



Defining chronic obstructive pulmonary disease in older persons

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Summary

Objective: To develop a more age-appropriate spirometric definition of chronic obstructive pulmonary disease (COPD) among older persons.

Methods: Using data from the Third National Health and Nutrition Examination Survey (NHANES III), we developed a two-part spirometric definition of COPD in older persons, aged 65–80 years, that 1) determines a cut-point for the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV₁/FVC) based on mortality risk; and 2) among persons below this critical FEV₁/FVC threshold, determines cut-points for the FEV₁, expressed as a standardized residual percentile (SR-tile) and based on the prevalence of respiratory symptoms and mortality risk. Measurements included spirometry, health questionnaires, and mortality (National Death Index).

Results: There were 2480 older participants with a mean age of 71.7 years; 1372 (55.4%) had a smoking history, 1097 (44.2%) had respiratory symptoms and, over the course of 12-years, 868 (35.0%) had died. Among participants with an FEV₁/FVC < .70 and FEV₁ < 5th SR-tile, representing 7.7% of the cohort, the risk of death was doubled (adjusted hazard ratio, 2.01; 95% confidence interval [CI], 1.60–2.54). Among participants with an FEV₁/FVC < .70 and FEV₁ < 10th SR-tile, representing 13.4% of the cohort, the prevalence of respiratory symptoms was elevated (adjusted odds ratio, 2.44; CI, 1.79–3.33).

Conclusion: In a large, nationally representative sample of community-living older persons, defining COPD based on an FEV₁/FVC < .70, with FEV₁ cut-points at the 10th and 5th SR-tiles, identifies individuals with an increased prevalence of respiratory symptoms and an increased risk of death, respectively.

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Introduction

Chronic obstructive pulmonary disease (COPD), a leading cause of disability and death worldwide, is defined by chronic airflow limitation that is not fully reversible.^{1–9} The airflow limitation is established spirometrically, based solely on a reduced ratio of forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC), with severity subsequently categorized according to the FEV₁.^{2–9} This strategy for defining COPD has a physiological basis because airflow limitation increases the risk of death and usually precedes the onset of dyspnea or exercise intolerance.^{10,11} In contrast, defining COPD on the basis of disease criteria alone (e.g. chronic bronchitis) lacks diagnostic accuracy, because cough and sputum production may occur in the absence of airflow limitation and are not independent predictors of death.^{10–12}

Current spirometric guidelines are potentially problematic, however, for at least three reasons. First, the threshold that establishes a reduced FEV₁/FVC remains controversial.^{6–8} For example, the Global Initiative for Obstructive Lung Disease (GOLD) and the American College of Physicians (ACP) advocate an FEV₁/FVC threshold based on a fixed-ratio,^{4,13} but this by itself cannot distinguish clinically-significant pathology from normal age-related increases in airflow limitation.⁷ Alternatively, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) advocate an FEV₁/FVC threshold based on the lower limit of normal (LLN),⁹ but this is derived from regression equations that have limited explanatory ability when applied to an elderly population (i.e., R^2 range of .03–.08).^{8,14,15} Second, the present method of reporting the FEV₁ as percent predicted (%Pred) is fundamentally flawed, because it does not account for differences in the variability of the reference group across the lifespan.^{16,17} As a result, a given FEV₁ %Pred value is not equivalent for all persons regardless of age, height, sex, and ethnicity.^{16,17} Third, current spirometric guidelines, in general, lack clinical validation regarding important measures such as mortality and respiratory symptoms.^{4,9,13}

These problems with current spirometric guidelines are most evident among older persons. Specifically, conventional cut-points for the FEV₁/FVC ratio yield prevalence rates for COPD (in the U.S.) that range widely from 16% to 42%, with most affected individuals subsequently categorized by the FEV₁ %Pred as having “mild” COPD.^{6,7} Hence, current spirometric guidelines may lead to misclassification (mainly over-diagnosis) of COPD among older persons and, in turn, potentially compromise patient care.^{7,13,18}

As an alternative spirometric strategy, we propose that COPD be defined by a two-step process that 1) determines a cut-point for the FEV₁/FVC based on mortality risk; and 2) among persons below this critical FEV₁/FVC threshold, determines cut-points for the FEV₁, expressed as a standardized residual percentile (SR-tile) and based on the prevalence of respiratory symptoms and mortality risk. An SR-tile is simply a Z-score that has been converted to a percentile,^{16,17} and is analogous to what is currently reported for bone mineral density testing.¹⁹ Importantly, the SR-tile method accounts for variability in age, height, sex, and ethnicity.^{16,17} In the present study, we have applied our strategy for defining COPD in a large nationally representative sample of community-living older persons, which

included a large proportion of women and minorities, and discuss how this approach is more clinically meaningful than those provided in published guidelines.^{4,9,13}

