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ORIGINAL RESEARCH

Risk of All-Cause Mortality in US Adults With Preserved Ratio Impaired Spirometry: An Observational Study

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Background: Preserved ratio impaired spirometry (PRISm) is defined as forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC)≥0.70 and FEV_1<80% predicted. Previous studies have shown that individuals with PRISm may develop airflow obstruction and have an increased mortality risk. However, studies with long-term follow-up are lacking, and this topic has not been evaluated in the general population. We explored the all-cause mortality risk of individuals with PRISm in a large sample of the general population.

Methods: We used data from the National Health and Nutrition Examination Survey III and 2007–2012. Participants aged 20–79 years at baseline and who underwent spirometry were included. Normal spirometry was defined as a prebronchodilator FEV_1/FVC≥0.70 and FEV_1≥80% predicted. We used Cox proportional hazards regression models to compare all-cause mortality between the groups. We performed sensitivity analyses stratified by the lower limit of normal definition of spirometry criteria. Subgroup analyses by sex, age, smoking status, race, body mass index, level of education, poverty-to-income ratio, respiratory symptoms, and comorbidities were performed in participants with the different spirometry classifications.

Results: Overall, 24,691 participants were included, with a median follow-up time of 25.7 years. Of these, 19,969 had normal spirometry and 1,452 had PRISm. PRISm was associated with a high all-cause mortality risk (unadjusted hazard ratio [HR]=2.47, 95% confidence interval [CI]: 2.25–2.71, P<0.001; adjusted HR=1.69, 95% CI: 1.54–1.86, P<0.001) compared with normal spirometry. Sensitivity analyses and subgroup analyses showed a similar increased all-cause mortality risk in PRISm.

Conclusion: Our finding revealed that PRISm was significantly associated with increased risk of all-cause mortality in the general population compared with normal spirometry. Further research is needed to explore the intervention effect of PRISm.

Keywords: PRISm, preserved ratio with impaired spirometry, normal spirometry, all-cause mortality, symptom, comorbidity

Introduction

Preserved ratio impaired spirometry (PRISm) is defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC)≥0.70 with FEV_1<80% of the predicted value, also known as "restrictive pattern" or "unclassified" spirometry.[1–4] The reported global prevalence of PRISm ranges from 7.1% to 11% in population-based studies.[2,5–8] Previous studies have suggested that PRISm is associated with sex, body mass index (BMI), smoking status, race, and comorbidities.[2,5,6,9] Findings from other cohort studies have revealed that PRISm might be associated with the degree of airway disease, reduced total lung capacity, and emphysema.[10–12] Other studies suggest that PRISm might be associated with an increased risk of respiratory symptoms; comorbidities, such as obesity, diabetes mellitus, and cardiac disease;

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increased healthcare expenses; and increased all-cause mortality.[2,13–16] According to the latest epidemiological survey, compared with individuals with normal spirometry, those with PRISm have reduced lung functional and an increased all-cause mortality risk.[1,5,14,17–19]

PRISm is not always stable, with some longitudinal studies showing that it can transition from airflow obstruction to normal spirometry over time.[14,20,21] PRISm has been proposed as a precursor to chronic obstructive pulmonary disease (COPD).[9,22–24] Wan et al discovered that approximately 50% of people with PRISm transition to COPD after 5 years.[14] COPD is a leading cause of mortality and morbidity, and it poses a huge social and economic burden.[25–27] Therefore, it is important to understand the prevalence and mortality risks associated with abnormal spirometry of different severities.

Previous studies are limited by their short follow-up periods and the inclusion of specific populations rather than the general population.[9,14] For example, the COPDGene cohort only included individuals aged 45–80 years who were classed as former and current smokers.[8] Therefore, studies conducted in the general multi-ethnic adult population, including younger adults and non-smokers, are needed to verify previous observations.

We used data from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 2007–2012 to evaluate all-cause mortality risk in individuals with PRISm, as well as associated respiratory symptoms and comorbidities in the general population.

Methods

Study Design and Data Collection

The NHANES is a survey based on the US population. The survey uses a multistage, and probabilistic sampling technique to supply extensive information about the nutrition and health of the US population. In this study, NHANES data were gathered by household interviews, physical examinations, and laboratory tests. Additional information is available online (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). The survey was approved by the ethics review board of the National Center for Health Statistics, and all participants provided written informed consent before participation. Overall, 50,492 participants with available spirometry data were included from the NHANES III (1988–1994) and three subsequent NHANES waves (2007–2008, 2009–2010, and 2011–2012). The mortality status and follow-up time of all participants were collected from the National Death Index up to 31 December 2019.

Participants

Individuals aged 20–79 years with qualifying spirometry test results were included. In NHANES III, qualifying pulmonary function results included reproducible FEV_1 and FVC measurements with ≥2 acceptable tests. In NHANES 2007–2012, we referred to the American Thoracic Society and European Respiratory Society standards for quality-controlled spirometry and included only those with at least grade B quality.[28] Participants without available information on smoking status, follow-up time for death, and incomplete physical measurements at baseline, as well as pregnant women, were excluded. The research included 24,691 participants. Figure 1 depicts the participant selection process.

Definitions of Normal Spirometry, PRISm, and COPD

The Global Initiative for Chronic Obstructive Lung Disease criteria is postbronchodilator (FEV_1/FVC<0.70).[29] Most participants in the NHANES study lacked data on postbronchodilator spirometry, and thus we diagnosed PRISm or COPD based on prebronchodilator spirometry. We defined COPD is prebronchodilator spirometry (FEV_1/FVC<0.70). PRISm was defined as prebronchodilator spirometry FEV_1/FVC≥0.70 and FEV_1<80% of the predicted value.[2,25] Normal spirometry was defined as FEV_1/FVC≥0.70 and FEV_1≥80% of the predicted value. Percent-predicted FEV_1 and FVC were calculated according to the NHANES III value prediction formula.[30] Asthma and chronic bronchitis were obtained through questionnaires and self-reported by patients.

