

Journal Club

## Journal Club: Respiratory Impairment With A Preserved Spirometric Ratio

Takudzwa Mkorombindo, MD<sup>1</sup> Ron Balkissoon, MD<sup>2</sup>

**Abbreviations:** chronic obstructive pulmonary disease, **COPD**; forced expiratory volume in 1 second, **FEV<sub>1</sub>**; forced vital capacity, **FVC**; COPD Genetic Epidemiology, **COPDGene**; SubPopulations and Intermediate Outcome Measures in COPD Study, **SPIROMICS**; modified Medical Research Council, **mMRC**; COPD Assessment Test, **CAT**

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1. Lung Health Center, Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Alabama, Birmingham, Alabama, United States
2. Denver, Colorado

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**Address correspondence to:**

Takudzwa Mkorombindo, MD  
Email: [tmkorombindo@uabmc.edu](mailto:tmkorombindo@uabmc.edu)

### Introduction

The societal and economic impact of chronic obstructive pulmonary disease (COPD) is substantial, however, despite the significant knowledge we have gained about the inflammatory and structural changes in both the airway and alveoli, we continue to struggle with the early identification of people suffering from this respiratory disease.<sup>1,2</sup> Presently, the diagnosis of COPD<sup>3</sup> is predicated on confirmation of persistent post-bronchodilator airflow obstruction with an absolute ratio of forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity (FVC) below either the lower limit of normal or the fixed value of 0.70. Consensus guidelines for the diagnosis and management of COPD strongly encourage the use of spirometry to diagnose COPD at an early stage and to guide treatment, however, there remains under-utilization of spirometry for numerous and complex reasons.<sup>4,5</sup> Clinical diagnosis of COPD without spirometric confirmation results in

the inaccurate diagnosis of COPD and inadequate/inappropriate treatments. It has been suggested that spirometric criteria are also insensitive to identifying patients who suffer significant respiratory morbidity from non-asthmatic obstructive lung disease.

Spirometry is the most validated diagnostic tool for identifying COPD.<sup>3</sup> Spirometry has prognostic implications with spirometric measures such as FEV<sub>1</sub>/FVC<sub>6</sub> and FEV<sub>1</sub> predicting the risk of COPD exacerbations and mortality at the population level even though they do not perform well at the individual level.<sup>6-9</sup> While not all persons exposed to high levels of noxious particles, such as tobacco smoke and other environmental pollutants, will develop COPD as identified by spirometric cutoffs, a subset of people with such exposures will also have inadequate repair processes that lead to airway remodeling and chronic inflammatory changes and resulting respiratory disease.<sup>10,11</sup> It has become increasingly evident with advancements in thoracic imaging that cigarette smoke and other exposures can lead to emphysema, vascular and airway abnormalities such as airway wall thickening, and small airway fibrosis, all of which are not readily identified with spirometry alone.<sup>12</sup> Spirometry does not always correlate with symptoms, and often, particularly in the early stages of the disease, it is normal or almost normal despite significant lung pathology.

The population with structural and functional abnormalities who do not meet spirometric criteria for identifying COPD is clinically under-recognized. In addition to having significant respiratory morbidity, this

population is at risk for progression to COPD. A variety of spirometric, anatomic, and functional abnormalities are observed in this population. Patients who have decrements in FEV<sub>1</sub> and FVC, but a normal FEV<sub>1</sub>/FVC are referred to as the preserved ratio-impaired spirometry (PRISm) group. PRISm is characterized<sup>13</sup> by a proportionate reduction in FEV<sub>1</sub> and FVC, with FEV<sub>1</sub> <80% and FEV<sub>1</sub>/FVC ratio ≥0.7. PRISm is distinct from patients with chronic bronchitis with normal spirometry (previously GOLD stage 0) and those with other imaging or functional abnormalities alone. Our understanding of the pathology of these subgroups of “at-risk” populations is limited. Not only do these patients experience COPD-like exacerbation events, but they also have significant quality of life impairment.<sup>14,15</sup> In longitudinal cohorts such as the COPD Genetic Epidemiology (COPDGene®) study and the SubPopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS), a significant proportion of PRISm patients have a modified Medical Research Council (MRC) dyspnea score ≥2. Furthermore, in the SPIROMICS cohort, patients with normal spirometry but with a COPD Assessment Test (CAT) score ≥10, had more airway thickening and had more features similar to COPD.<sup>16,17</sup> The management and prognosis of patients without marked spirometric impairment is enigmatic but recently, several reports have improved our understanding of PRISm.