Methods

Study population

We used data from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of Americans assembled in 1988–1994, with mortality surveillance through December 31, 2000.^{20,21} Our source population included 2480 community-living NHANES III participants, aged 65–80 years, who were white, African-American, or Mexican-American, had no self-reported asthma, and had completed a health questionnaire, a brief cognitive assessment, and at least two ATS acceptable spirometric maneuvers.²² As per current ATS recommendations, we did not exclude participants based on spirometric reproducibility criteria.³

Clinical measures

As described elsewhere,²⁰ NHANES III recorded the presence of respiratory symptoms in the prior 12 months, including chronic cough or sputum production lasting 3 or more consecutive months, dyspnea on exertion, and wheezing or “whistling in the chest”. Other clinical data included chronic conditions, including self-reported, physician-diagnosed COPD and asthma, as well as smoking history, self-reported health status, body mass index (BMI), and cognitive function. Memory impairment was defined as a score less than 2 on delayed recall of a 3-item word list or a score less than 4 on delayed recall from a 6-item story.

Spirometry

NHANES III utilized a customized Ohio Sensormed 827 dry rolling seal spirometer.²⁰ After calibration, each participant performed 5–8 FVC maneuvers, with the goal of meeting ATS criteria.^{20,22}

As shown in the [appendix](#), and following current guidelines,⁹ we determined regression equations in an NHANES III reference group of age-matched never-smokers, with no chronic conditions and no respiratory symptoms. Also as per guidelines,⁹ we used age and height as predictor variables for FEV₁ and FVC within each sex and ethnic group. Our subsequent procedures, however, differed from those of prior studies that calculated the FEV₁ as %Pred (i.e., measured/predicted \times 100).^{4,5,6,8} Instead, in a reference group of age-matched, healthy never-smokers, we calculated the constant that quantified the spread of the reference data, namely the standard deviation of the residuals. (A “residual” is the difference between a measured and predicted value.) Based on the regression equations and the spread of the reference data, we then expressed the measured FEV₁ of each participant as a standardized residual (SR), calculated as [(measured – predicted)/(standard deviation of the residuals)]; a percentile based on the SR was subsequently computed (SR-tile).^{16,17} To illustrate, an SR of –1.64 corresponds to the 5th

percentile, an SR of 0 corresponds to the 50th percentile, and an SR of 1.64 corresponds to the 95th percentile.^{16,17} By standardizing the residuals to the spread of the reference data, the SR method accounts for variability due to age, sex, height, and ethnicity and reports FEV₁ SR-tile values on an easy-to-interpret scale of 0–100, whereas %Pred does not.^{16,17}

We next classified participants based on their SR-tile values for FEV₁, using cut-points established for the FEV₁%Pred (80, 50, and 30) by the Global Initiative for Obstructive Lung Disease (GOLD).⁴ We modified these cut-points to 50, 30, 10, and 5 SR-tiles because only a small number of NHANES III participants with FEV₁/FVC values below the critical threshold, as defined below, had an FEV₁ > 80th SR-tile ($n = 21$) whereas a large number had an FEV₁ < 30th SR-tile ($n = 321$).

Lastly, we calculated the LLN for the FVC, to help define the referent group for our mortality risk analysis, i.e., the FVC criterion was used to exclude persons with restrictive lung disease.⁸

We do not report the LLN for the FEV₁/FVC because predicted values could not be determined reliably. In contrast to the FEV₁ and FVC, regression equations for the FEV₁/FVC had very low R^2 values, ranging from 0.01 to 0.07, with only one exception (the value for Mexican-females was 0.15). This lack of explanatory capacity persisted when we analyzed the ratio of the FEV₁ to the forced expiratory volume in 6 s (FEV₆), which yielded R^2 values of 0.01–0.08. These results are similar to those published in other cohorts of older persons.^{14,15}

Primary outcome

Our primary outcome was all-cause mortality, ascertained from a public-use linked mortality file that contains information based on the National Death Index, with follow-up through December 31, 2000.²¹ Vital status was available on all but one participant.²¹

Statistical analysis

SUDAAN version 9.0.1 (Research Triangle Park) was used to estimate hazard ratios (Cox proportional hazards analysis) and odds ratios (logistic regression), with a p -value < 0.05 (two-sided) denoting statistical significance.²³ Proportional hazard assumptions for survival models were tested using interaction terms crossing the time-to-event outcome with each variable in the multivariable model. If significant at the 0.05 level, these interaction terms were retained in the final model. The incidence rate and 95% confidence interval (CI) for death were expressed in person–years. Participants who had not died were censored at the end of the follow-up period.

As a first step, we varied the cut-point for the FEV₁/FVC in 0.05 decrements below a ratio of 0.80, and fit separate Cox regression models for all-cause mortality, each adjusted for age, height, sex, ethnicity, smoking history, BMI, chronic conditions, self-reported health status, and cognition. Higher order effects were tested for the continuous covariates and were included in the final models if they met the forward selection criterion of $p < 0.20$.²⁴ The first FEV₁/FVC cut-point below 0.80 that yielded

a statistically significant increase in the risk of death was termed the “critical” threshold.