Covariates

Covariates, including demographic characteristics (age, sex, race, smoking status, level of education, marital status, poverty income ratio [PIR], and comorbidities), were collected by personal interviews. Physical examination parameters

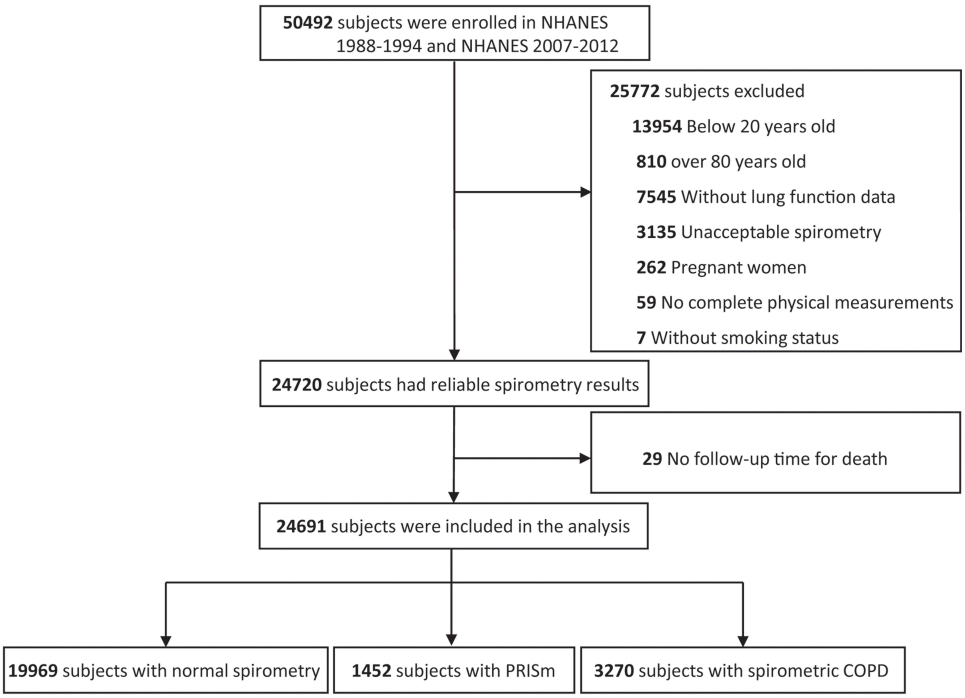

Figure 1 Study flow chart.
Abbreviations: PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease.

and spirometry were measured at mobile examination centers. In standard lung function prediction equations, the FEV_1 predictive value is influenced by age, sex, race, and hight.[25,31,32] In this study, we divided race into four categories: non-Hispanic White, non-Hispanic Black, Mexican–American, and other. BMI was classified as underweight (BMI<18.5kg/m^2), normal (18.5kg/m^2 ≤BMI<25.0kg/m^2), overweight (25.0kg/m^2 ≤BMI<30.0kg/m^2), and obese (BMI≥30.0kg/m^2). Age was classified as <50 years and ≥50 years. Smoking status was self-reported and included never smokers, former smokers, and current smokers. Never smokers were those who had not smoked 100+ cigarettes in their lifetime. Current smokers were those who had smoked 100+ cigarettes in their lifetime and who were current smokers. Former smokers were those who had smoked 100+ cigarettes in their lifetime and who were not current smokers. The PIR was divided into three categories: low income (PIR<1.30), middle income (1.30≤PIR<3.50), and high income (PIR≥3.50). Level of education was divided into <9th grade, 9th–12th grade, and >12th grade. Comorbidities included hypertension, diabetes mellitus, cancer, asthma, chronic bronchitis, and emphysema. Respiratory symptoms included chronic cough, chronic phlegm, and wheezing.

Mortality Assessment

We downloaded the mortality data from the National Death Index, with data available up to December 31 2019. The primary endpoint was all-cause mortality in the PRISm group compared with the normal spirometry group. The secondary endpoint was all-cause mortality in subgroups with PRISm compared with the corresponding normal spirometry subgroups.

Statistical Analyses

R software (version 4.2.2) and SPSS 25.0 were used to perform the statistical analyses. Two-sided P<0.05 was considered statistically significant. Categorical variables are expressed as frequencies and percentages. Continuous variables are reported as the median (interquartile range). To compare categorical variables among the groups, the chi-square test was used, while continuous variables were compared by one-way analysis of variance. The incidence of all-cause mortality was calculated during follow-up. Multivariable Cox proportional hazards regression was used to

calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) to identify differences in event-free survival between the groups. We performed an unadjusted Kaplan–Meier survival analysis to identify differences in event-free survival between the groups. Three Cox regression models were built to adjust for confounding factors. The crude model was not adjusted; Model 1 was adjusted for age, BMI, sex, and race; Model 2 was adjusted for age, sex, BMI, race, and smoking status; and Model 3 was adjusted for sex, age, BMI, race, smoking status, congestive heart failure, stroke, asthma, cancer, diabetes, and hypertension. Age and BMI were analyzed as continuous variables in Model 1, Model 2, and Model 3. To evaluate the robustness of the results, subgroup analyses were performed to compare the normal spirometry group with the PRISm group. Multiplication terms were used to test the interactions in the models that showed major effects, with stratification by baseline characteristics, sex, age, smoking status, race, BMI, level of education, and comorbidities.

Given the debate around the use of race-specific predictive equations for lung function, we performed sensitivity analyses. We used the Global Lung Function Initiative's race-neutral predictive equation for the secondary analyses.[33] We also performed sensitivity analyses stratified by age, sex, race, and BMI, and we repeated the analysis with the lower limit of normal (LLN) spirometry criteria. The normal spirometry LLN was defined as $FEV_1/FVC \geq LLN$ and $FEV_1 \geq 80\%$ of the predicted value. The PRISm LLN was defined as $FEV_1/FVC \geq LLN$ and $FEV_1 < 80\%$ of the predicted value. The spirometric COPD LLN was defined as $FEV_1/FVC < LLN$.

Patient and Public Involvement

This was a prospective cohort study, and no patients were directly involved in our study design, setting the research questions or the outcome measures. No patients were asked to advise on interpretation or writing up of the results.

