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Postbronchodilator Spirometry Reference Values Are Needed and Helpful for Identifying Pre–Chronic Obstructive Pulmonary Disease

In this issue of the *Journal*, Huang and colleagues (pp. 881–889) published both pre- and postbronchodilator reference values that were derived from a large population in the China Pulmonary Health Study (1). Unsurprisingly, they found that the prevalence of airway obstruction was higher with postbronchodilator reference values than with prebronchodilator reference values. More important, they showed that subjects characterized as having airflow obstruction with postbronchodilator reference values had significantly higher rates of self-reported respiratory symptoms, even those who would not be characterized as having airflow obstruction with prebronchodilator values. The study by Huang and colleagues is a validation of a previous study on a smaller Swedish population of a limited age range: 50–64 years. In that study, higher prevalence of airflow obstruction was found when postbronchodilator reference values were used and subjects identified with postbronchodilator reference values had a higher respiratory burden on the basis of self-reported symptoms and computed tomography–assessed emphysema (2). Both these studies suggest that postbronchodilator reference values can be used to identify subjects with a higher burden of respiratory symptoms and emphysema changes. This field was opened in 2006 by Johannessen and colleagues, who published postbronchodilator spirometry reference values and assessed their implications for disease management (3). The authors of the 2006 study concluded that use of postbronchodilator reference values instead of prebronchodilator reference values helped avoid falsely high percent predicted FEV_1. Although other studies, such as the PLATINO study (4), confirmed the effect of bronchodilation on spirometry results, no further attempts were made to reevaluate the clinical use of the postbronchodilator values before the two studies recently published in the *Journal* (1, 2).

The study by Huang and colleagues is important in a disease prevention perspective, as it once more puts a focus on pre–chronic obstructive pulmonary disease (pre-COPD), even if this term is not explicitly used. The term "pre-COPD" is used for individuals in whom spirometry is unable to detect airflow obstruction but who are at risk of developing COPD. Pre-COPD is defined as a normal ratio of FEV_1 to FVC combined with the presence of respiratory symptoms and/or structural and/or functional abnormalities (5). In a recent paper from the EPISCAN II study in Spain, Cosío and colleagues (6) showed that almost a quarter of the general population over 40 years of age may have pre-COPD, with symptomatic and structural changes similar to those of people with well-established disease, but without spirometry-measured airflow obstruction.

We believe that the use of postbronchodilator reference values may be useful in identifying patients with pre-COPD, capturing those who do not have obstruction on the basis of prebronchodilator reference values. This is in line with the results of the study of Huang and colleagues (1) and previous studies by Malinovschi and colleagues (2) and Johannessen and colleagues (3). However, as all three of the studies mentioned were of a cross-sectional nature, we need more investigations of longitudinal disease development patterns. This might also be suggested, given the relation to higher burden of emphysema changes (7) and respiratory symptoms (8), which, in turn, are linked to future COPD diagnosis.

We must acknowledge that the use of postbronchodilator reference values is only one of several pulmonary function testing methods that could have potential for use in identifying pre-COPD, along with forced oscillation technique/impulse oscillometry (9, 10), inert gas washout (11, 12), measures of small airway dysfunction from spirometry (13), impaired $D_{L_{CO}}$ (14), measures of hyperinflation (15), preserved ratio impaired spirometry pattern (16), and proof of accelerated lung function decline (17), as discussed by Han and colleagues (18) (Figure 1). Still, because of the high availability of spirometry, and its being part of the diagnostic routine, we believe that use of postbronchodilator reference values would be easy to implement. However, to do this, postbronchodilator reference values would be needed. Both Huang and colleagues (1) and Malinovschi and colleagues (2) used their own locally generated reference values from the same population as the respective study cohort. There are currently no internationally accepted postbronchodilator reference values.

However, it is likely that the use of postbronchodilator reference values would have to be combined with data on other patient characteristics to estimate the likelihood of developing COPD. The Simple, Low cost and easy to IMplement (or, SLIM) risk calculator is one such tool; it combines FEV_1/FVC ratio, body mass index, smoking history, and chronic bronchitis symptoms to predict incident chronic airflow limitation (19). However, its authors used only a fixed cutoff value of 0.75 for assessing the FEV_1/FVC ratio. Therefore, it could be of interest in future studies to address the FEV_1/FVC ratio in relation to postbronchodilator reference values. A recent study suggested that asthma and smoking history were the strongest predictors of incident COPD in two Danish population-

