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Chronic obstructive pulmonary disease in older persons: A comparison of two spirometric definitions

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Summary
Background: Among older persons, we previously endorsed a two-step spirometric definition of chronic obstructive pulmonary disease (COPD) that requires a ratio of forced expiratory volume in 1 sec to forced vital capacity (FEV_1/FVC) below .70, and an FEV_1 below the 5th or 10th standardized residual percentile (''SR-tile strategy'').
Objective: To evaluate the clinical validity of an SR-tile strategy, compared to a current definition of COPD, as published by the Global Initiative for Obstructive Lung Disease (GOLD-COPD), in older persons.
Methods: We assessed national data from 2480 persons aged 65–80 years. In separate analyses, we evaluated the association of an SR-tile strategy with mortality and respiratory symptoms, relative to GOLD-COPD. As per convention, GOLD-COPD was defined solely by an $FEV_1/FVC < .70$, with severity staged according to FEV_1 cut-points at 80 and 50 percent predicted (%Pred).
Results: Among 831 participants with GOLD-COPD, the risk of death was elevated only in 179 (21.5%) of those who also had an $FEV_1 <$ 5th SR-tile; and the odds of having respiratory symptoms were elevated only in 310 (37.4%) of those who also had an $FEV_1 <$ 10th SR-tile. In contrast, GOLD-COPD staged at an FEV_1 50–79%Pred led to misclassification (overestimation) in terms of 209 (66.4%) and 77 (24.6%) participants, respectively, not having an increased risk of death or likelihood of respiratory symptoms.

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Conclusion: Relative to an SR-tile strategy, the majority of older persons with GOLD-COPD had neither an increased risk of death nor an increased likelihood of respiratory symptoms. These results raise concerns about the clinical validity of GOLD guidelines in older persons.
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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation, defined spirometrically by a reduced ratio of forced expiratory volume in 1 sec (FEV_1) to forced vital capacity (FVC), with severity subsequently staged according to the FEV_1 expressed as percent predicted (%Pred).[1–4] In particular, the Global initiative for Obstructive Lung Disease (GOLD), a frequently cited spirometric guideline, establishes COPD based solely on an $FEV_1/FVC < .70$, with severity subsequently staged according to FEV_1 cut-points of 80, 50, and 30%Pred.[1]

Among older persons, GOLD guidelines are problematic, however, for at least three reasons. First, an FEV_1/FVC threshold of .70 cannot distinguish clinically-significant pathology from normal age-related increases in airflow limitation.[2,5] Developmentally, after achieving peak pulmonary function at about 20 years of age, airflow limitation increases with age, principally due to increasing rigidity of the chest wall and decreasing elastic recoil of the lung.[6,7] Although COPD is also characterized by airflow limitation, this effect is due to small airways disease and parenchymal destruction.[1,8] Consequently, an $FEV_1/FVC < .70$ may simply reflect airflow limitation that is due to normal aging, rather than COPD.[2,5] Second, GOLD assumes incorrectly that a given FEV_1%Pred cut-point is equivalent for all persons regardless of age, height, sex and ethnicity.[9–11] For example, a white male of average height has a value for the FEV_1 at the 5th percentile of 74%Pred at age 30 years, but only 63%Pred at age 70 years.[9] Third, GOLD guidelines have not been validated using clinically relevant measures such as mortality and respiratory symptoms.[1] Because of these limitations, GOLD may misclassify COPD in older persons and, in turn, potentially compromise patient care.[2,3,5,9–13]

To address the above limitations, we have proposed that COPD be defined by a two-step spirometric strategy that 1) determines a cut-point for the FEV_1/FVC based on mortality risk; and 2) among persons below this FEV_1/FVC threshold, determines cut-points for the FEV_1, expressed as a standardized residual percentile (SR-tile) and based on the prevalence of respiratory symptoms and mortality risk.[11] An SR-tile is simply a *Z*-score that has been converted to a percentile,[9–11] and is analogous to results reported for bone mineral density testing.[14] Importantly, the SR-tile method accounts for variability in age, height, sex, and ethnicity, whereas %Pred does not.[9–11] Using this approach and data from the Third National Health and Nutrition Examination Survey (NHANES III), we have shown that, among persons aged 65–80 years, defining COPD based on an $FEV_1/FVC < .70$, with FEV_1 cut-points at the 5th and 10th SR-tile, identifies individuals with an increased risk of death and prevalence of respiratory symptoms, respectively.[11]

In the current study, we evaluated the clinical validity of an SR-tile based strategy, relative to GOLD-defined COPD, using data from a large, nationally representative sample of community-living older persons, which included a large proportion of women and minorities. We postulated that GOLD guidelines would misclassify older persons who have neither an increased risk of death nor an increased prevalence of respiratory symptoms.

