More importantly, the fixed ratio is simple and, indeed, comparable to what has been a successful way of obtaining better acceptance and management of hypertension [7]. The fixed ratio has been endorsed in the clinical European Respiratory Society/American Thoracic Society COPD guidelines [8] as well as the often quoted COPD guidelines from the UK National Institute for Health and Clinical Excellence [9]; the GOLD document and these two clinical guidelines are the most common guidelines followed by the medical community. It has been used extensively in research and as an inclusion criterion in numerous clinical trials; in fact, evidence-based management of COPD is more or less entirely based on studies using the fixed ratio. For this reason, GOLD believes that on balance we serve the clinicians managing COPD best by continuing with the fixed ratio.

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From the authors:

We welcome this opportunity for an open debate of the best definition of mild chronic obstructive pulmonary disease (COPD). The pulmonary clinicians and physiologists who signed the open letter to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee agree that: 1) COPD is a very important health problem; 2) too many cases are detected too late; 3) airways obstruction can only be detected by spirometry; 4) spirometry is greatly under-utilised and requires skilled personnel; and 5) misinterpretation of spirometry results is a cause for concern. During the past decade, the GOLD guidelines have greatly improved worldwide awareness of COPD and provided a ''living document'' for the diagnosis and treatment of COPD with the laudable goal of annual updates based on newly published evidence. However, the current GOLD guidelines [1] continue to define mild COPD as post-bronchodilator ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) <0.70 with a normal FEV_1, without evidence that even the majority of these adults so identified actually have COPD (even when including only those who report respiratory symptoms). It is illogical to teach generations of doctors to respect the normal range in biochemical and other clinical indices, but not in respiratory medicine because it is too difficult.

More than 80% of smokers report a chronic cough or dyspnoea on exertion, but a diagnosis of COPD should not be made unless they also have airway obstruction and an abnormally low FEV_1. Regardless of their spirometry results, they all should be encouraged and helped to stop smoking. Likewise, more than one-third of smokers develop cardiovascular disease or lung cancer. Thus, even smokers with a normal FEV_1 in GOLD stage I have a substantially increased risk of morbidity and premature death, but that fact does not provide evidence that they have COPD.

Some 10–20% of smokers will develop clinically important COPD (FEV_1 <60% predicted). In a population sample, we simply cannot yet identify the 10–20% of adult smokers currently in GOLD stage I. Hence, using the current GOLD guidelines, we are wrong 80% of the time; in the study by GEIJER *et al*. [2] even fewer (8.3%) symptomatic subjects and smokers moved from GOLD stage I to stage II in 5.2 years, and none developed GOLD stages III or IV.

We should have a high degree of confidence in the diagnosis before we label a person as having a progressive, incurable disease and then prescribe an expensive drug therapy (such as a long-acting bronchodilator) for the rest of their life. For patients in GOLD stages III–IV we are highly confident of the diagnosis of COPD, and large clinical trials of bronchodilator inhalers show some reduction in dyspnoea in some patients, and some reduction in exacerbations in those with a previous history of exacerbations. However, there is a paucity of such evidence for those with a FEV_1 >60% pred (GOLD stage I and the top half of GOLD stage II) [3]. Only smoking cessation has been proven to reduce the risk of rapid loss of lung function, and this benefit is evident at any baseline level of lung function.

The GOLD committee acknowledges that a fixed ratio leads to over-diagnosis of airway obstruction but continues to

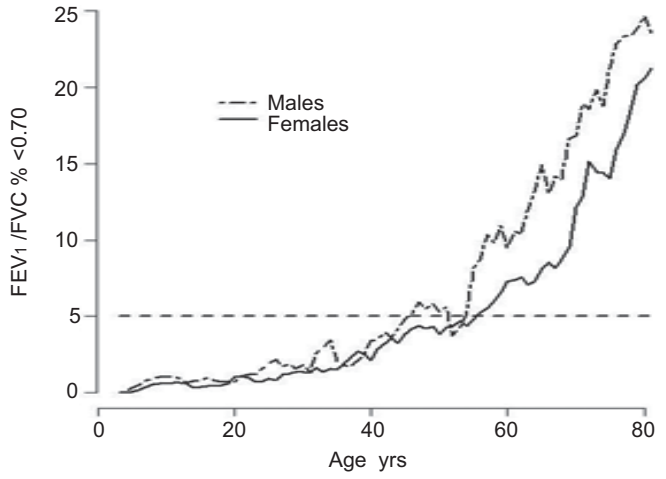

FIGURE 1. Percentage of males and females (n=78,433) in whom ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) is <0.70. Data courtesy of the Global Lungs Initiative.

recommend it for the sake of simplicity. Are doctors in developing countries, who are capable of having spirometry administered professionally, really incapable of understanding or computing the lower limit of normal (LLN)? Should doctors and epidemiologists in affluent societies, who can easily compute the appropriate LLN, continue to use the fixed ratio at the expense of higher misclassification rates?

