0
40–44	1320	16797329	3228±734	98.1±13.2	4069±951	101.2±13.1	79.7±6.4	97.6±7.7
45–49	871	12041677	3056±744	96.1±15.1	3933±963	99.5±13.7	78.0±7.4	97.0±9.1
50–54	777	9354798	2856±765	93.0±16.6	3767±1005	97.0±14.6	76.2±8.0	96.0±9.9
55–59	734	8811569	2676±724	91.9±16.9	3600±965	96.6±15.1	74.7±8.3	95.4±10.4
60–64	940	7913347	2525±716	92.0±19.1	3452±934	97.4±16.7	73.4±9.3	95.1±11.9
65–69	827	7681211	2407±704	92.6±20.1	3331±937	98.0±18.1	72.6±9.3	95.4±12.0
70–74	805	6123341	2248±662	92.8±20.7	3186±901	98.1±17.7	71.2±10.5	95.0±13.8
75–80	622	4361424	2013±641	94.0±22.8	2899±881	99.3±19.6	70.1±11.5	95.1±15.4
Sex								
Male	4705	53264661	3367±847	95.0±16.9	4439±917	98.6±14.2	75.5±9.5	96.1±11.0
Female	5133	56218776	2472±630	96.3±16.6	3141±699	100.6±15.9	78.4±8.3	97.1±9.4
Race/ethnicity								
Mexican-American	2575	4868314	3028±820	98.0±14.6	3823±977	103.7±14.6	79.2±7.6	98.2±8.3
Non-Hispanic Black	2735	11234876	2745±797	97.1±17.2	3498±940	100.2±15.7	78.5±8.8	96.4±9.9
Non-Hispanic White	4528	93380248	2921±916	93.5±17.3	3887±1098	97.0±14.5	74.9±9.5	95.9±11.2
Smoking status								
Never	4313	45490508	2850±839	99.0±15.2	3592±1016	101.3±15.0	79.4±7.4	99.0±8.5
Former	2846	33672918	2941±880	94.8±17.2	3907±1034	99.1±14.9	75.0±9.5	95.8±10.9
Current	2679	30320012	2938±889	91.3±17.5	3882±1037	97.5±15.2	75.4±10.0	93.6±11.0

Data are presented as n or mean±SD. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: % predicted. [#]: results are weighted to the general USA population.

different age distributions or smoking rates. Indeed, if these two factors are changing over time (as they are in the USA), there may be systematic artificial differences between measurements made at different times, even within the same country. This can yield biased trend estimates, which may mislead population projections or public health planning efforts.

Since 1991, the ATS has discouraged defining obstruction based upon a fixed ratio between the FEV1 and the FVC because this ratio is inversely related to both age and height [15]. However, the more recent 1995 guidelines of the ATS do not provide a definitive cut-off that is amenable to creating a reproducible algorithm for evaluating populations. The European Respiratory Society (ERS), on the other hand, has explicitly specified a definition of obstruction that may be applied to populations. The definition of obstruction "assessed

Table 3. – Airway obstruction by diagnostic definition

	Self-report	GOLD stage IIA	Lower limit of normal	% pred	Fixed ratio
Prevalent cases	8.5	8.6	15.6	17.5	18.4
Rate per 1000 population					
Overall	77.3	78.7	142.1	160.0	167.8
Age yrs					
30–34	49.3	17.3	83.7	90.4	44.7
35–39	39.5	18.2	92.5	100.1	54.6
40–44	65.6	35.7	115.8	127.1	94.8
45–49	77.1	50.2	138.8	152.5	133.5
50–54	86.8	102.5	156.1	178.8	181.9
55–59	92.3	137.6	191.8	212.1	255.6
60–64	109.4	152.4	197.7	234.4	311.5
65–69	124.0	179.3	212.5	256.1	345.4
70–74	137.0	189.0	228.6	258.3	406.2
75–80	121.9	194.8	227.2	261.8	416.9
Sex					
Male	58.2	84.8	150.0	160.9	199.0
Female	95.5	72.9	134.5	159.2	138.3
Race/Ethnicity					
Mexican-American	35.7	27.2	91.5	87.0	73.2
Non-Hispanic Black	58.0	58.5	119.6	144.8	116.8
Non-Hispanic White	81.8	83.8	147.4	165.6	178.9
Smoking Status					
Never	45.9	36.0	72.4	86.8	90.5
Former	86.4	89.0	156.6	178.9	213.9
Current	114.4	131.2	230.4	248.8	232.6

Prevalent cases are presented as n (millions). Results are weighted to the general USA population. GOLD: Global Initiative for Chronic Obstructive Lung Disease; % pred: % predicted.