Methods

Study population

NHANES III is a large, nationally representative sample of Americans assembled in 1988–1994, with mortality surveillance through December 31, 2000.[15,16] Our study 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 American Thoracic Society (ATS) acceptable spirometric maneuvers.[17] As per current ATS recommendations, we did not exclude participants based on spirometric reproducibility criteria.[18]

The Yale Human Investigation Committee approved the study, granting exemption from review and subject consent because it involved existing data that was publicly available and recorded in a manner that subjects could not be identified.

Clinical measures

Participants were classified as having a respiratory symptom if they answered ''yes'' to one or more of the following four questions: ''Do you usually cough on most days for 3 consecutive months or more during the year?'', ''Do you bring up phlegm on most days for 3 consecutive months or more during the year?'', ''Have you had wheezing or whistling in your chest at any time in the past 12 months?'', or ''Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?''.

Self-reported asthma was defined by a ''yes'' response to: ''Has a doctor ever told you that you had asthma?'' Self-reported COPD was defined by a ''yes'' response to: ''Has a doctor ever told you that you had chronic bronchitis?'' or ''Has a doctor ever told you that you had emphysema?'' Current smokers were defined by a ''yes'' response to: ''Do you smoke cigarettes now?'' Former smokers were defined by a ''no'' response to: ''Do you smoke cigarettes now?'' but a ''yes'' response to: ''Have you smoked at least 100 cigarettes during your entire life?'' Never smokers were defined by ''no'' responses to both questions.

To assess health status, participants were asked, ''Would you say your health in general is excellent, very good, good, fair, or poor?'' Reduced health status was defined as a rating of ''fair-to-poor.'' To assess comorbidity, participants were asked about the presence of several chronic conditions in addition to COPD, including hypertension, diabetes, congestive heart failure, stroke, myocardial infarction, and lung cancer. Body mass index (BMI) was defined as a ratio of the measured weight in kilograms to measured height in meters-squared. Finally, memory impairment was defined as a score <2 on delayed recall of a 3-item word list or a score <4 on delayed recall from a 6-item story.[15]

Spirometry

NHANES III utilized a dry rolling seal spirometer, with each participant performing 5–8 forced vital capacity (FVC) maneuvers.[15] For predicted values, we used previously published NHANES III reference equations based on age, height, sex, and ethnicity.[11] As described earlier, an FEV_1/FVC threshold of .70 defined COPD with GOLD guidelines (i.e., GOLD-COPD),[1] but was considered only a first step in an SR-tile based definition of COPD.[11]

As proposed by GOLD, we expressed the measured FEV_1 as %Pred, calculated as (measured ÷ predicted) × 100.[1] Among participants with GOLD-COPD, we then staged the FEV_1 at 80, 50, and 30%Pred.[1] However, because only a small number of NHANES III participants had an $FEV_1 < 30$%Pred ($n = 10$), we subsequently used only the cut-points of 80 and 50%Pred to define three GOLD-COPD stages: Stage 1 ($FEV_1 \geq 80$%Pred), Stage 2 (FEV_1 50–79%Pred), and (combined) Stage 3/4 ($FEV_1 < 50$%Pred).