Results

Baseline Characteristics of the Participants

Overall, 50,492 participants were screened. Of these, 13,954 individuals aged <20 years and 810 individuals aged ≥80 years, 7,545 without lung function data, 3,135 with unacceptable spirometry results, 262 pregnant woman, 59 without complete body measurements, 7 without information on smoking status, and 29 without information on follow-up to death were excluded. Finally, 24,691 participants were included in the analysis, with a median follow-up time of 25.7 years. There were 19,969 participants with normal spirometry, 1,452 with PRISm, and 3,270 with COPD. A flowchart of participant selection is provided in Figure 1.

The baseline characteristics of the participants are shown in Table 1. The median age was 49 years in the PRISm group, 43 years in the normal spirometry group, and 59 years in the COPD group. The median BMI was 28.0 kg/m^2 in the normal spirometry group, 30.5 kg/m^2 in the PRISm group, and 27.0 kg/m^2 in the COPD group. Age and BMI were significantly different among the three groups. Overall, 9,368 participants (46.9%) with normal spirometry, 647 (44.6%) with PRISm, and 2,001 (61.2%) with COPD were male. A higher proportion of participants in the PRISm group were current smokers than in the normal spirometry group (442/1,452 [30.4%] vs 4,701/19,969 [23.5%], P<0.001), while the proportion was lower in the PRISm group than in the COPD group. Compared with the normal spirometry group, the median FEV_1 and FVC were lower in the PRISm group (FEV_1: 2.20 [1.70–2.60] L vs 3.25 [2.62–3.80] L, P<0.001; FVC: 2.83 [2.21–2.35] L vs 4.01 [3.23–4.67] L vs 2.83 [2.21–2.35] L, P<0.001).

Respiratory symptoms were more prevalent in the PRISm group than in the normal spirometry group, including chronic cough (147 [10.1%] vs 1,094 [5.5%], P<0.001), chronic phlegm (122 [8.4%] vs 1,094 [5.5%], P<0.001), and wheezing (321 [22.1%] vs 2,335 [11.7%], P<0.001). Hypertension was more common in the PRISm group than in the normal spirometry group (596 [41.2%] vs 4,936 [24.8%], P<0.001) and the COPD group (1,286 [39.4%], P<0.001), Diabetes mellitus was more common in the PRISm group than in the normal spirometry group (258 [17.8%] vs 1,466 [7.3%], P<0.001) and COPD group (368 [14.1%], P<0.001). The prevalence of cancer, asthma, chronic bronchitis, and emphysema was higher in the PRISm group than in the normal spirometry group, while it was lower than in the COPD group.

Table 1 Baseline Clinical Characteristics of Participants With Different Spirometry Classifications

Characteristic	Normal Spirometry (N=19969)	PRISm (N=1452)	P value*	Spirometric COPD (N=3270)	P value†
Age, years	43 (30–55)	49 (37–63)	<0.001	59 (52–73)	<0.001
Male sex, n (%)	9368 (46.9)	647 (44.6)	<0.001	2001 (61.2)	<0.001
Body mass index, kg/m^2	28.0 (23.7–31.1)	30.5 (24.9–34.4)	<0.001	27.0 (23.0–30.4)	<0.001
Race, n (%)			<0.001		<0.001
Non-Hispanic white	7695 (38.5)	654 (45.0)		1968 (60.2)	
Non-Hispanic black	4944 (24.8)	465 (32.0)		682 (20.9)	
Mexican-American	4928 (24.7)	249 (17.1)		394 (12.0)	
Other	2402 (12.0)	84 (5.80)		226 (8.30)	
Smoking status, n (%)			<0.001		<0.001
Never smoker	11025 (55.2)	664 (45.7)		897 (27.4)	
Current smoker	4701 (23.5)	442 (30.4)		1208 (36.9)	
Former smoker	4243 (21.2)	346 (23.8)		1165 (35.6)	
Education Level, n (%)			<0.001		<0.001
Less than 9th grade	2833 (14.2)	235 (16.3)		633 (19.4)	
9th–12th grade	8535 (42.9)	729 (50.4)		1473 (45.2)	
Above 12th grade	8533 (42.9)	482 (33.3)		1152 (35.4)	
Poverty income ratio, n (%)			<0.001		<0.001
Low-income (PIR<1.30)	5584 (30.5)	513 (38.3)		862 (28.8)	
Middle-income (1.30≤PIR<3.50)	7471 (40.8)	519 (38.8)		1236 (41.2)	
High-income (PIR≥3.50)	5256 (28.7)	307 (22.9)		899 (30.0)	
Respiratory symptoms, n (%)					
Chronic cough	1094 (5.5)	147 (10.1)	<0.001	485 (14.8)	<0.001
Chronic phlegm	1094 (5.5)	122 (8.4)	<0.001	469 (14.3)	<0.001
Wheezing	2335 (11.7)	321 (22.1)	<0.001	848 (25.9)	<0.001
Pre-bronchodilator spirometry					
FEV_1, L	3.25 (2.62–3.80)	2.20 (1.70–2.60)	<0.001	2.38 (1.71–2.88)	<0.001
FVC, L	4.01 (3.23–4.67)	2.83 (2.21–3.35)	<0.001	3.76 (2.82–4.45)	<0.001
FEV_1/FVC, %	81.2 (77.0–85.0)	78.1 (73.0–82.0)	<0.001	62.8 (60.0–68.0)	<0.001
Comorbidity, n (%)					
Hypertension	4936 (24.8)	596 (41.2)	<0.001	1286 (39.4)	<0.001
Diabetes	1466 (7.3)	258 (17.8)	<0.001	368 (14.1)	<0.001
Cancer	1004 (5.0)	132 (9.1)	<0.001	459 (14.0)	0.524
Asthma	1667 (8.4)	220 (15.2)	<0.001	597 (18.3)	<0.001
Chronic bronchitis	774 (3.9)	120 (8.3)	<0.001	362 (11.1)	<0.001
Emphysema	90 (0.5)	26 (1.8)	<0.001	218 (6.7)	<0.001

Notes: * Comparison of differences between participants with normal spirometry and participants with PRISm. † Comparison of differences between participants with PRISm and patients with COPD.