It is now evident that a significant fraction of these patients will progress to develop spirometric airflow limitation. It is unclear which predictors identify patients who will progress to spirometric COPD. In this Journal Club, we will review some more recent papers that have addressed these issues.<sup>18-21</sup>

**Note: Abstracts are presented in their original, published format and have not been edited to match JCOPDF style.**

## Abstract 1 Trajectory and Mortality of Preserved Ratio Impaired Spirometry: the Rotterdam Study

Wijnant SRA, DeRoos E, Kavousi M, et al. *Eur Respir J*. 2020;55(1):1901217.

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Preserved ratio impaired spirometry (PRISm) is a heterogeneous condition and its course and disease progression remain to be elucidated. In the Rotterdam Study (population-based prospective cohort) we examined prevalence, trajectories and prognosis of subjects with normal spirometry (controls; forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) ≥0.7, FEV<sub>1</sub> ≥80%), PRISm (FEV<sub>1</sub>/FVC ≥0.7, FEV<sub>1</sub> <80%) and chronic obstructive pulmonary disease (COPD) (FEV<sub>1</sub>/FVC <0.7) at two study visits. Hazard ratios with 95% confidence intervals for mortality (until December 30, 2018) were adjusted for age, sex, body mass index, current smoking and pack-years. Of 5487 subjects (age 69.1±8.9 years; 7.1% PRISm), 1603 were re-examined after 4.5 years. Of the re-examined PRISm subjects, 15.7% transitioned to normal spirometry and 49.4% to COPD. Median lung function decline was highest in subjects with incident PRISm (FEV<sub>1</sub> -92.8 mL·year<sup>-1</sup>, interquartile range (IQR) -131.9- -65.8 mL·year<sup>-1</sup>; FVC -93.3 mL·year<sup>-1</sup>, IQR -159.8- -49.1 mL·year<sup>-1</sup>), but similar in persistent PRISm (FEV<sub>1</sub> -30.2 mL·year<sup>-1</sup>, IQR -67.9- -7.5 mL·year<sup>-1</sup>; FVC -20.1 mL·year<sup>-1</sup>, IQR -47.7-21.7 mL·year<sup>-1</sup>) and persistent controls (FEV<sub>1</sub> -39.6 mL·year<sup>-1</sup>, IQR -64.3—12.7 mL·year<sup>-1</sup>; FVC -20.0 mL·year<sup>-1</sup>, IQR -55.4-18.8 mL·year<sup>-1</sup>). Of 5459 subjects with informed consent for follow-up, 692 (12.7%) died during 9.3 years (maximum) follow-up: 10.3% of controls, 18.7% of PRISm subjects and 20.8% of COPD subjects. Relative to controls, subjects with PRISm and COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2-4 had increased all-cause mortality (PRISm: HR 1.6, 95% CI 1.2-2.0; COPD GOLD 2-4: HR 1.7, 95% CI 1.4-2.1) and cardiovascular mortality (PRISm: HR 2.8, 95% CI 1.5-5.1; COPD 2-4: HR 2.1, 95% CI 1.2-3.6). Mortality within <1 year was highest in PRISm, with patients often having cardiovascular comorbidities (heart failure or coronary heart disease; 70.0%). PRISm is associated with increased mortality and this population encompasses at least three distinct subsets: one that develops COPD during follow-

up, a second with high cardiovascular burden and early mortality, and a third with persistent PRISm and normal age-related lung function decline.

## Comments

This analysis of the Rotterdam study follows the trajectory of participants in the cohort with PRISm. Several reports have demonstrated increased all-cause mortality with increased adverse cardiopulmonary outcomes in PRISm.<sup>22-24</sup> Wijnant and colleagues showed that patients with PRISm had overall higher all-cause and cardiovascular mortality. This analysis highlights the importance of cardiovascular mortality, however, it is unclear if the relationship is causal. The authors identified 3 separate groups that may be distinct: those who developed COPD, those who have expected decline of lung function due to aging, and a subgroup with high cardiovascular risk and more likely to die prematurely. These data highlight the importance of identifying PRISm patients, the significance of heightened awareness of the subgroup with significant cardiovascular comorbidities, and adds to the growing body of literature on PRISm.