As per the SR-tile strategy,[11] we expressed the measured FEV_1 as a standardized residual (SR), calculated as [(measured minus predicted)/(standard deviation of the residuals)].[9–11] A ''residual'' is the difference between a measured and predicted value, and the standard deviation of the residuals is a constant that quantifies the spread of the reference data, based on age, height, sex, and ethnicity (i.e., derived from reference equations for the FEV_1).[9–11] A percentile based on the SR was then computed (SR-tile), with an easy-to-interpret scale of 0–100.[9–11] Among participants with an $FEV_1/FVC < .70$, we then established COPD based on the FEV_1, using previously validated cut-points at the 5th and 10th SR-tiles, respectively.[11]

Lastly, for our regression analyses (described below), we excluded persons with restrictive lung disease from the referent group ($FEV_1/FVC \geq .70$), based on an FVC < LLN.[19]

Primary outcome

Our primary outcome was all-cause mortality, ascertained from a public-use linked mortality file that contains information from the National Death Index, with follow-up through December 31, 2000.[16] Vital status was available on all but one participant.[16]

Statistical analysis

SUDAAN version 9.0.1 (Research Triangle Park) was used to estimate hazard ratios (from Cox proportional hazards regression) and odds ratios (from logistic regression), with a $p < .05$ (two-sided) denoting statistical significance.[20]

Among participants with an $FEV_1/FVC < .70$, we determined the independent association between FEV_1 stage and death, using Cox proportional hazards analysis. Models were adjusted for age, height, sex, ethnicity, smoking history, chronic conditions, health status, BMI, and cognition. The proportional hazards assumption was tested using interaction terms crossing the time-to-event outcome with each variable in the multivariable model. If significant at the $p < .05$ level, these interaction terms were retained in the final model. Higher order effects were tested for the continuous covariates and were included in the final models if they met the forward selection criterion of $p < .20$.[21] Participants who had not died were censored at the end of the follow-up period.

The FEV_1 stages were based, in separate analyses, on an FEV_1 at the 5th SR-tile or GOLD cut-points. The groups demarcated by these cut-points were treated as nominal categories, with the referent group including participants having normal pulmonary function, defined by an $FEV_1/FVC \geq .70$ and an FVC ≥ LLN.[19] Mortality risk was subsequently evaluated for GOLD stages stratified by FEV_1 at the 5th SR-tile. Similarly, among participants with an $FEV_1/FVC < .70$, we also evaluated the association between GOLD stages stratified by an FEV_1 at the 10th SR-tile and the presence of respiratory symptoms, by calculating odds

Table 1 Baseline characteristics of the study population.

Characteristic	$N = 2480$
Age, mean (SD), years	71.7 (4.5)
Females, No. (%)	1252 (50.5)
Ethnicity, No. (%)	
White	1497 (60.4)
African-American	517 (20.8)
Mexican-American	466 (18.8)
Education, mean (SD), years	9.7 (4.4)
Smoking status, No. (%)	
Never	1108 (44.7)
Former	1001 (40.4)
Current	371 (15.0)
Self-reported chronic conditions, No. (%)	
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[a]	199 (8.0)
Stroke	173 (7.0)
Fair-to-poor self-reported health, No. (%)	824 (33.3)
Memory impairment, No. (%)[b]	859 (34.9)

SD = standard deviation; FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; %Pred = percent predicted; LLN = lower limit of normal.

[a] Minor skin cancers are not included.

[b] A score <2 on delayed recall of a 3-item word list or a score < 4 on delayed recall from a 6-item story.

Table 2 All-cause mortality and prevalence of respiratory symptoms, according to GOLD and SR-tile cut-points.

A. All-cause mortality:				
Spirometric group	No. (%) of deaths among participants[a]			
Normal pulmonary function[b]	429/1488 (28.8)			
$FEV_1/FVC < .70$: FEV_1 stage	GOLD Stage 1 ≥80%Pred	GOLD Stage 2 50—79%Pred	GOLD Stage 3/4 <50%Pred	Total
≥5th SR-tile	163/443 (36.8)	90/209 (43.1)	0	253/652 (38.8)
<5th SR-tile	0	55/105 (52.4)	56/74 (75.7)	111/179 (62.0)
Total	163/443 (36.8)	145/314 (46.2)	56/74 (75.7)	364/831 (43.8)
B. Respiratory symptoms[c]:				
Spirometric group	No. (%) of participants with respiratory symptoms[d]			
Normal pulmonary function[b]	614/1483 (41.4)			
$FEV_1/FVC < .70$: FEV_1 Stage	GOLD Stage 1 ≥80%Pred	GOLD Stage 2 50—79%Pred	GOLD Stage 3/4 <50%Pred	Total
≥10th SR-tile	172/442 (38.9)	40/77 (52.0)	0	212/519 (40.8)
<10th SR-tile	1/1 (100)	141/236 (59.8)	59/74 (79.7)	201/311 (64.6)
Total	173/443 (39.0)	181/313 (57.8)	59/74 (79.7)	413/830 (49.8)

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; %Pred = percent predicted; SR-tile = standardized residual percentile; GOLD = Global Initiative for Obstructive Lung Disease; LLN = lower limit of normal.