Abbreviations: COPD, chronic obstructive pulmonary disease; PRISm, preserved ratio impaired spirometry; PIR, poverty income ratio; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

All-Cause Mortality

Over the median 25.7-year follow-up period, of the 24,691 participants included in the mortality analysis, 5,611 (22.7%) died, including 3,515 participants (17.6%) with normal spirometry, 515 (35.5%) with PRISm, and 1,581 (48.3%) with COPD. The PRISm group had an unadjusted all-cause mortality rate that was intermediate between that of the normal spirometry group and the COPD group (Figure 2). The Kaplan–Meier curves showed a statistically significant difference among the three groups (log-rank P<0.001 for the comparison between the normal spirometry and PRISm groups; P<0.001 for the comparison between the normal spirometry group and the COPD group).

Table 2 shows the HR and 95% CI for mortality of the participants with different spirometry classifications. Participants with PRISm had a higher all-cause mortality risk than those with normal spirometry in the unadjusted model. These associations remained significant after adjustment for sex, age, BMI, and race (Model 1: HR 1.81, 95% CI 1.65–1.99, P<0.001 for the

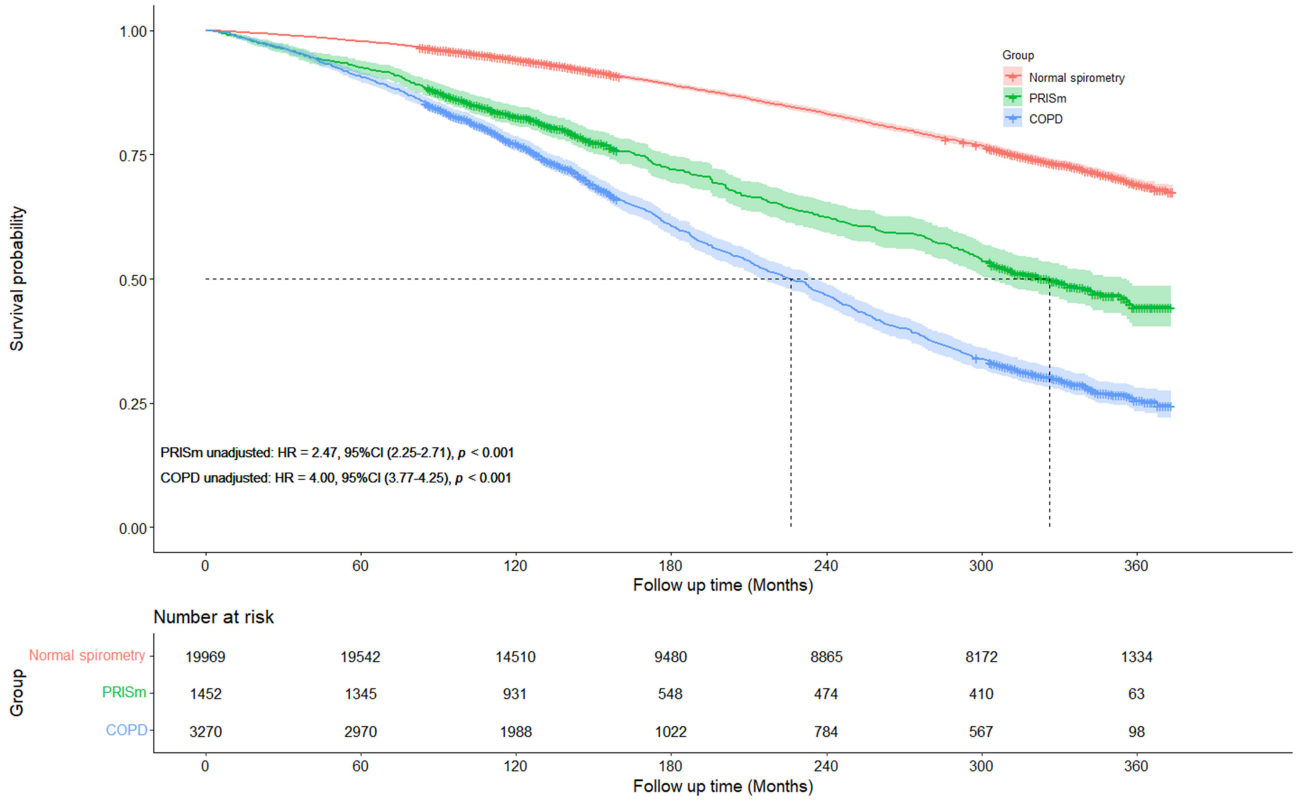

Figure 2 Risk of all-cause mortality for participants with different spirometry classifications.
Abbreviations: PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

comparison between the normal spirometry and PRISm groups; HR 1.51, 95% CI 1.42–1.61, P<0.001 for the comparison between the normal spirometry and COPD groups). These associations also remained significant after adjustment for sex, age, BMI, race, and smoking status (Model 2: HR 1.69, 95% CI 1.54–1.86, P<0.001 for the comparison between the normal spirometry and PRISm groups; HR 1.34, 95% CI 1.26–1.43, P<0.001 for the comparison between the normal spirometry and COPD groups) and after adjustment for sex, age, body mass index, race, smoking status, congestive heart failure, stroke, asthma, cancer, diabetes, and hypertension (Model 3: HR 1.60, 95% CI: 1.46–1.76, P<0.001 for the comparison between the normal spirometry and PRISm groups; HR 1.34, 95% CI 1.25–1.43, P<0.001 for the comparison between the normal spirometry and COPD groups).

Sensitivity Analysis

When the LLN criteria were used to define these spirometry categories, the results of the primary outcome of all-cause mortality risk were consistent with the results produced with the fixed-threshold criteria. Both in sensitivity analysis Model 1 (adjusted HR 1.78, 95% CI 1.64–1.93, P<0.001), sensitivity analysis Model 2 (adjusted HR 1.66, 95% CI 1.53–1.80, P<0.001), and sensitivity analysis Model 3 (adjusted HR 1.57, 95% CI 1.45–1.71, P<0.001), we observed a higher all-cause mortality risk in the PRISm group than in the normal spirometry group.