Next, among participants with an FEV₁/FVC below the critical threshold, we evaluated time-to-death using the Kaplan–Meier method with strata defined according to FEV₁ cut-points, expressed as SR-tile. We then determined the independent association between the FEV₁ SR-tile cut-points and death using Cox proportional hazards, adjusted for the same covariates as described earlier. The FEV₁ SR-tile cut-points were treated as nominal categories, with the referent group including participants with normal pulmonary function, defined by an FEV₁/FVC \geq critical threshold and an FVC \geq LLN. Similarly, we also evaluated the associations between FEV₁ SR-tile cut-points and the presence of respiratory symptoms, by calculating odds ratios using logistic regression.

To enhance the interpretation of our findings, we evaluated the prevalence of smoking exposure and reduced health status according to the FEV₁ SR-tile cut-points among participants with an FEV₁/FVC below the critical threshold, and we calculated the FEV₁ %Pred values that corresponded to these SR-tile cut-points.

Table 1 Characteristics of the study population.

Characteristic	$n = 2,480$
Age, mean (SD), years	71.7 (4.5)
Females, No. (%)	1252 (50.5)
<i>Ethnicity, No. (%)</i>	
White	1497 (60.4)
African-American	517 (20.8)
Mexican-American	466 (18.8)
Education, mean (SD), years	9.7 (4.4)
<i>Smoking status, No. (%)</i>	
Never	1108 (44.7)
Former	1001 (40.4)
Current	371 (15.0)
<i>Chronic conditions, No. (%)^a</i>	
Hypertension	1194 (48.3)
Arthritis	1107 (44.6)
Diabetes mellitus	407 (16.4)
Myocardial infarction	272 (11.1)
Chronic obstructive pulmonary disease	214 (8.6)
Congestive heart failure	205 (8.3)
Cancer ^b	199 (8.0)
Stroke	173 (7.0)
Fair-to-poor self-reported health, No. (%)	824 (33.3)
Respiratory symptoms, No. (%) ^c	1097 (44.4)
Memory impairment, No. (%) ^d	859 (34.9)

Abbreviation: SD = standard deviation.

^a Self-reported, physician-diagnosed.

^b Minor skin cancers are not included.

^c Included cough or sputum production, wheezing, or exertional dyspnea.

^d Defined by a score of 0–1 on delayed recall of a 3-item word list or a score of 0–3 on delayed recall from a 6-item story.

Table 2 Adjusted hazard ratios for all-cause mortality according to FEV₁/FVC cut-points (N = 2406).^a

FEV ₁ /FVC models ^b	No. (%) of participants below cut-point	No. (%) of deaths among participants below cut-point	Hazard ratio for mortality (95% CI)	p-value
<.80	1941 (80.7)	693 (35.7)	1.07 (0.90, 1.28)	.440
<.75	1376 (57.2)	529 (38.4)	1.11 (0.96, 1.28)	.152
<.70	831 (34.5)	364 (43.8)	1.23 (1.03, 1.47)	.020
<.65	454 (18.9)	229 (50.4)	1.33 (1.12, 1.58)	.002
<.60	241 (10.0)	136 (56.4)	1.42 (1.15, 1.76)	.002
<.55	136 (5.6)	92 (67.6)	1.67 (1.33, 2.09)	<.001

Abbreviations: FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; CI = confidence interval; BMI = body mass index.

^a 74 participants (3.0%) had missing covariates.

^b Each FEV₁/FVC cut-point represents a separate Cox regression model, adjusted for age, age², height, sex, ethnicity, smoking history, BMI, BMI², BMI³, memory impairment, self-reported health status by time interaction, and chronic conditions. The referent group for each FEV₁/FVC cut-point is the population above the specified cut-point.

Results

As shown in Table 1, our study population had a mean age of approximately 72 years, with a majority being current or former smokers. The five most common self-reported chronic conditions were hypertension, arthritis, diabetes mellitus, myocardial infarction, and chronic obstructive pulmonary disease. About a third of the participants had fair-to-poor health status and memory impairment, respectively, and 44.4% endorsed respiratory symptoms. Over the 12-year follow-up period, 868 (35.0%) participants died, yielding a mortality rate of 4.6 per 100 person-years (95% confidence interval [CI] 4.3, 4.9).

Table 2 provides adjusted hazard ratios for all-cause mortality according to the FEV₁/FVC. An increased mortality risk was first observed at a cut-point below .70, with an

adjusted hazard ratio of 1.23 (95%CI, 1.03–1.47). Fig. 1 displays Kaplan–Meier survival curves among participants with an FEV₁/FVC < .70, stratified by FEV₁ SR-tile. Survival was notably lower for participants with an FEV₁ < 5th SR-tile. As shown in Table 3, a threshold effect for mortality was observed at an FEV₁ < 5th SR-tile, with an adjusted hazard ratio of 2.01 (95%CI, 1.60–2.54), representing 7.7% of the cohort.