The comparison of the fixed ratio with blood pressure for disease management is flawed [4]. Blood pressure is the result of a feedback control system, which can be pharmacologically manipulated to lower blood pressure and the risk of cardiovascular disease. By contrast, the FEV1/FVC ratio is not the outcome of a control system and cannot be treated to reduce the risk of COPD. ''Senile emphysema'' (reduced tissue elasticity) is an inevitable result of normal ageing, which causes FEV1/FVC to slowly decline, decade by decade, in healthy never-smokers with no workplace or environmental exposures known to cause respiratory disease.

In subjects with FEV1/FVC <0.70 but >LLN there is no increased risk of all-cause death when corrected for age, smoking and sex [5], unlike in subjects with FEV_1/FVC <LLN [6, 7]. GOLD stage I is not associated with dyspnoea, accelerated decline in FEV1, respiratory care utilisation or quality of life scores compared with a reference group [8].

The fact that various organisations adopted the GOLD guidelines is not scientific evidence for their validity. As demonstrated by investigators from the Burden of Obstructive Lung Disease (BOLD) study [9], the 5th percentile LLN for FEV_1/FVC and for FEV_1 should be used by pulmonary epidemiologists when computing COPD prevalence.

J. Vestbo and R. Rodriguez-Roisin express concern that the choice of reference population will have a major impact, particularly in developing countries. That is as true in developed as in developing countries [10]. The GOLD committee should consider the impact of the use of a fixed ratio in different ethnic groups, or in males *versus* females. The GOLD committee should also appreciate that using FEV1 as a per cent of the predicted value, where the choice of reference value comes into play, forms an inherent problematic part of the GOLD and any other recommendations [10], independent of geographic location. The European Respiratory Society has acknowledged that the worldwide problem of reference values needs resolving. Together with the American Thoracic Society, the Asian Pacific Society of Respirology, the Australian and New Zealand Society of Respiratory Science and the American Association of Chest Physicians, they established the Global Lungs Initiative, which will issue recommendations on predicted values for spirometric indices (www.lungfunction.org). These are based on >80,000 records from 70 sources in 34 countries worldwide and address ethnic/geographic differences; a report is due later this year, and many manufacturers have recently updated their software to ensure that spirometry results can be expressed as z-scores and with the LLN for each outcome clearly displayed. By convention the LLN is at the 5th centile; figure 1 shows that before about age 50 yrs the fixed ratio misses very many cases of airflow limitation, and grossly overestimates the number above that age. Thus, at age 80 yrs ~80% of males and females identified by the fixed ratio as having airway obstruction represent false-positive results.

Symptomatic and/or smoking subjects, and subjects in whom there is other prior evidence of respiratory disease, are at risk of developing overt airways obstruction once their FEV1/FVC ratio nears the LLN, and need the counselling that the GOLD committee recommends. Classifying FEV1/FVC <LLN and FEV1 <LLN as mild COPD avoids under- and over-estimates of airflow limitation at any age, and has been shown to be clinically valid [4–7].

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COPD: an autoimmune disease?

To the Editors:

HEMMINKI *et al*. [1] report an increased prevalence of chronic obstructive pulmonary disease (COPD) in patients with autoimmune disease and suggest the presence of autoimmunity is a risk factor for the development of COPD. We have previously reported an increased prevalence of autoimmune disease in patients with COPD who have never smoked [2]. These patients tended to be elderly females and many had a blood lymphopenia, positive autoantibodies and airway inflammation. We have also reported a four-fold increase in the prevalence of COPD in patients with autoimmune bowel disease [3, 4]. The association with autoimmune disease is not limited to COPD; patients with unexplained chronic cough (UCC) are eight times more likely to have autoimmune disease compared to matched controls [5]. Patients with UCC are largely middle-aged females and have evidence of lymphocytic airway inflammation [6]. The mechanism for the association of cough with airway lymphocytosis may be homing of inflammation from the primary site of autoimmune disease to the airways [7]. A recent study has reported that patients with UCC have an increased decline in lung function, which raises the possibility that some patients with UCC may develop COPD [8].

It is likely that the presence of factors other than smoking is necessary for the development of COPD since most smokers do not develop COPD [9]. Examples of co-factors include autoimmunity and chronic airway infection. Further studies should investigate whether therapy targeting co-factors could prevent or treat COPD.

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