Subgroup Analysis

In the subgroup analysis, compared with the normal spirometry group, the PRISm group had a significantly higher risk of most of the study outcomes, with the exception of BMI. In the subgroup analysis of the PRISm group, the characteristic of being underweight was no longer a risk factor for increased mortality compared with the normal spirometry group (unadjusted HR 1.86, 95% CI 0.92–3.74, P=0.084; adjusted HR 1.23, 95% CI 0.60–2.53, P=0.581). Individuals with PRISm in most subgroups had a higher all-cause mortality risk than individuals with normal spirometry. In the multivariable models adjusted for sex, age, BMI, race, and smoking status, the PRISm group consistently had a higher all-cause mortality risk than the normal spirometry group. The absolute risks and risk differences for each outcome in the PRISm, normal spirometry, and COPD spirometry groups are

Table 2 Hazard Ratios and 95% Confidence Intervals for Mortality in Participants With Different Spirometry Classifications

Classification	No. of Participants	No. of Deaths	Crude Model		Model 1*		Model 2†		Model 3‡	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Main analysis§										
Normal spirometry	19969	3515 (17.6%)	Reference		Reference		Reference		Reference	
PRISm	1452	515 (35.5%)	2.47 (2.25–2.71)	<0.001	1.81 (1.65–1.99)	<0.001	1.69 (1.54–1.86)	<0.001	1.60 (1.46–1.76)	<0.001
Spirometric COPD	3270	1581 (48.3%)	4.00 (3.77–4.25)	<0.001	1.51 (1.42–1.61)	<0.001	1.34 (1.26–1.43)	<0.001	1.34 (1.25–1.43)	<0.001
Sensitivity analysis¶										
Normal spirometry	20336	3938 (19.4%)	Reference		Reference		Reference			
PRISm	1647	681 (41.3%)	2.80 (2.58–3.04)	<0.001	1.78 (1.64–1.93)	<0.001	1.66 (1.53–1.80)	<0.001	1.57 (1.45–1.71)	<0.001
Spirometric COPD	2708	1012 (37.3%)	2.38 (2.22–2.55)	<0.001	1.66 (1.55–1.78)	<0.001	1.42 (1.32–1.53)	<0.001	1.42 (1.32–1.53)	<0.001

Notes: * Model 1: Adjusted covariates for model 1 included sex, age, body mass index, and race. † Model 2: Adjusted covariates for model 2 included sex, age, body mass index, race, and smoking status. ‡ Model 3: Adjusted covariates for model 2 included sex, age, body mass index, race, smoking status, congestive heart failure, stroke, asthma, cancer, diabetes, and hypertension. § Normal spirometry was defined as $FEV_1/FVC \geq 0.70$ and $FEV_1 \geq 80\%$ predicted value. PRISm was defined as was defined as $FEV_1/FVC \geq 0.70$ and $FEV_1 < 80\%$ predicted value. Spirometric COPD was defined as $FEV_1/FVC < 0.70$. ¶ Normal spirometry was defined as $FEV_1/FVC \geq$ LLN and $FEV_1 \geq 80\%$ predicted value. PRISm was defined as was defined as $FEV_1/FVC \geq$ LLN and $FEV_1 < 80\%$ predicted value. Spirometric COPD was defined as $FEV_1/FVC <$ LLN.

Abbreviations: PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; LLN, lower limit of normal.

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shown in Table 3. The magnitude of the association between PRISm all-cause mortality was higher risk compared normal spirometry.

Table 4 shows the proportional hazards model for mortality in the subgroups with and without comorbidities. Compared with the normal spirometry group, the PRISm groups with hypertension, diabetes mellitus, cancer, asthma, chronic bronchitis, and emphysema as comorbidities had higher relative risks of all-cause mortality. These associations were similar in the participants without comorbidities. The PRISm group had a higher relative risk of all-cause mortality than the normal spirometry group.

Table 3 Proportional Hazards Model for Death in Subgroup

Subgroup	No. of Participants	No. of Deaths	Univariate Models		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Male Sex	12016	3020				
Normal spirometry	9368	1799	Reference		Reference	
PRISm	647	231	2.38 (2.08–2.74)	<0.001	1.79 (1.56–2.05)	<0.001
Spirometric COPD	2001	990	3.85 (3.56–4.16)	<0.001	1.49 (1.37–1.62)	<0.001
Female Sex	12675	2611				
Normal spirometry	10601	1736	Reference		Reference	
PRISm	805	284	2.58 (2.27–2.92)	<0.001	1.71 (1.50–1.94)	<0.001
Spirometric COPD	1269	591	3.98 (3.62–4.37)	<0.001	1.32 (1.20–1.46)	<0.001
<50 years old	14998	1337				
Normal spirometry	13533	1110	Reference		Reference	
PRISm	686	108	2.05 (1.69–2.50)	<0.001	1.64 (1.34–2.00)	<0.001
Spirometric COPD	779	119	2.16 (2.47–4.04)	<0.001	1.37 (1.13–1.66)	<0.001
≥50 years old	9693	4294				
Normal spirometry	6436	2425	Reference		Reference	
PRISm	766	407	1.77 (1.59–1.96)	<0.001	1.75 (1.58–1.95)	<0.001
Spirometric COPD	2491	1462	1.96 (1.84–2.09)	<0.001	1.34 (1.25–1.44)	<0.001
Never smoker	12586	2077				
Normal spirometry	11025	1552	Reference		Reference	
PRISm	664	185	2.26 (2.07–2.88)	<0.001	1.67 (1.43–1.95)	<0.001
Spirometric COPD	897	340	3.61 (3.75–4.61)	<0.001	1.26 (1.12–1.42)	<0.001
Current smoker	6351	1701				
Normal spirometry	4701	916	Reference		Reference	
PRISm	442	166	2.44 (2.07–2.88)	<0.001	1.69 (1.43–2.00)	<0.001
Spirometric COPD	1208	619	4.16 (3.75–4.61)	<0.001	1.53 (1.36–1.72)	<0.001
Former smoker	5754	1853				
Normal spirometry	4243	1067	Reference		Reference	
PRISm	346	164	2.69 (2.28–3.17)	<0.001	1.73 (1.46–2.04)	<0.001
Spirometric COPD	1165	662	3.14 (2.84–3.47)	<0.001	1.27 (1.14–1.41)	<0.001

(*Continued*)

Table 3 (Continued).