Table 4 reports adjusted odds ratios for respiratory symptoms, based on FEV₁ SR-tile among participants with an FEV₁/FVC < .70 versus those with normal pulmonary function. A graded relationship was observed, with FEV₁ stages at <5th SR-tile and 5th–9th SR-tiles, respectively, demonstrating statistically significant elevations in the odds ratio. When these two stages were combined, i.e., FEV₁ < 10th SR-tile, the adjusted odds ratio for respiratory symptoms was 2.44 (95%CI, 1.79–3.33), representing 13.4% of the cohort.

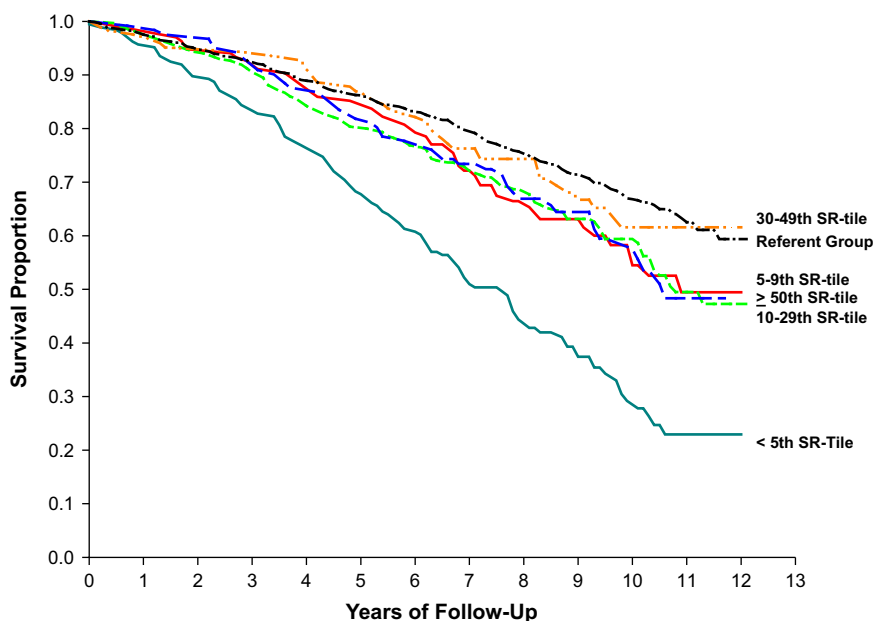


Figure 1 Kaplan–Meier survival curves in participants with airflow limitation, stratified by FEV₁ SR-tile. Airflow limitation was established by an FEV₁/FVC < .70, with severity defined by FEV₁ SR-tile. The number of participants at risk in the FEV₁ groups of <5th, 5–9th, 10–29th, 30–49th, and ≥50th SR-tiles was 179, 133, 281, 122, and 116, respectively, for a total of 831. The referent group, which included 1488 participants, had normal pulmonary function defined by an FEV₁/FVC ≥ .70 and an FVC ≥ lower limit of normal. Abbreviations: FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; SR-tile = standardized residual percentile.

Table 3 Adjusted hazard ratios for all-cause mortality according to FEV₁ SR-tile, among participants with airflow limitation versus those with normal pulmonary function (N = 2319).^a

Spirometric category	No. (%) of participants	No. (%) of deaths among participants	Hazard ratio for mortality (95% CI) ^b	p-value
Normal pulmonary function ^c	1488 (64.2)	429 (28.8)	1.00	—
Airflow limitation ^d FEV ₁ SR-tile				
≥50th	116 (5.0)	46 (39.7)	1.12 (0.80, 1.58)	.507
30th–49th	122 (5.3)	40 (32.8)	.85 (0.61, 1.19)	.332
10th–29th	281 (12.1)	114 (40.6)	1.12 (0.90, 1.40)	.291
5th–9th	133 (5.7)	53 (40.0)	1.06 (0.82, 1.39)	.636
<5th	179 (7.7)	111 (62.0)	2.01 (1.60, 2.54)	<.001

Abbreviations: FEV₁ = forced expiratory volume in 1 s; SR-tile = standardized residual percentile; FVC = forced vital capacity; CI = confidence interval; BMI = body mass index; LLN = lower limit of normal.

^a 74 participants (3.6%) had missing covariates and 87 (3.5%) were excluded because of restrictive pulmonary physiology, i.e., an FEV₁/FVC ≥ .70 and an FVC < LLN.