## Abstract 2 Significant Spirometric Transitions and Preserved Ratio Impaired Spirometry Among Ever Smokers

Wan E, Hokanson JE, Regan EA, et al. *Chest*. 2021;In press. doi: <https://doi.org/10.1016/j.chest.2021.09.021>

**Background:** Emerging data from longitudinal studies suggest that preserved ratio impaired spirometry (PRISm), defined by proportionate reductions in FEV<sub>1</sub> and FVC, is a heterogeneous population with frequent transitions to other lung function categories relative to individuals with normal and obstructive spirometry. Controversy regarding the clinical significance of these transitions exists (eg, whether transitions merely reflect measurement variability or noise).

**Research question:** Are individuals with PRISm enriched for transitions associated with substantial changes in lung function?

**Study design and methods:** Current and former smokers enrolled in COPDGene with spirometry available in phases 1 through 3 (enrollment, 5-year

follow-up, and 10-year follow-up) were analyzed. Postbronchodilator lung function categories were as follows: PRISm (FEV<sub>1</sub> <80% predicted with FEV<sub>1</sub>/FVC ratio ≥0.7), Global Initiative for Chronic Obstructive Lung Disease stage 0 (FEV<sub>1</sub> ≥80% predicted and FEV<sub>1</sub>/FVC ≥0.7), and obstruction (FEV<sub>1</sub>/FVC <0.7). Significant transition status was affirmative if a subject belonged to two or more spirometric categories and had >10% change in FEV<sub>1</sub> % predicted and/or FVC % predicted between consecutive visits. Ever-PRISm was present if a subject had PRISm at any visit. Logistic regression examined the association between significant transitions and ever-PRISm status, adjusted for age, sex, race, FEV<sub>1</sub> % predicted, current smoking, pack-years, BMI, and ever-positive bronchodilator response.

**Results:** Among subjects with complete data (N=1,775) over 10.1±0.4 years of follow-up, the prevalence of PRISm remained consistent (10.4%-11.3%) between phases 1 through 3, but nearly one-half of subjects with PRISm transitioned into or out of PRISm at each visit. Of the subjects, 19.7% had a significant transition; ever-PRISm was a significant predictor of significant transitions (unadjusted OR, 10.3; 95% CI, 7.9-13.5; adjusted OR, 14.9; 95% CI, 10.9-20.7). Results were similar with additional adjustment for radiographic emphysema stable and gas trapping, when lower limit of normal criteria were used to define lung function categories, and when FEV<sub>1</sub> alone (regardless of change in FVC % predicted) was used to define significant transitions.

**Interpretation:** PRISm is an unstable group, with frequent significant transitions to both obstruction and normal spirometry over time.

## Comments

In longitudinal studies, it has become evident that in PRISm there are variations in lung function resulting in fluctuations between other lung function categories ranging from normal spirometry to varying degrees of COPD severity. In this report by Wan and colleagues, the authors sought to elucidate the validity and clinical significance of the variation. For most analyses, the annual variability in lung function (FEV<sub>1</sub> or FVC) considered significant ranges from 5% to 15%. Wan and colleagues utilized a 10% or greater change in FEV<sub>1</sub> or FVC % predicted over 5 years as their measure for significance. They showed that even when utilizing a methodology that eliminates artificial transitions, time-

varying processes result in frequent transitions in PRISm to spirometric obstruction and normal spirometry. The reason for these transitions remains unclear, but it is now evident that these transitions are significant.

### Abstract 3

## Prevalence, Risk Factors, and Clinical Implications of Preserved Ratio Impaired Spirometry: A UK Biobank Cohort Analysis

Higbee DH, Granell R, Smith GD, Dodd JW. *Lancet Respir Med*. 2021 Nov 2; In press. doi: [https://doi.org/10.1016/S2213-2600\(21\)00369-6](https://doi.org/10.1016/S2213-2600(21)00369-6)

**Background:** Preserved ratio impaired spirometry (PRISm) is defined as a FEV1 of less than 80% predicted and a FEV1/forced vital capacity (FVC) ratio of 0.70 or higher. Previous research has indicated that PRISm is associated with respiratory symptoms and is a precursor of chronic obstructive pulmonary disease (COPD). However, these findings are based on relatively small selective cohorts with short follow-up. We aimed to determine the prevalence, risk factors, clinical implications, and mortality of PRISm in a large adult general population.