[a] 74 Participants (3.6%) were excluded because of missing covariates and 87 (3.5%) were excluded because of restrictive pulmonary physiology, i.e., $FEV_1/FVC \geq .70$ and $FVC < LLN$.

[b] Defined by an $FEV_1/FVC \geq .70$ and $FVC \geq LLN$.

[c] Included cough or sputum production, wheezing, or exertional dyspnea — see Methods.

[d] 80 Participants (3.2%) were excluded because of missing covariates or missing respiratory symptoms ($n = 6$), and 87 (3.5%) were excluded because of restrictive pulmonary physiology, i.e., $FEV_1/FVC \geq .70$ and $FVC < LLN$.

ratios using logistic regression. Respiratory symptoms were evaluated as a composite measure but, to enhance the interpretation of our findings, we also evaluated the symptoms of dyspnea, wheezing, and ''bronchitis'' (i.e., cough or sputum production) separately.

Results

The baseline characteristics of our study population are shown in Table 1. The mean age was approximately 72 years. The majority of participants were current or former smokers. The five most common self-reported chronic conditions were hypertension, arthritis, diabetes mellitus, myocardial infarction, and COPD. About a third of the participants had fair-to-poor health status and memory impairment, respectively. 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 4.3, 4.9).

Table 2 provides all-cause mortality and the prevalence of respiratory symptoms among participants with normal pulmonary function versus those with an $FEV_1/FVC < .70$, stratified according to the FEV_1 as defined by GOLD and SR-tile cut-points. As shown in Panel A, the highest mortality occurred among participants who had an $FEV_1 < 50\%$Pred and <5th SR-tile. As shown in Panel B, the highest prevalence of respiratory symptoms occurred among participants who had an $FEV_1 < 50\%$Pred and <10th SR-tile.

Table 3 provides unadjusted and adjusted hazard ratios (HR) for all-cause mortality among participants with an $FEV_1/FVC < .70$, stratified according to GOLD and SR-tile cut-points, relative to a reference group with normal pulmonary function. As shown in Panel A, the unadjusted HR was significantly elevated among participants with an $FEV_1/FVC < .70$, regardless of FEV_1 cut-point. After adjustment for potential confounders, however, as shown in Panel B, the adjusted HR was significantly elevated only at an $FEV_1 <$ 5th SR-tile, regardless of GOLD staging. Consequently, of the 831 participants who had GOLD-COPD ($FEV_1/FVC < .70$), the risk of death was elevated only in 179 (21.5%) of those who also had an $FEV_1 <$ 5th SR-tile; and, of the 314 participants with GOLD-COPD Stage 2 (FEV_1 50—79%Pred), the risk of death was misclassified in 209 (66%) of those who also had an $FEV_1 \geq$5th SR-tile.

Table 4 provides unadjusted and adjusted odds ratios (OR) for having respiratory symptoms among participants with an $FEV_1/FVC < .70$, stratified to GOLD and SR-tile cut-points, relative to a reference group with normal pulmonary function. As shown in Panel A, the unadjusted odds ratios were significantly elevated among participants with an $FEV_1/FVC < .70$, regardless of FEV_1 cut-point. After adjustment for potential confounders, however, as shown in Panel B, the adjusted OR was significantly elevated only at an $FEV_1 <$ 10th SR-tile, regardless of GOLD staging. Consequently, of the 829 participants who had GOLD-COPD ($FEV_1/FVC < .70$), the odds of having respiratory symptoms was elevated only in 310 (37.4%) of those who also had an $FEV_1 <$ 10th SR-tile; and, of the 313 participants with GOLD-COPD Stage 2 (FEV_1 50—79%Pred), the likelihood of having respiratory symptoms was misclassified in 77 (24.6%) of those who also had an $FEV_1 \geq$ 10th SR-tile. Similar results were obtained when each of the respiratory symptoms was analyzed separately (data not shown).