^b Values were calculated using a single Cox regression mortality model that was adjusted for age, age², height, sex, ethnicity, smoking history, BMI, BMI², BMI³, memory impairment, self-reported health status by time interaction, and chronic conditions.

^c Defined by an FEV₁/FVC ≥ .70 with an FVC ≥ LLN.

^d Defined by an FEV₁/FVC < .70.

Table 5 provides the mean values for the FEV₁/FVC and the prevalence of ever-smokers and reduced health status according to FEV₁ SR-tile stages among participants with an FEV₁/FVC < .70. Graded relationships were observed, with an FEV₁ < 5th SR-tile having the lowest mean value for the FEV₁/FVC and the highest prevalence of ever-smokers and reduced health status, respectively.

Table 6 provides the FEV₁ %Pred values that corresponded to the 10th and 5th SR-tiles, respectively, for a person of average height. For each of these SR-tile cut-points, the %Pred values varied considerably based on age, ethnicity, and sex. For example, a 65-year old male of average height had an

FEV₁ value at the 5th SR-tile that ranged from 51%Pred in African-Americans to 69%Pred in white Americans.

Discussion

In a large, nationally representative sample of community-living persons aged 65–80 years, we found that a two-part spirometric definition of COPD that includes an FEV₁/FVC < .70, with FEV₁ cut-points at the 10th and 5th SR-tiles, identifies individuals with an increased prevalence of respiratory symptoms and an increased risk of death, respectively.

Table 4 Adjusted odds ratios for respiratory symptoms according to FEV₁ SR-tile, among participants with airflow limitation versus those with normal pulmonary function (N = 2313).^a

Spirometric category	No. (%) of participants	No. (%) of participants with respiratory symptoms	Respiratory symptoms versus no symptoms ^b	
			Odds Ratio (95% CI) ^c	p-value
Normal pulmonary function ^d	1483 (64.1)	614 (41.4)	1.00	—
Airflow limitation ^e FEV ₁ SR-tile				
≥50th	116 (5.0)	46 (39.7)	1.09 (0.78, 1.51)	.600
30th–49th	122 (5.3)	42 (34.4)	.89 (0.62, 1.29)	.544
10th–29th	281 (12.2)	124 (44.1)	1.24 (0.96, 1.59)	.094
5th–9th	132 (5.7)	78 (59.1)	2.14 (1.45, 3.17)	<.001
<5th	179 (7.7)	123 (68.7)	2.71 (1.91, 3.86)	<.001

Abbreviations: FEV₁ = forced expiratory volume in 1 s; SR-tile = standardized residual percentile; FVC = forced vital capacity; CI = confidence interval; BMI = body mass index; LLN = lower limit of normal.

^a 80 participants (3.2%) had missing covariates and 87 (3.5%) were excluded because of restrictive pulmonary physiology, i.e., an FEV₁/FVC ≥ .70 and an FVC < LLN.

^b 1027 participants had respiratory symptoms (i.e., cough or sputum production, wheezing, or dyspnea), while 1286 had none.

^c Values were calculated using a single logistic regression model that was adjusted for age, age², height, sex, ethnicity, smoking history, BMI, memory impairment, self-reported health status, and chronic conditions.

^d Defined by an FEV₁/FVC ≥ .70 with an FVC ≥ LLN.

^e Defined by an FEV₁/FVC < .70.

Table 5 Mean FEV₁/FVC values and prevalence of ever-smokers and reduced health status among participants with normal pulmonary function and airflow limitation, staged according to FEV₁ SR-tile.

Spirometric category	No. (%)	Mean FEV ₁ /FVC	No. (%) of ever-smokers among participants	No. (%) of participants with reduced health status ^a
Normal pulmonary function ^b	1488 (64.2)	.78	686 (46.1)	496 (33.3)
Airflow limitation ^c FEV ₁ SR-tile				
≥50th	116 (5.0)	.67	62 (53.4)	31 (26.7)
30th–49th	122 (5.3)	.66	87 (71.3)	23 (18.8)
10th–29th	281 (12.1)	.63	201 (71.5)	80 (28.5)
5th–9th	133 (5.7)	.60	107 (80.4)	46 (34.6)
<5th	179 (7.7)	.54	147 (82.1)	74 (41.3)

^a Based on self-report of fair-to-poor health status.

^b Defined by an FEV₁/FVC ≥ .70 with an FVC ≥ LLN.

^c Defined by an FEV₁/FVC < 0.70.