**Methods:** For this cohort analysis, we used data from the UK Biobank to assess PRISm prevalence, risk factors and associated symptoms, and associated comorbidities in a large adult population. Participants with spirometry deemed acceptable by an investigator (best measure FEV1 and FVC values) at baseline were included. Participants were excluded if they did not have acceptable spirometry or were missing data on body-mass index or smoking status. Control spirometry was defined as a FEV1 of 80% or more predicted and a FEV1/FVC ratio of 0.70 or higher. Airflow obstruction was defined as a FEV1/FVC ratio of less than 0.70. We used multivariable regression to determine risk factors for PRISm and associated comorbidities. Individuals who lived within close proximity to an assessment centre were invited for follow-up, with repeat spirometry. Only participants who had been included at baseline were examined in follow-up. This allowed for a longitudinal analysis of PRISm over time and risk factors for transition to airflow obstruction. We also did the survival analysis for a 12-year period.

**Findings:** Participants were recruited by UK Biobank between Dec 19, 2006, and Oct 10, 2010. We included

351 874 UK Biobank participants (189 247 women and 162 627 men) in our study, with a median follow-up of 9.0 years (IQR 8.0-10.0). 38 639 (11.0%) of 351 874 participants had PRISm at baseline. After adjustment, PRISm was strongly associated with obesity (odds ratio [OR] 2.40 [2.26-2.55],  $p < 0.0001$ ), current smoking (1.48 [1.36-1.62],  $p < 0.0001$ ), and patient reported doctor-diagnosed asthma (1.76 [1.66-1.88],  $p < 0.0001$ ). Other risk factors identified included female sex, being overweight, trunk fat mass, and trunk fat percentage. PRISm was strongly associated with symptoms and comorbidity including increased risk of breathlessness (adjusted OR 2.0 [95% CI 1.91-2.14],  $p < 0.0001$ ) and cardiovascular disease (adjusted OR 1.71 [1.64-1.83],  $p < 0.0001$  for heart attack). Longitudinal analysis showed that 241 (12.2%) of 1973 participants who had PRISm at baseline had transitioned to airflow obstruction consistent with COPD. PRISm was associated with increased all-cause mortality (adjusted hazard ratio 1.61 [95% CI 1.53-1.69],  $p < 0.0001$ ) versus control participants.

**Interpretation:** PRISm was associated with breathlessness, multimorbidity, and increased risk of death, which does not seem to be explained by smoking, obesity, or existing lung disease. Although for many patients PRISm is transient, it is important to understand which individuals are at risk of progressive lung function abnormalities. Further research into the genetic, structural and functional pathophysiology of PRISm is warranted.

## Comments

In this timely report, the authors present the results of an analysis investigating clinical features of over 38,000 participants in the UK Biobank with PRISm at baseline (represents 11% of the overall population). They confirmed previously established associations between PRISm and breathlessness, increased risk of death, and more comorbidities. The ongoing discussion about the pathophysiology observed in PRISm has been centered around multi-morbidity and whether these are causal or a result of a shared exposure. Obesity and continued tobacco exposure were associated with increased risk of incident PRISm and remaining PRISm, and current tobacco smoke was associated with progression to airflow obstruction. Sensitivity analysis controlling for BMI and smoking showed that the observed effects were not fully explained by obesity, prior diagnosis of another lung

disease, or tobacco smoke exposure. This observation does not exclude the potential impact of comorbidities in PRISm outcomes but it does help us appreciate the heterogeneity of the PRISm group. This group is worth further study with computed tomography scans and full pulmonary function tests, including gas trapping.