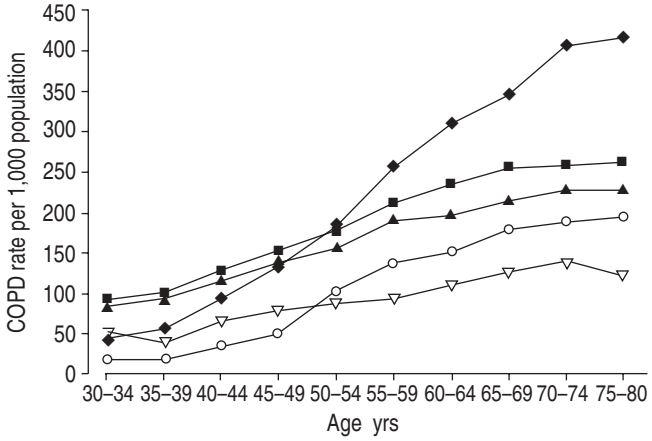

Fig. 1. – Prevalence of airway obstruction, by diagnostic definition and age group. COPD: chronic obstructive pulmonary disease. ◆: fixed ratio; ■: % predicted; ▲: lower limit of normal; ○: Global Initiative for Chronic Obstructive Lung Disease stage IIA; ▽: self-report.

as FEV1/VC <88% predicted in men or <89% predicted in women" is followed by the parenthetical statement, "*…i.e.* >1.64 residual standard deviation below predicted value" [14]. Results from this study are not directly comparable to the ERS guidelines for reasons discussed in more detail below.

The recently published GOLD guidelines define COPD in subjects with an FEV1/FVC <0.70 [12]. This fixed ratio definition of obstruction may offer some benefits as a compromise solution among competing definitions, as it provides rate estimates that are generally comparable to those obtained using the "lower limit of normal" and "per cent predicted" methods for general population estimates as well as for subgroups of sex, race/ethnicity, or smoking status. The fixed ratio is easy to remember and does not require the use of population-specific reference tables. These qualities may lend themselves to practical use for primary care screening in all parts of the world. They also make it less daunting for the nonspecialist to interpret pulmonary function tests, which might increase the likelihood of testing in persons with respiratory symptoms. Since underdiagnosis is arguably one of the major barriers to more effective treatment of COPD [3], the widespread adoption of a definition that is "sensitive, specific, reproducible, and relatively uncomplicated to administer" [4] is desirable. However, the potential benefits of using this simplified method do not come without cost. In the results from this study, the fixed ratio produced higher rate estimates for older persons than any other definition, and these differences increased with age as the FEV1/FVC ratio declines. For the purposes of screening, a higher sensitivity may be acceptable in older, higher-risk patients. This increased sensitivity must be balanced against the increased cost of spirometry among false positives incorrectly identified as having COPD. However, the fixed ratio most closely approximates the rate produced by the lower limit of normal definition in the highest-risk subgroup, current smokers.

The GOLD Stage IIA definition (FEV1/FVC <0.70 and FEV1 <80% pred) is often used as a "practical" threshold for identifying COPD. When applied to the NHANES III data, this definition consistently provided the lowest rates among the spirometry-based methods. The similarity between the rates obtained using GOLD Stage IIA and self-report suggests that this may indeed be a practical definition for identifying persons with symptomatic disease.

Without a definitive "gold standard," the NHANES III dataset does not show which definition is most likely to reflect the "true" rate of COPD. Because of differences in methodology (mainly the exclusion of persons aged <30 yrs), results from this study are slightly higher than prior analyses of the NHANES III dataset. Based on the GOLD Stage IIA criteria, NHANES III has yielded population estimates of 6.8% among subjects aged ⩾17 yrs [16], and 6.6% in subjects aged ⩾25 yrs (age-adjusted to the 2000 USA population) [17], compared with 7.9% in the current study. For GOLD Stage I criteria, a rate of 13.9% has been previously reported [18], compared with 16.8% with the "fixed ratio" definition used in this study. Outside the USA, published COPD prevalence estimates based on spirometry have ranged 3.7–11.0% [7].