Our strategy for defining COPD has a strong clinical and physiological basis. First, we have established spirometric cut-points that are associated with important clinical measures.²⁵ All-cause mortality is considered the most definitive health outcome, and was the primary endpoint in landmark studies of oxygen therapy in COPD.²⁵ In addition, respiratory symptoms are the most common and distressing feature of COPD.²⁵ Second, we have evaluated the FEV₁ as an SR-tile rather than %Pred.^{4,9,13} Because it does not consider the spread of the reference data, reporting the FEV₁ as %Pred incorrectly assumes that a given value is equivalent for persons of different age, height, sex, and ethnicity.^{16,17} The SR-tile method yields, however, a value that is applicable to all persons because it considers the spread of the reference data.^{16,17} To illustrate, for an NHANES III participant of average height, we found that FEV₁ values at the 5th SR-tile varied from 51%Pred to 77%Pred, depending on the ethnicity, sex, and age of the individual; see Table 6. In contrast to our proposed strategy, current guidelines for COPD recommend spirometric cut-points that have not been clinically validated among older persons, and report the FEV₁ as %Pred.^{4,9,13}

Our results also help to clarify the best approach for establishing a critical threshold for the FEV₁/FVC ratio, as

part of a spirometric definition of COPD. We found that a fixed-ratio at a threshold of .70 is associated with an increased risk of death, which is consistent with GOLD guidelines.⁴ Among persons with an FEV₁/FVC ratio below this critical threshold, we established COPD—in contrast to GOLD and other spirometric guidelines^{4,9,13}—on the basis of FEV₁ SR-tile cut-points that were defined by mortality risk and the prevalence of respiratory symptoms. Using this strategy, 7.7% of our study population had a severe form of COPD, defined by an FEV₁/FVC < .70 and an FEV₁ < 5th SR-tile, which conferred an increased risk of death and an increased prevalence of respiratory symptoms. This subgroup also had the highest prevalence of smoking exposure and reduced health status, and the lowest mean value for the FEV₁/FVC. Participants with an FEV₁/FVC < .70 and an FEV₁ at the 5th–9th SR-tiles, representing 5.7% of the study population, had a milder form of COPD, which conferred an increased prevalence of respiratory symptoms but not an increased risk of death. This subgroup had the second highest prevalence of smoking exposure and reduced health status, and the second lowest mean value for the FEV₁/FVC.

Because neither the risk of death nor prevalence of respiratory symptoms was elevated, we would argue that

Table 6 FEV₁ %Pred values corresponding to the 10th and 5th SR-tiles, stratified according to ethnicity, sex, and age, in an individual of average height.^a

FEV ₁ SR-tile cut-points	FEV ₁ %Pred values											
	White				African-American				Mexican-American			
	Male		Female		Male ^b		Female		Male ^b		Female	
	65 years	80 years	65 years	80 years	65 years	80 years	65 years	80 years	65 years	80 years	65 years	80 years
10th	79	73	79	73	70	70	80	72	80	80	72	71
5th	69	61	74	67	51	51	77	68	59	59	69	67

FEV₁ = forced expiratory volume in 1 s; %Pred = percent predicted, calculated as [(measured/predicted) × 100]; SR-tile = standardized residual percentile, calculated as (measured – predicted)/residual standard deviation.

^a The FEV₁ predicted values were calculated from sex- and ethnic-specific regression equations – see appendix; while measured values were calculated from the SR-tile equation.

^b Does not vary by age because the regression equations for African-American and Mexican-American males do not include an age term (age was not a significant predictor variable).

participants with an $FEV_1/FVC < .70$ but an $FEV_1 \geq 10$ th SR-tile have airflow limitation, but not COPD. Although longitudinal studies are needed, this latter group may be heterogeneous, including persons who simply have normal age-related increases in airflow limitation and those who will experience declines in pulmonary function over time (i.e., transition to COPD).²⁶

As compared with current guidelines,^{4,9,13} our two-part spirometric definition posits that a reduced FEV_1/FVC , although necessary for defining airflow limitation, is insufficient to establish a diagnosis of COPD. Developmentally, after achieving peak pulmonary function at about 20 years of age, airflow limitation increases with age,²⁷ principally due to increasing rigidity of the chest wall and decreasing elastic recoil of the lung.³⁵ Although COPD is also characterized by airflow limitation, this effect is due to small airways' disease and parenchymal destruction.^{4,36} Consequently, a reduced FEV_1/FVC as a measure of airflow limitation can be caused by normal aging and/or clinically-significant pathology.^{7,8} To make this distinction, it is necessary to consider the FEV_1 because it is associated with COPD-related airway inflammation in persons with established airflow limitation.³⁶ Consequently, among older persons, our spirometric strategy likely reduces potential misclassification of COPD, as evidenced by an overall prevalence (13.4%) that is more clinically realistic than that generated by GOLD guidelines (34.5%).