Subgroup	No. of Participants	No. of Deaths	Univariate Models		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Non-Hispanic white	10317	2826				
Normal spirometry	7695	1565	Reference		Reference	
PRISm	654	255	2.27 (1.99–2.59)	<0.001	1.59 (1.39–1.82)	<0.001
Spirometric COPD	1968	1006	3.62 (3.34–3.92)	<0.001	1.38 (1.27–1.50)	<0.001
Non-Hispanic black	6091	1474				
Normal spirometry	4944	980	Reference		Reference	
PRISm	465	159	2.33 (1.97–2.75)	<0.001	1.70 (1.44–2.02)	<0.001
Spirometric COPD	682	335	3.80 (3.35–4.31)	<0.001	1.24 (1.09–1.43)	0.002
Mexican-American	5571	1105				
Normal spirometry	4928	830	Reference		Reference	
PRISm	249	82	2.40 (1.91–3.01)	<0.001	1.85 (1.47–2.33)	<0.001
Spirometric COPD	394	193	4.03 (3.44–4.71)	<0.001	1.25 (1.05–1.47)	0.01
Other Race	2712	226				
Normal spirometry	2402	160	Reference		Reference	
PRISm	84	19	3.68 (2.28–5.92)	<0.001	2.55 (1.58–4.13)	<0.001
Spirometric COPD	226	47	3.58 (2.58–4.95)	<0.001	1.40 (0.99–1.97)	0.056
Body mass index <18.5 kg/m^2 (underweight)	389	101				
Normal spirometry	261	36	Reference		Reference	
PRISm	42	10	1.86 (0.92–3.74)	0.084	1.23 (0.60–2.53)	0.581
Spirometric COPD	86	55	7.89 (5.13–12.08)	<0.001	1.49 (0.90–2.47)	0.123
Body mass index: 18.5–25 kg/m^2 (normal)	8188	1733				
Normal spirometry	6647	1006	Reference		Reference	
PRISm	319	111	2.78 (2.29–3.38)	<0.001	2.04 (1.67–2.48)	<0.001
Spirometric COPD	1222	616	5.22 (4.72–5.78)	<0.001	1.35 (1.20–1.50)	<0.001
Body mass index≥25–30 kg/m^2 (overweight)	8412	2018				
Normal spirometry	6834	1296	Reference		Reference	
PRISm	399	153	2.29 (1.94–2.71)	<0.001	1.49 (1.25–1.76)	<0.001
Spirometric COPD	1179	569	3.74 (3.38–4.13)	<0.001	1.29 (1.16–1.43)	<0.001
Body mass index≥30 kg/m^2 (obese)	7702	1779				
Normal spirometry	6227	1197	Reference		Reference	
PRISm	692	241	2.22 (1.94–2.55)	<0.001	1.67 (1.45–1.92)	0.004
Spirometric COPD	783	341	3.04 (2.69–3.43)	<0.001	1.27 (1.12–1.44)	<0.001

(*Continued*)

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Table 3 (Continued).

Subgroup	No. of Participants	No. of Deaths	Univariate Models		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Less than 9th grade education level	3701	1482				
Normal spirometry	2833	927	Reference		Reference	
PRISm	235	133	2.15 (1.79–2.58)	<0.001	1.50 (1.24–1.80)	<0.001
Spirometric COPD	633	422	3.13 (2.78–3.51)	<0.001	1.12 (1.02–1.32)	0.021
9th–12th grade education level	10737	2706				
Normal spirometry	8535	1679	Reference		Reference	
PRISm	729	272	2.42 (2.13–2.75)	<0.001	1.68 (1.48–1.91)	<0.001
Spirometric COPD	1473	755	4.03 (3.70–4.40)	<0.001	1.42 (1.29–1.56)	<0.001
Above 12th grade education level	10167	1414				
Normal spirometry	8533	914	Reference		Reference	
PRISm	482	106	2.52 (2.06–3.08)	<0.001	1.72 (1.40–2.11)	<0.001
Spirometric COPD	1152	394	4.37 (3.88–4.92)	<0.001	1.35 (1.19–1.54)	<0.001
Low-income (poverty income ratio<1.30)	6959	1636				
Normal spirometry	5585	1022	Reference		Reference	
PRISm	513	187	2.49 (2.13–2.91)	<0.001	1.68 (1.43–1.96)	<0.001
Spirometric COPD	862	427	4.16 (3.71–4.66)	<0.001	1.25 (3.71–4.66)	<0.001
Middle-income (1.30≤poverty income ratio<3.50)	9226	2304				
Normal spirometry	7471	1456	Reference		Reference	
PRISm	519	189	2.29 (1.97–2.66)	<0.001	1.55 (1.33–1.80)	<0.001
Spirometric COPD	1236	659	4.30 (3.92–4.72)	<0.001	1.38 (1.25–1.53)	<0.001
High-income (poverty income ratio≥3.50)	6462	1155				
Normal spirometry	5256	709	Reference		Reference	
PRISm	307	92	2.71 (2.18–3.36)	<0.001	1.90 (1.53–2.38)	<0.001
Spirometric COPD	899	354	3.75 (3.30–4.26)	<0.001	1.39 (1.21–1.59)	<0.001
Chronic cough						
Yes	1726	657				
Normal spirometry	1094	303	Reference		Reference	
PRISm	147	73	2.42 (1.82–3.12)	<0.001	2.04 (1.57–2.65)	<0.001
Spirometric COPD	485	281	3.32 (2.82–3.92)	<0.001	1.36 (1.12–1.64)	0.002
No	19352	4916				
Normal spirometry	15563	3186	Reference		Reference	
PRISm	1162	438	2.37 (2.14–2.62)	<0.001	1.64 (1.48–1.82)	<0.001
Spirometric COPD	2627	1292	3.78 (3.55–4.04)	<0.001	1.31 (1.22–1.40)	<0.001

(*Continued*)

Table 3 (Continued).