Table 3 Unadjusted and adjusted hazard ratios for all-cause mortality, according to GOLD and SR-tile cut-points.[a]

A. Unadjusted hazard ratios:

Spirometric group	Unadjusted hazard ratio (95% CI) for mortality			
Normal pulmonary function[b]	1.00			
$FEV_1/FVC < .70$: FEV_1 Stage	GOLD Stage 1 ≥80%Pred	GOLD Stage 2 50—79%Pred	GOLD Stage 3/4 <50%Pred	Total
≥5th SR-tile	1.25 (1.04, 1.50)	1.59 (1.29, 1.96)	NA	1.35 (1.14, 1.61)
<5th SR-tile	NA	2.27 (1.83, 2.81)	3.94 (3.08, 5.03)	2.85 (2.36, 3.45)
Total	1.25 (1.04, 1.50)	1.81 (1.51, 2.16)	3.93 (3.08,5.02)	1.62 (1.37, 1.91)

B. Adjusted hazard ratios:

Spirometric group	Adjusted hazard ratio (95% CI) for mortality[c]			
Normal pulmonary function[b]	1.00			
$FEV_1/FVC < .70$: FEV_1 Stage	GOLD Stage 1 ≥80%Pred	GOLD Stage 2 50—79%Pred	GOLD Stage 3/4 <50%Pred	Total
≥5th SR-tile	1.03 (0.85, 1.26) $n = 443$	1.11 (0.91, 1.36) $n = 209$	NA $n = 0$	1.06 (0.89, 1.25) $n = 652$
<5th SR-tile	NA $n = 0$	1.83 (1.41, 2.37) $n = 105$	2.24 (1.65, 3.04) $n = 74$	2.01 (1.60, 2.54) $n = 179$
Total	1.04 (0.85, 1.27) $n = 443$	1.31 (1.08, 1.59) $n = 314$	2.24 (1.65, 3.03) $n = 74$	1.24 (1.04, 1.47) $n = 831$

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; %Pred = percent predicted; SR-tile = standardized residual percentile; GOLD = Global Initiative for Obstructive Lung Disease; LLN = lower limit of normal; CI = confidence interval; NA = not applicable.

[a] 74 Participants (3.6%) were excluded because of missing covariates and 87 (3.5%) were excluded because of restrictive pulmonary physiology, i.e., $FEV_1/FVC \geq .70$ and $FVC < LLN$.

[b] Defined by an $FEV_1/FVC \geq .70$ and $FVC \geq LLN$.

[c] Covariates included age, age^2, height, sex, ethnicity, smoking history, BMI, BMI^2, BMI^3, memory impairment, self-reported health status by time interaction, and chronic conditions. All covariates were significant at the $p \leq .05$ level, except age^2 at a p value of .196 but this was kept in the model because we used the .20 level for higher order terms.

Discussion

In a large, nationally representative sample of community-living older persons, the majority of participants with GOLD-defined COPD had neither an increased risk of death (78.5%) nor an increased prevalence of respiratory symptoms (62.5%), relative to a two-step, SR-tile based spirometric definition of COPD. In addition, the risk of death and likelihood of having respiratory symptoms were misclassified in 209 (66.4%) and 77 (24.6%) participants, respectively, who had GOLD-COPD Stage 2 (FEV_1 50—79%Pred). These results raise concerns about the clinical validity of GOLD guidelines in older persons.

Our two-step, SR-tile based spirometric strategy for defining COPD in older persons offers three major advantages over GOLD guidelines. First, unlike GOLD, we have previously established spirometric cut-points that are associated with important clinical measures.[11] All-cause mortality is an objective and definitive health outcome that is resistant to miscoding and has been the primary endpoint in landmark studies of oxygen therapy in COPD.[22] In addition, respiratory symptoms are the most distressing feature of COPD and can lead to disability and increased healthcare utilization.[22,23]

Second, we have evaluated the FEV_1 as an SR-tile rather than as %Pred, which is the practice espoused by GOLD and others.[1—4] Prior work has shown that reporting the FEV_1 as %Pred is seriously flawed, because it does not account for differences in the variability of the reference group across the lifespan.[9—11] In contrast, because it considers the spread of the reference data, the SR-tile method yields a value that is applicable to all persons.[9,10]