If routinely implemented, our spirometric strategy for defining COPD could lead to improvements in patient care. For example, with GOLD guidelines, exercise intolerance in an older patient who has coexisting cardiopulmonary risk factors, anemia, and a history of physical inactivity might be attributed primarily to COPD instead of to one or more of the patient's comorbid conditions. Because cut-points are based on clinical measures relevant to COPD, our spirometric strategy could lead to a more targeted use of COPD-specific pharmacotherapy and, as a result, reduce the frequency of medication-related adverse events.¹⁸

We recognize potential limitations to our study. First, a threshold based on the LLN for the FEV_1/FVC could not be reliably determined. Unlike the FEV_1 and FVC, regression equations for the FEV_1/FVC lack explanatory ability in older persons. This may be attributable to age-related increases in lung function variability, leading to normal values for the FEV_1/FVC that range widely and are significantly skewed – in comparison to the FEV_1 and FVC alone.²⁷ Moreover, because prior work has shown that elderly persons with an $FEV_1/FVC < .70$ but $>LLN$ have an increased risk of death,⁸ the clinical validity of the LLN is uncertain. Our inability to calculate the LLN of the FEV_1/FVC likely had little effect on our estimate of COPD prevalence, since our strategy relies ultimately on the FEV_1 SR-tile to establish a diagnosis.

Second, the cut-points that we identified for the FEV_1/FVC and FEV_1 SR-tile were based on a single cohort of older persons. Further validation of these cut-points, with an expanded array of clinically relevant outcomes (including health care utilization), will be required in other cohorts of older persons, as well as in other age groups.

Third, evaluating an outcome based on all-cause mortality rather than COPD-specific mortality might be considered a limitation. Prior work has shown, however,

that COPD is commonly underreported as a cause of death, even among patients with symptomatic COPD.²⁸ Furthermore, COPD increases the risk of death from cardiovascular disease and lung cancer, and the number of deaths from these causes is much greater than those from respiratory disease among patients with COPD.^{28–30}

Fourth, our spirometric definition of mild COPD is based on the presence of respiratory symptoms, which are not necessarily specific to COPD.³⁷ Nonetheless, respiratory symptoms are the most distressing feature of COPD and can lead to disability and increased healthcare utilization.^{25,37} In addition, the graded relationship observed for the presence of respiratory symptoms across the FEV_1 SR-tile stages (Table 4) enhances the validity of our spirometric definition of COPD.

Finally, because spirometry in NHANES III was not obtained after a bronchodilator, we could not assess reversibility, a recommended criterion for defining COPD.⁴ It is unlikely, however, that the absence of information on “reversibility” had a meaningful effect on our results, because 1) persons with self-reported asthma were excluded, 2) prior work has shown that only 3% of abnormal prebronchodilator FEV_1/FVC ratios normalize in response to a bronchodilator,^{31,32} and 3) bronchodilator reversibility, as defined by the FEV_1 response, is neither a sufficient criterion to exclude COPD nor an independent predictor of mortality.^{33,34} Nevertheless, we acknowledge that our spirometric analyses may have included a small number of participants with asthma, either as a sole form of obstructive airways disease or comorbidity.

In conclusion, among older persons, we are proposing a revised spirometric definition of COPD that identifies individuals with an increased prevalence of respiratory symptoms and an increased risk of death. If confirmed in other populations of older persons, this definition of COPD could lead to improvements in patient care.

Conflict of interest

The investigators retained full independence in the conduct of this research and report no conflicts of interest.

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Appendix Multiple regression models for spirometric measures in "healthy" NHANES III participants aged 65–80 years.^{a,b}

Ethnicity/sex	N	Spirometric measure	Intercept _{PRD}	Intercept _{LLN}	Age	Age ²	Height	Height ²	RSD	R ²
White Males	112	FEV ₁	3.0439	2.9736	-.0444	—	.0548	—	.5299	.42
		FVC	4.1667	4.0716	-.0439	—	.0750	—	.6421	.45
White Females	215	FEV ₁	2.0299	1.9934	-.0314	—	.0228	—	.3501	.28
		FVC	2.6875	2.6406	-.0361	—	.0369	—	.4840	.28
African-American Males	33	FEV ₁	2.5797	2.3653	—	—	.0484	—	.6396	.14
		FVC	3.4461	3.1946	—	—	.0712	—	.8032	.18
African-American Females	75	FEV ₁	1.7095	1.6558	-.0384	—	.0348	—	.3156	.42
		FVC	2.2253	2.1493	-.0447	—	.0459	—	.4067	.41
Mexican-American Males	32	FEV ₁	2.8544	2.6667	—	—	.0336	—	.5302	.15
		FVC	3.8422	3.6331	—	—	.0571	—	.6374	.26
Mexican-American Females	85	FEV ₁	1.8013	1.7271	-.0322	.0052	.0329	—	.3620	.31
		FVC	2.4082	2.3044	-.0323	.0067	.0448	-.0011	.4652	.33

Abbreviations: NHANES III = The third national health and nutrition examination survey; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; Intercept_{PRD} = predicted intercept; Intercept_{LLN} = lower limit of normal for the intercept (i.e., intercept_{PRD} - [1.645 × standard error of the intercept_{PRD}]); Age = years; height = cm; RSD = standard deviation of the residual; R² = the explained variation; — = represent effects that were not statistically significant at the .05 level (all other listed effects were significant at $p < .05$).