Using a definition that included asthma, the NHANES III prevalence of self-reported obstructive lung disease in persons aged ⩾17 yrs was 12.5% in smokers, 9.4% in former smokers, and 5.8% in never-smokers [16], compared with 11.4, 8.6, and 4.6%, respectively, in the current study. Self-reported rates derived from another national-level survey in the USA, the National Health Information Survey, consistently range 5.6–6.4% [17]. These compare well with prevalence estimates based on patient-reported disease from outside the USA, which range 3.7–10.7% [7]. The authors initially assumed that self-reported disease was unlikely to be confounded by age, sex, or smoking status. However, a recently published evaluation of respiratory symptom questionnaires in Norway suggests that self-report may indeed be differentially affected by smoking status [19].

Regardless of the "true" baseline prevalence of COPD, findings from the current study suggest that differences in age distribution, racial composition, and smoking prevalence between countries can result in systematic differences in prevalence rates when international comparisons are being made using different definitions. These results emphasise the need for an internationally agreed-upon definition of COPD, one which may serve as a population-based criterion as well as a guide to clinicians. Ideally, such a definition should be unambiguous, unbiased, and reproducible in different settings.

The reference equations derived by HANKINSON *et al.* [10] have been shown to perform well when compared to previously published reference populations [20]. However, more recent work suggests small but systematic differences between the NHANES III equations and other standards [21]. Of note, using the NHANES III equations resulted in fewer FEV1/FVC abnormalities indicative of obstruction than using equations by CRAPO *et al.* [22] or KNUDSON *et al.* [23]. Many of these older standards were based on smaller samples than the NHANES III, and were drawn from single regions. For example, the widely used equations published by CRAPO *et al.* [22] in 1981 were derived from 251 healthy nonsmokers from Salt Lake City, UT, USA. Of these, >90% of these were Mormons. KNUDSON *et al.* [23] based their equations on 697 White, non-Hispanic nonsmokers living in Tucson, AZ, USA. The NHANES III equations, on the other hand, are based on 7,429 healthy nonsmokers drawn from a population-based sample of ambulatory civilian residents in the USA [10].

Results from this study are not directly comparable to the ERS guidelines, since FVC was used rather than VC measured as "slow" vital capacity (SVC), or inspiratory vital capacity (IVC), as recommended by the ERS. The 1993 ERS report on "Lung Volumes and Forced Ventilatory Flows" states that "the FVC may be considerably less than the IVC in patients with airflow limitation…" [24]. Unfortunately, neither SVC nor IVC are available in the NHANES III dataset. Despite the known differences between slow and forced measures of VC, the relationship between FEV1/FVC and FEV1/VC, particularly the measurement of differences in the % pred values for these two ratios, has not been well characterised using large population datasets. Studies using small groups of patients (*i.e.* <100) have been published by several authors

[25–27]. The most robust comparison is probably that of PISTELLI *et al.* [28], which found systematic differences in reference equations for FEV1/FVC and FEV1/VC based on a population of 1,039 normal subjects. However, the effect of these differences on population estimates has not been studied and it is not clear how results from the current study would compare to results using slow VC.

The spirometry examination performed in NHANES III did not include a test of reversibility of obstruction. While the authors expect that a significant proportion of respondents had some reversible component (*i.e.* "mixed disease"), some subset of the study population also had pure asthma, that is, completely reversible obstruction. Without detailed diagnostic and severity information, it is not possible to determine how large a role reversible obstruction played in these findings. However the primary study goal of the authors was not the measured prevalence of COPD (*i.e.* the absolute number), but rather the relative difference in prevalence estimates between differing diagnostic criteria. Spirometric definitions of COPD generally require postbronchodilator measurement of lung parameters. The GOLD definition of COPD, for example, explicitly specifies, "all FEV1 values refer to a postbronchodilator FEV1" [12]. While differences in the prevalence of completely reversible obstruction may have introduced some bias between the different definitions, reversible disease is unlikely to completely explain the between-definition differences seen in findings from the current study.

International opinion leaders should agree upon a clear definition of chronic obstructive pulmonary disease that can serve as a population-based measurement criterion as well as a guide to clinicians. This definition should be simple and capable of identifying patients likely to suffer from the disease. This concept has been very useful in the clinical and epidemiological management of hypertension. Despite the complexities of actual blood pressure distributions, the use of a fixed lower limit for systolic and diastolic blood-pressures contributed to significant advances in the treatment of this disease and in the prevention of its complications, including myocardial infarction and strokes [29–31]. By reaching consensus, opinion leaders could provide comparable benefits in the area of chronic obstructive pulmonary disease.

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