Subgroup	No. of Participants	No. of Deaths	Univariate Models		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Chronic phlegm						
Yes	1685	649				
Normal spirometry	1094	305	Reference		Reference	
PRISm	122	60	2.53 (1.92–3.34)	<0.001	2.05 (1.54–2.72)	<0.001
Spirometric COPD	469	284	3.64 (3.08–4.29)	<0.001	1.35 (1.12–1.62)	0.002
No	19389	4922				
Normal spirometry	15562	3184	Reference		Reference	
PRISm	1185	449	2.38 (2.15–2.63)	<0.001	1.66 (1.50–1.83)	<0.001
Spirometric COPD	2642	1289	3.74 (3.50–3.99)	<0.001	1.31 (1.22–1.40)	<0.001
Wheezing						
Yes	3504	1049				
Normal spirometry	2335	479	Reference		Reference	
PRISm	321	133	2.48 (2.05–3.00)	<0.001	1.70 (1.39–2.06)	0.012
Spirometric COPD	848	437	3.47 (3.05–3.96)	<0.001	1.42 (1.23–1.63)	<0.001
No	21177	4579				
Normal spirometry	17626	3055	Reference		Reference	
PRISm	1131	382	2.40 (2.16–2.67)	<0.001	1.67 (1.50–1.86)	<0.001
Spirometric COPD	2420	1142	4.07 (3.80–4.36)	<0.001	1.27 (1.19–1.38)	<0.001

Notes: * Adjusted covariates included sex, age, body mass index, race, and smoking status.
Abbreviations: PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

Table 4 Proportional Hazards Modeling of Death in Subgroup With Comorbidity and Without Comorbidity

Subgroup	No. of Participants	No. of Deaths	Univariate Model		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Hypertension						
Yes	6818	2439				
Normal spirometry	4936	1478	Reference		Reference	
PRISm	598	271	1.94 (1.70–2.20)	<0.001	1.73 (1.52–1.97)	<0.001
Spirometric COPD	1286	690	2.53 (2.31–2.77)	<0.001	1.23 (1.11–1.35)	<0.001
No	17756	3176				
Normal spirometry	14931	2046	Reference		Reference	
PRISm	851	242	2.36 (2.06–2.69)	<0.001	1.61 (1.41–1.84)	<0.001
Spirometric COPD	1974	888	4.72 (4.36–5.11)	<0.001	1.44 (1.32–1.57)	<0.001

(*Continued*)

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Table 4 (Continued).

Subgroup	No. of Participants	No. of Deaths	Univariate Model		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Diabetes						
Yes	2092	895				
Normal spirometry	1466	555	Reference		Reference	
PRISm	258	129	1.83 (1.51–2.21)	<0.001	1.64 (1.35–2.00)	<0.001
Spirometric COPD	368	211	2.54 (2.16–2.98)	<0.001	1.19 (1.00–1.41)	0.056
No	22367	4708				
Normal spirometry	18315	2962	Reference		Reference	
PRISm	1177	383	2.34 (2.10–2.60)	<0.001	1.64 (1.47–1.82)	<0.001
Spirometric COPD	2875	1363	4.25 (3.98–4.53)	<0.001	1.38 (1.29–1.48)	<0.001
Cancer						
Yes	1595	702				
Normal spirometry	1004	368	Reference		Reference	
PRISm	132	67	1.65 (1.27–2.15)	<0.001	1.91 (1.46–2.51)	<0.001
Spirometric COPD	459	267	2.25 (1.92–2.64)	<0.001	1.28 (1.08–1.52)	0.004
No	23084	4927				
Normal spirometry	18955	3165	Reference		Reference	
PRISm	1320	448	2.48 (2.25–2.74)	<0.001	1.67 (1.51–1.85)	<0.001
Spirometric COPD	2809	1314	4.02 (3.77–4.29)	<0.001	1.35 (1.26–1.45)	<0.001
Asthma						
Yes	2484	477				
Normal spirometry	1667	191	Reference		Reference	
PRISm	220	62	2.63 (1.98–3.50)	<0.001	1.63 (1.21–2.18)	0.001
Spirometric COPD	597	224	3.64 (3.00–4.41)	<0.001	1.38 (1.12–1.71)	0.003
No	22197	5153				
Normal spirometry	18296	3343	Reference		Reference	
PRISm	1232	453	2.47 (2.24–2.73)	<0.001	1.70 (1.53–1.87)	<0.001
Spirometric COPD	2269	1357	4.16 (3.90–4.43)	<0.001	1.33 (1.24–1.43)	<0.001
Chronic bronchitis						
Yes	1256	433				
Normal spirometry	774	178	Reference		Reference	
PRISm	120	52	2.47 (182–3.37)	<0.001	1.58(1.15–2.17)	0.005
Spirometric COPD	362	203	3.30 (2.70–4.04)	<0.001	1.37(1.10–1.71)	0.005

(*Continued*)

Table 4 (Continued).

Subgroup	No. of Participants	No. of Deaths	Univariate Model		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
No	23418	5194				
Normal spirometry	19186	3355	Reference		Reference	
PRISm	1331	463	2.43 (2.20–2.67)	<0.001	1.70 (1.54–1.87)	<0.001
Spirometric COPD	2901	1376	3.99 (3.74–4.25)	<0.001	1.32 (1.23–1.41)	<0.001
Emphysema						
Yes	334	228				
Normal spirometry	90	38	Reference		Reference	
PRISm	26	20	2.23 (1.29–3.83)	0.004	2.10 (1.18–3.76)	0.012
Spirometric COPD	218	170	3.24 (2.26–4.63)	<0.001	1.90 (1.31–2.77)	<0.001
No	24343	5398				
Normal spirometry	19873	3494	Reference		Reference	
PRISm	1426	495	2.43 (2.21–2.66)	<0.001	1.68 (1.53–1.85)	<0.001
Spirometric COPD	3044	1409	3.76 (3.54–4.00)	<0.001	1.28 (1.20–1.37)	<0.001

Notes: * Adjusted covariates included sex, age, body mass index, race, and smoking status.
Abbreviations: PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

Discussion

The main finding of this population-based study was that PRISm was associated with a higher risk of mortality, respiratory symptoms, and comorbidities in adults from the general US population, except in the subgroup with underweight, compared with normal spirometry.