Third, contrary to GOLD, our spirometric strategy posits that the FEV_1/FVC, when expressed as a fixed ratio, is insufficient to establish a diagnosis of COPD. As discussed earlier, an FEV_1/FVC threshold at a ratio of .70 cannot distinguish clinically-significant pathology from normal age-related increases in airflow limitation.[2,5] To better make this distinction, it is necessary to also consider the FEV_1, because it is the primary determinant of a reduced FEV_1/FVC, is a more robust predictor of adverse outcomes (than the FEV_1/FVC), and is associated with COPD-related airway inflammation.[2,8,11,24] Nonetheless, the first step in the diagnostic sequence for establishing COPD still requires the FEV_1/FVC, because a reduced FEV_1 may be also due to restrictive lung physiology.[1,2,11]

Using our spirometric strategy and data from NHANES III, we have previously shown that 7.7% of persons aged 65—80 years had a severe form of COPD, defined by an $FEV_1/FVC < .70$ and an $FEV_1 <$ 5th SR-tile, which conferred an increased risk of death and an increased prevalence of respiratory symptoms; this subgroup had the highest prevalence of smoking exposure and reduced health status.[11] Participants with an $FEV_1/FVC < .70$ and an FEV_1 at the 5th to 9th SR-tile, representing 5.7% of the study population, had a milder form of COPD, which conferred an increased

Table 4 Unadjusted and adjusted odds ratios for having respiratory symptoms, according to GOLD and SR-tile cut-points.[a,b]

A. Unadjusted odds ratios:

Spirometric group	Unadjusted odds ratio (95% CI) for respiratory symptoms			
Normal pulmonary function[c]	1.00			
$FEV_1/FVC < .70$: FEV_1 Stage	GOLD Stage 1 ≥80%Pred	GOLD Stage 2 50–79%Pred	GOLD Stage 3/4 <50%Pred	Total
≥10th SR-tile	0.90 (0.75–1.09)	1.53 (0.96–2.45)	NA	0.98 (0.82–1.16)
<10th SR-tile	NA	2.10 (1.50–2.94)	5.57 (3.13–9.89)	2.57 (1.91–3.48)
Total	0.90 (0.75–1.09)	1.94 (1.43–2.63)	5.57 (3.13–9.89)	1.40 (1.18–1.66)

B. Adjusted odds ratios:

Spirometric group	Adjusted odds ratio (95% CI) for respiratory symptoms[d]			
Normal pulmonary function[c]	1.00			
$FEV_1/FVC < .70$: FEV_1 Stage	GOLD Stage 1 ≥80%Pred	GOLD Stage 2 50–79%Pred	GOLD Stage 3/4 <50%Pred	Total
≥10th SR-tile	1.08 (0.88–1.33) $n = 442$	1.41 (0.84–2.38) $n = 77$	NA $n = 0$	1.12 (0.92–1.35) $n = 519$
<10th SR-tile	NA $n = 1$	2.06 (1.44–2.93) $n = 236$	5.04 (2.88–8.83) $n = 74$	2.45 (1.80–3.34) $n = 310$
Total	1.08 (0.88–1.33) $n = 442$	1.88 (1.34–2.63) $n = 313$	5.05 (2.88–8.85) $n = 74$	1.48 (1.23–1.80) $n = 829$

FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; %Pred = percent predicted; SR-tile = standardized residual percentile; GOLD = Global Initiative for Obstructive Lung Disease; LLN = lower limit of normal; CI = confidence interval.

[a] Respiratory symptoms included cough or sputum production, wheezing, or exertional dyspnea – see Methods.

[b] 80 Participants (3.2%) were excluded because of missing covariates or missing respiratory symptoms ($n = 6$), and 87 (3.5%) were excluded because of restrictive pulmonary physiology, i.e., $FEV_1/FVC \geq .70$ and $FVC < LLN$. In addition, we excluded from analysis the single participant who had an $FEV_1/FVC < .70$, with an $FEV_1 \geq 80\%Pred$ but <10th SR-tile (cell size too small).

[c] Defined by an $FEV_1/FVC \geq .70$ and $FVC \geq LLN$.