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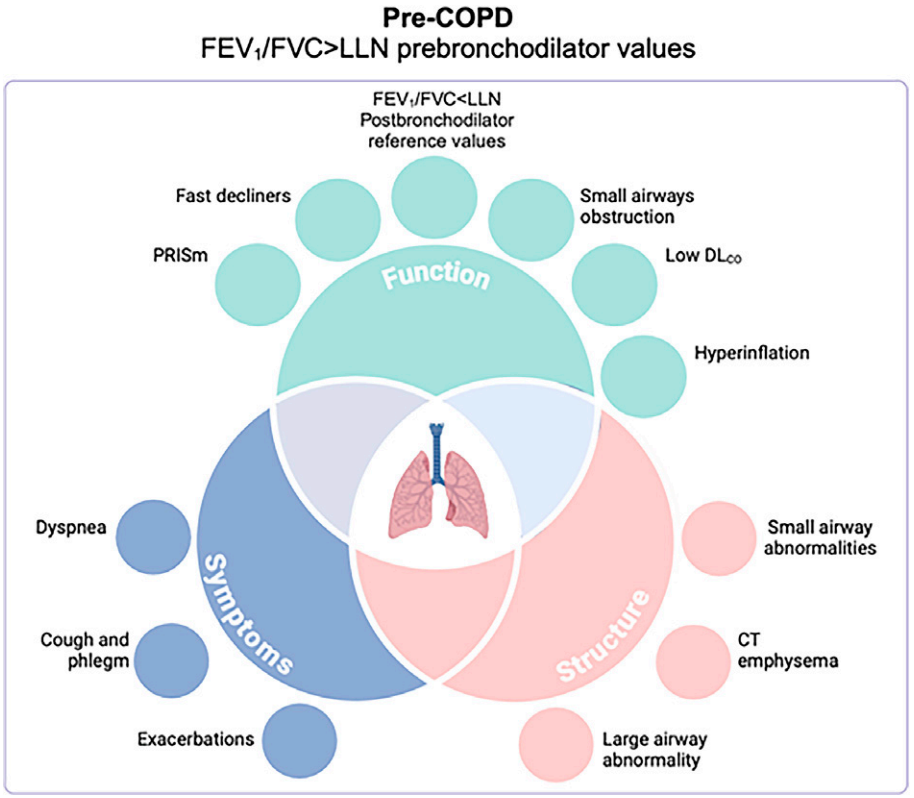

Figure 1. Proposed place of use of postbronchodilator reference value for FEV_1/FVC within the current concept of pre-COPD. COPD = chronic obstructive pulmonary disease; CT = computed tomography; LLN = lower limit of normal; PRISm = preserved ratio impaired spirometry. Figure 1 is adapted from reference 18 in the reference list from https://pubmed.ncbi.nlm.nih.gov/33211970/. The authors thank Claudia Dührkop, Ph.D. who provided assistance with the figure.

based cohorts (20). Chronic bronchitis and small airway dysfunction were the two factors related to incident COPD in a Chinese study based on a COPD national surveillance program (8). The complementary value of other spirometry findings, such as preserved ratio impaired spirometry or small airway dysfunction, along with computed tomography findings, would also need to be assessed in future studies to identify individuals who have a higher likelihood of developing COPD. Finally, the identification of these individuals and their treatable traits might lead to interventions that can prevent the development of COPD (21). ■

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Why Is Body Mass Index Related to Chronic Obstructive Pulmonary Disease? Is It All in the Genes?

Over 390 million individuals around the world have chronic obstructive pulmonary disease (COPD) (1). COPD accounts for more than 3.2 million deaths per year, making it the sixth leading cause of mortality worldwide (2). Although its exact pathogenesis is not known, COPD is believed to arise from a complex interplay between environmental and genetic factors over many decades, with genetics ultimately accounting for 20–40% of the variation in airflow limitation in adults and smoking behavior for up to 60% (3). Although cigarette smoking and air pollution exposures are leading environmental risk factors for COPD (4), it is now well established that low body mass index (BMI), a biomarker for reduced fat and lean mass and physical deconditioning, is a consistent and significant risk factor for rapid disease progression in patients with COPD (5, 6). The overall relationship between BMI and COPD outcomes such as mortality is, however, more complicated. For example, although low BMI is associated with an elevated risk of COPD, accelerated FEV_1 decline, exacerbations (7), and respiratory mortality (6), high BMI is associated with elevated risks for all-cause mortality and deaths of cardiovascular but not respiratory causes in the general population (6). On the basis of these and other observations, investigators have generated prognostic equations to predict risk of mortality in COPD by including measured BMI, together with other health metrics. The most notable example is the BODE index (body mass index, airflow obstruction, dyspnea, and exercise), a validated predictor of disease severity and outcomes, which incorporates BMI with measures of airflow obstruction, dyspnea, and exercise capacity to arrive at a mortality prediction for patients with COPD (8). However, because of the complexity in these relationships and the relatively poor signal-to-noise ratio, measured BMI cannot be used clinically as a standalone biomarker to predict outcomes in COPD (9).

Both lung function and BMI are highly heritable traits, with genetics accounting for 40–70% of the variation in the BMI and lung function accounting for a slightly lower percentage (10). It is therefore logical to ask the question: Can the addition of genetic information for BMI to measured BMI improve the performance of prognostic models in COPD? Zhang and colleagues (pp. 890–899) address this critical question in this issue of the *Journal* by investigating the relationship of genetically predicted BMI with all-cause, cardiovascular, and respiratory mortality in patients with COPD (11). Their study first involved the development of a BMI polygenic risk score through a meta-analysis of two large general population-based cohorts: GIANT (Genetic Investigation of Anthropometric Traits) and the UK Biobank. They then examined the association between BMI polygenic risk score and mortality in participants with COPD from three well-established cohorts: the COPDGene study (Genetic Epidemiology of COPD study), the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Study), and the Framingham Heart Study.

There were several notable findings in this study. First, they showed that the relationship of BMI with cardiovascular mortality was positively linear, whereas that for all-cause mortality was U-shaped. Second, they found that the differences between the measured and genetically predicted BMI predicted the future risk of mortality. The lowest mortality risk was observed in patients whose

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