## Abstract 4 From GOLD 0 to Pre-COPD

Han MK, Agusti A, Celli BR, et al. *Am J Respir Crit Care Med.* 2021;203(4):414-423. doi: <https://doi.org/10.1164/rccm.202008-3328PP>

The diagnosis of chronic obstructive pulmonary disease (COPD) currently requires the demonstration of poorly reversible airflow limitation, defined as a post-bronchodilator FEV1/FVC <0.7 (1–3). Although some have argued that the lower limit of normal rather than a fixed value to define obstruction may be more accurate and theoretically more appropriate, recent pooled data from multiple NIH cohorts demonstrate that the fixed FEV1/FVC ratio <0.70 provides discrimination of COPD-related hospitalization and mortality that is equal to or better than other thresholds and the lower limit of normal (4). At present, FEV1/FVC remains the most robust and widely available marker of airflow limitation (5), although it may be less sensitive than some other measures (e.g., forced oscillometry). Likewise, FEV1 is one of the most powerful predictors of clinically relevant outcomes, including symptoms, exacerbations, and mortality (6, 7). Spirometry is inexpensive and widely available, even in many developing countries. Yet, at the same time, at an individual level, FEV1 may not fully indicate the extent of disease severity and progression, which may instead be manifest by symptoms, exacerbations, and increased risk of death. Furthermore, significant lung damage may have already occurred before abnormalities in FEV1 are evident. Identifying individuals who will eventually develop airflow obstruction consistent with a diagnosis of COPD may enable therapeutic interventions with the potential to modify the course of disease. In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease, proposed an “at risk” stage (GOLD stage 0). It was defined by the presence of risk factors (smoking) and symptoms (chronic cough and sputum production) in the absence of spirometric abnormalities that cross

the diagnostic threshold for COPD (3). This category was later abandoned because not all these individuals progressed to COPD (8). In retrospect, this may not have been the best decision, as many other medical disciplines have adopted the concept of “predisease” status (e.g., prediabetes, prehypertension, precancer, or preeclampsia). In those disciplines, predisease does not imply that all will develop the disease, but rather, the classification identifies an especially at-risk population for closer follow-up and risk management. Here, we propose to adopt a similar concept in the field of COPD. As has been highlighted in the recent perspective by Martinez and colleagues (9, 10), more is becoming understood about the pathogenesis of early COPD and the importance of identifying such individuals, in particular, for the development of disease-modifying therapies. In this perspective, our goal is to review the evidence available today that supports the need for the recognition of individuals at risk for COPD and discuss whether it is time to consider the evolution of the GOLD stage 0 concept to that of “pre-COPD” from a clinically relevant perspective (11). Although not an official GOLD document, this manuscript was generated on the basis of discussions within the GOLD Science Committee for the purposes of engaging the scientific community around the concept of pre-COPD.

## Comments

Han and colleagues propose utilizing pre-COPD as a terminology similar to a pre-disease state for diabetes or chronic kidney disease that captures individuals similarly at risk for full-fledged disease. The increased research and heightened awareness of PRISm have unearthed important prognostic and clinical information about this unique entity. The clinical behaviors, trajectories, and pathogenesis of other at-risk populations that are not PRISm (i.e., GOLD stage 0, normal spirometry with imaging abnormalities, etc.) remain underexplored. The authors advocate this approach hoping that intentional investigation of physiologic and radiographic abnormalities in this population will result in improved identification of individuals most likely to progress to COPD and identify modifiable factors early in the disease course. This approach is rational and pragmatic, but as the authors state, it is not ready to deploy for routine clinical use.

## Bottom Line

Global estimates suggest that over 300 million suffer from COPD.<sup>1</sup> Estimates on the impact of COPD likely underestimate the burden of disease as they do not capture all the people with significant respiratory morbidity related to former or current cigarette smoking but who do not meet current spirometric criteria for COPD. There are no guidelines on management or proven therapeutic interventions for patients who do not have a guideline-based diagnosis of COPD but have functional and anatomical abnormalities. Clearly, individuals who demonstrate this susceptibility to the injurious effects of cigarette smoking and environmental pollutants should be encouraged and supported to stop smoking if they are still doing so. It should also signal to their providers to make sure that they are evaluated for significant comorbidities (particularly cardiovascular disease) associated with cigarette smoking.

Early detection of COPD has been a topic of significant interest as it offers the potential for early and perhaps preventive or curative interventions. Proposals for multidimensional diagnostic approaches beyond spirometry alone show promise for detecting early pathophysiologic changes, but it is debatable whether these patients should be included in a broader COPD definition. It is also unclear whether these patients would benefit from therapeutics that have been proven effective for patients with COPD as currently defined. It is evident that patients with PRISm and other similar entities have significant impairment, poor long-term prognosis, and are in dire need of advancements in care. Fortunately, the respiratory community has heightened awareness of this pressing issue, and hopefully, solutions are soon coming.

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