[d] Covariates included age, age^2, age^3, height, sex, ethnicity, smoking history, BMI, memory impairment, self-reported health status, and chronic conditions. Of these, age^2, ethnicity, smoking, BMI, self-reported health status, and chronic conditions were significant at the $p \leq .05$ level. The non-significant variables were kept in the model to have a consistent set of predictors, as in the mortality analysis.

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.[11] Because neither the risk of death nor prevalence of respiratory symptoms was elevated, we would suggest that an $FEV_1/FVC < .70$ with an $FEV_1 \geq$ 10th SR-tile is insufficient to establish 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).[25]

The ATS and the European Respiratory Society (ERS) have recommended an alternative strategy for establishing COPD, based on the lower limit of normal (LLN) for the FEV_1/FVC, defined as the 5th percentile of the frequency distribution.[2] This strategy, however, may not be viable in older persons. Because aging is associated with an increase in the variability of pulmonary function, there is substantial scatter of the reference data, particularly for a ratio of two different spirometric measures.[6,26] Specifically, among older persons, normal values for the FEV_1/FVC range widely and are highly skewed, in comparison to the FEV_1 and FVC alone.[6,26] Consequently, a threshold based on the LLN for the FEV_1/FVC may have limited diagnostic accuracy in an older population. To illustrate, prior work has shown that elderly persons with an $FEV_1/FVC < .70$ but ≥LLN have an increased risk of death and COPD-related hospitalization.[19]

An alternative strategy for calculating the LLN of the FEV_1/FVC, which accounts for the increase in variability of pulmonary function with advancing age, has been recently proposed by Stanojevic and colleagues.[6,26] Although this approach offers promise, reference values are currently available for white persons only and the clinical validity of this approach has not yet been established in older persons.[6,26] Other investigators have reported that the BODE Index, which includes dyspnea, body mass index, 6-min walking distance, and FEV_1, is a better predictor of mortality than the FEV_1 alone, in patients with COPD. By defining COPD based solely on an $FEV_1/FVC \leq .70$ and expressing the FEV_1 as %Pred, however, the BODE Index suffers from similar limitations as GOLD.

We recognize potential limitations to our study. Because cause of death in NHANES III was based only on information from death certificates, we evaluated all-cause mortality as an outcome rather than COPD-specific mortality. Prior work has demonstrated that COPD is commonly underreported as a cause of death, even among patients with symptomatic COPD.[27] 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] Nonetheless, our findings should be validated in cohorts that include adjudicated data on cause of death.

Whether our results are applicable to middle-aged persons is uncertain, but should be the focus of future research. The variability of pulmonary function (i.e., the spread of the reference data) is less pronounced in middle-aged persons than in older persons,[6,26] which may attenuate the bias introduced by age-related changes on %Pred. Lastly, because spirometry in NHANES III was not obtained after a bronchodilator, we could not assess reversibility of airflow limitation, a recommended criterion for defining COPD.[1,2] It is unlikely, however, that the absence of information on ''reversibility'' had a meaningful effect on our results, for at least three reasons. First, prior work has shown that reversibility, when defined by an FEV_1/FVC that normalizes to $>.70$, is observed in persons who have a minimally reduced pre-bronchodilator FEV_1/FVC (i.e., mean value of .68).[31] In contrast, our spirometric definition of mild and severe COPD yielded a mean FEV_1/FVC of .60 and .54, respectively.[11] Second, reversibility as defined by the FEV_1 response is neither a sufficient criterion to exclude COPD nor an independent predictor of mortality.[32,33] Third, persons with self-reported asthma were excluded from our study population. Although asthma may have been underreported,[34] we would argue that NHANES III participants who had airflow limitation defined by an $FEV_1/FVC \leq .70$ and an FEV_1 cut-points at the 5th and 10th SR-tile, respectively, were much more likely to have had COPD than asthma given their high prevalence of smoking exposure.

In conclusion, relative to our evidence-based, two-step spirometric definition of COPD, the majority of older persons with GOLD-defined COPD had neither an increased risk of death nor an increased prevalence of respiratory symptoms. These results raise concerns about the clinical validity of GOLD guidelines in older persons.

Conflict of interest

The authors report no conflict of interest.

Author contributions

Dr. Fragoso had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors made substantial contributions to study concept and design, to data acquisition, analysis and interpretation, and to drafting the submitted article.

Role of the sponsors

The investigators retained full independence in the conduct of this research.

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