^a "Healthy" included never-smokers, with no chronic conditions and no respiratory symptoms.

^b To enhance interpretability, the predictor variables of age and height were centered, i.e., for each participant the mean spirometric value was subtracted from the measured value.

References

- Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007;**30**:993–1013.
- West JB. *Pulmonary pathophysiology: the essentials*. 6th ed. Baltimore: Lippincott Williams and Wilkins; 2003.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–38.
- GOLD executive summary. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;**176**:532–55.
- Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the third national health and nutrition examination survey. *Am J Med* 2005;**118**:1364–72.
- Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. *Eur Respir J* 2003;**22**:268–73.
- Hansen JF, Sun X-G, Wasserman K. Spirometric criteria for airway obstruction. *Chest* 2007;**131**:349–55.
- Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax* 2007;**62**:237–41.
- Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;**26**:948–68.
- Sin DD, Jones RL, Mannino DM, Man SFP. Forced expiratory volume in 1 second and physical activity in the general population. *Am J Med* 2004;**117**:270–3.
- Sutherland ER, Cherniak RM. Management of chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:2689–97.
- Peto R, Speizer FE, Cochrane AL, et al. The relevance in adults of airflow obstruction, but not of mucous hypersecretion, to mortality from chronic lung disease. *Am Rev Respir Dis* 1983;**128**:491–500.
- Qaseem A, Snow V, Shekelle P, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2007;**147**:633–8.
- Garcia-Rio F, Pino JM, Dorgham A, Alonso A, Villamor J. Spirometric reference equation for European females and males aged 65–85 years. *Eur Respir J* 2004;**24**:397–405.
- Enright PL, Kronmal RA, Higgins M, Schenker M, Haponik EF. Spirometry reference values for women and men 65–85 years of age: cardiovascular health study. *Am Rev Respir Dis* 1993;**147**:125–33.
- Miller MR, Pincocock AC. Predicted values: how should we use them? *Thorax* 1988;**43**:265–7.
- Official statement of the European Respiratory Society. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests European community for steel and coal. *Eur Respir J* 1993;**6**(S16): 5–40.
- Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008;**300**:1439–50.
- Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. *JAMA* 2002;**288**:1889–97.
- U.S. Department of Health and Human Services. National center for health statistics. In: *Third national health and nutrition examination survey, 1988–94, NHANES III laboratory data file (CD-ROM), public use data file documentation number 76200*. Hyattsville, Maryland: Centers for Disease Control and Prevention; 1996. Available from National Technical Information Service, Springfield, VA.
- Wheatcroft G, Cox CS, Lochner KA. *Comparative analysis of the NHANES III public-use and restricted-use linked mortality files*. Hyattsville, Maryland: National Center for Health Statistics, http://www.cdc.gov/nchs/data/datalinkage/h3_mort_compare_2007_final.pdf; 2007.
- American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. American thoracic society. *Am Rev Respir Dis* 1991;**144**: 1202–18.
- Research Triangle Institute. *SUDAAN language manual, release 9.0*. Research Triangle Park, NC: Research Triangle Institute; 2004.
- Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995;**48**:1503–10.

25. Gross NJ. Chronic obstructive pulmonary disease outcome measurements. *Proc Am Thorac Soc* 2005;**2**:267–71.
26. Burrows B, Knudson RJ, Camilli AE, Lyle SK, Lebowitz MD. The "horse-racing effect" and predicting decline in forced expiratory volume in one second from screening spirometry. *Am Rev Respir Dis* 1987;**135**:788–93.
27. Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages. *Am J Respir Crit Care Med* 2008;**177**:253–60.
28. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005;**128**:2640–6.
29. Nishimura K, Tsukino M. Clinical course and prognosis of patients with chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2000;**6**:127–32.
30. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality. *Ann Intern Med* 2005;**142**:233–9.
31. Johannessen A, Omenaas, Bakke PS, Gulsvik A. Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. *Thorax* 2005;**60**:842–7.
32. Zhong N, Wang C, Yao W, et al. Prevalence of chronic obstructive pulmonary disease in China. *Am J Respir Crit Care Med* 2007;**176**:753–60.
33. Vestbo J, Hansen EF. Airway hyperresponsiveness and COPD mortality. *Thorax* 2001;**56**(Suppl. 2):11–4.
34. Hansen EF, Vestbo J. Bronchodilator reversibility in COPD. *Eur Respir J* 2005;**26**:6–7.
35. Meyer KC. Aging. *Proc Am Thorac Soc* 2005;**2**:433–9.
36. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004;**364**:709–21.
37. Cherry DK, Burt CW, Woodwell DA. National ambulatory medical care survey: 1999 summary. *Advanced Data from Vital and Health Statistics (CDC)* 2001;**322**:1–36.