A previous study based on the US population showed that restrictive and obstructive lung disease is a significant predictor of early mortality during long-term follow-up.[19] The study focused on the PRISm subgroup, revealing that PRISm was associated with increased mortality, a high cardiovascular burden, and early mortality.[6,9,18,34] The study also suggested that individuals with PRISm had higher absolute and relative risks of all-cause mortality, coronary heart disease-related mortality, and coronary heart disease-related events than those with obstructive pulmonary disease.[6] We found that the all-cause mortality risk was lower in individuals with PRISm than in patients with COPD, which is inconsistent with a previous study.[6] This inconsistency may suggest that PRISm is a heterogeneous condition rather than a stable phenotype, and it may be affected by geography, smoking status, BMI, age, sex, and ethnicity.[16,17]

The high prevalence of comorbidities and high risk of respiratory symptoms among participants with PRISm require the attention of clinicians. In the present study, respiratory symptoms were more frequent in the PRISm group, and the rate of showing was between that of the subjects with normal spirometry and COPD. The frequency of hypertension and diabetes mellitus as comorbidities tended to be highest in the PRISm group. These results were also supported by another large population-based European cohort study, which found that the proportion of patients with any comorbidity was 49.3% in the PRISm group, 41.1% in the normal spirometry group, and 42.6% in the COPD spirometry group.[17] The COPDGene Study evaluated the factors influencing quality of life in individuals with PRISm. The results revealed that individuals with PRISm were similar to those with COPD in terms of the higher risk of exacerbation, higher comorbidity count, more symptoms, and worse baseline quality of life than individuals with normal spirometry at baseline.[35] The presence of COPD can lead to systemic inflammation or oxidative stress having a direct causal effect on extra-pulmonary disease.[36] Therefore, this process may also occur in individuals with PRISm.

The relationship between PRISm and BMI is incompletely understood. Although PRISm is often considered to be associated with obesity, in the present study, the BMI of individuals with PRISm was higher than that of people with normal spirometry or COPD spirometry. This is in agreement with the COPDGene cohort.[37] Previous reports have indicated that BMI is inversely associated with FVC and FEV_1, while increased total and abdominal adiposity are associated with reduced FVC and FEV_1.[38,39] Jones and Nzekwu also found that although there is a negative correlation between obesity and FVC, obesity is unlikely to reduce FVC below LLN in people without respiratory disease.[38] Therefore, these results cannot account for the severity of lung function impairment observed with PRISm. A historical study previously underscored that BMI may act via a different pathway to increase PRISm risk, such as by exerting inflammatory and metabolic effects on adipose tissue itself.[36] Whether the relationship of these conditions with PRISm is mediated through metabolic pathways or other inflammatory systemic processes has not been comprehensively evaluated, warranting additional investigations.

The strong relationship between smoking status and incident PRISm, persistent PRISm, and progression of PRISm to airflow obstruction illustrates the importance of smoking cessation. Computed tomography can be used to observe whether emphysema, airway wall thickness, and air trapping are associated with smoking, which could be useful to predict rapid lung function decline in people with PRISm.[40] Parekh et al found that continued smoking and frequent exacerbations were predictors of a decline in quality of life in smokers with normal spirometry and PRISm.[35] PRISm is a heterogeneous condition, and smoking cessation may improve the chance of reverting to normal spirometry and avoiding progression to COPD.[41]

Currently, smoking is widely recognized as a crucial etiological for PRISm. Some research found smoking would lead to inflammation, oxidative stress, imbalance between antiprotease and protease, and small airway diseases, increasing the risk of PRISm.[42,43] Another significant factor triggering PRISm is BMI, a previous study showed that lower BMI diminished impaired lung development, respiratory muscle function, and an increased risk of infections.[44] There is relationship between air pollution and PRISm confirmed by animal models, clarifying inflammatory reactions from inhalation exposure and reduced FVC.[45] Lastly, SNPs within the PLEKHA5 and CACNB2 genes may offer evidence to explore the genetic mechanisms with PRISm.[1]

Strengths and Limitations

This study has several notable strengths. First, the study was based on data from the general population and it had a relatively long mortality follow-up period. Second, the questionnaire and spirometry assessments were performed by trained technicians. Third, we performed sensitivity analyses using thresholds based on the LLN for FEV_1/FVC, as well as subgroup analyses. Our results remained robust in the sensitivity and subgroup analyses.

The limitations of our study include the large number of participants with unqualifying lung function data at baseline, which may raise the possibility of select bias. Furthermore, most of the participants included in the NHANES did not have postbronchodilator spirometry data. Therefore, prebronchodilator spirometry data were used, which may have resulted in overestimation of the prevalence of PRISm and COPD. Moreover, bronchodilators have been shown to decrease the prevalence of obstructive lung disease, but their effects on the prevalence of PRISm are not certain.[46] Finally, we could not prospectively observe the evolution of PRISm status over time, and the impact profiles identified should be cautiously interpreted.

Conclusions

In this large-sample study of the general US adult population, PRISm compared with normal spirometry was significantly associated with greater all-cause mortality and a higher risk of symptoms and comorbidities. Therefore, participants with PRISm require more attention and better management.

Abbreviations

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; LLN, lower limit of normal; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; PRISm, preserved ratio impaired spirometry.

Ethical Approval

The National Health and Nutrition Examination Survey was approved by the ethics committee of the National Center for Health Statistics and all subjects signed informed consent. The data analysis for this study was exempted from ethical review because all data were de-labeled.

Informed Consent

The written informed consent was obtained from all participants.

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Disclosure

The authors report no conflicts of interest in this work.

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