PostScript

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LETTERS

GOLD stage I is not a COPD risk factor

A retrospective analysis of data from the Cardiovascular Health Study (CHS) performed by Mannino et al[1] concludes that older adults with borderline abnormal spirometry results have an increased risk of death and hospitalisations related to chronic obstructive pulmonary disease (COPD). The all-cause mortality result from the analysis by Mannino et al merely confirms many previous reports.[2] However, the mechanism is not obstructive lung disease since the *vital capacity* (FVC), aptly named by British surgeon John Hutchinson more than 150 years ago, is a stronger predictor than forced expiratory volume in 1 s (FEV_1),[3] and respiratory muscle weakness accounts for much of the relationship.[4]

It is intuitive that patients with COPD must make a transition from normal spirometry to clinically relevant airway obstruction. However, only a small minority of adults with borderline abnormal spirometric results will ever develop COPD, regardless of their smoking status. For example, in the Lung Health Study, only 10% of the variability in the subsequent decline in lung function in continuing smokers was predicted by baseline spirometric results, even when bronchodilator responsiveness and airway reactivity were included in the predictive model.[5] Therefore, very few participants in the CHS whose FEV_1/FVC was *below* the middle quintile (falling into the arbitrary GOLD stage I) have ever developed COPD. In fact, chronic bronchitis, emphysema, asthma and dyspnoea (as reported at study entry) were not independent predictors of a subsequently more rapid decline in lung function in the CHS cohort.[6]

The paper by Mannino et al suggests that GOLD stage I predicted "COPD-related" hospitalisations. However, the medical records were not examined for spirometric test results. I believe that the vast majority of these hospitalisations were not due to an exacerbation of COPD. In one recent study only one-third of 800 consecutive patients with a discharge diagnosis of COPD had a spirometric test.[7] A history of chronic cough, dyspnoea on exertion and cigarette smoking in hospitalised patients is more likely to be associated with heart failure or pneumonia than COPD.

In CHS participants with a normal baseline FEV_1 (GOLD stage I), 11 years of follow-up was not sufficiently long for even the continuing smokers to have lost enough lung function to have developed a COPD exacerbation. Current smokers in the CHS lost an average of only 48 ml/year during the first 7 years of follow-up,[6] which extrapolates to a loss of only 0.5 litres after 11 years. The average baseline FEV_1 was 2.4 litres in men and 1.8 litres in women.

In summary, as the CHS investigator responsible for spirometric testing in this study, I am not convinced by the analyses of Mannino and colleagues that GOLD stage I spirometry was a risk factor for COPD morbidity or mortality.

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What defines abnormal lung function?

A major concern with the GOLD criteria for defining chronic obstructive pulmonary disease (COPD) is that the use of 70% as a fixed cut-off for forced expiratory volume in 1 s (FEV_1) will add a significant number of false positives compared with the use of a true lower limit of normal.[1 2] The recent paper in *Thorax* by Mannino et al[3] argues that this false positive rate is acceptable because they found that these false positive subjects had an increased hazard of death when compared with those with $FEV_1 > 70%$. This finding is to be expected because a group with a less good level of lung function is being compared with a group with better lung function, even though both groups are within the normal range. For example, in the Copenhagen City Heart Study data, if the 8101 subjects whose FEV_1% in standardised residuals (SR) was >0 (ie, above predicted) are compared with the 1876 subjects whose FEV_1%SR was between 0 and −0.5, the latter have a hazard ratio (HR) for death of 1.09 (95% CI 1.02 to 1.17) (Dr Peter Lange, personal communication). If, instead, those above predicted are compared with the 1292 subjects with FEV_1%SR between −0.5 and −1.0, then the latter have a HR of 1.24 (95% CI 1.14 to 1.34). So these 3168 normal subjects have results for FEV_1% well within the normal range but have an increased HR for death when compared with that part of the population with the best lung function. This effect is even more true for FEV_1 itself.

Is it then justifiable to label an asymptomatic individual with a disease on the basis of spirometric parameters that are within the accepted normal range just because they have an increased risk of death? If this argument is further developed, then male sex is also a disease since life expectancy in men is lower than in women.

Labelling an individual as having a disease can have a bad psychological effect and, if there is as yet no proven treatment for the presumed condition, this is an even more unacceptable state of affairs. Disease has been defined as "an impairment of health or a condition of abnormal functioning" (www.hyperdictionary.com) and as "a disorder of structure or function in a human, especially one that produces specific symptoms or that affects a specific part" (Oxford English Dictionary). The current GOLD definition of COPD does not meet these requirements for defining this disease and must be changed. Researchers may need to find another term to describe their point of interest rather than labelling normal individuals incorrectly as having the disease COPD.

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Definition of COPD GOLD stage I

Chronic obstructive pulmonary disease (COPD) is an important disease from a public health perspective, with a number of preventable occupational, environmental and personal risk factors. The Global Initiative for Obstructive Lung Disease (GOLD) was implemented to raise awareness of COPD and to improve the prevention and treatment of this lung disease.[1] A concern has been raised regarding use of the criterion "forced expiratory volume in 1 s/ forced vital capacity (FEV_1/FVC) <0.70" in the definition of GOLD stage I which may lead to overdiagnosis of COPD, particularly in older individuals.[2–5]

To address this controversy, Mannino and colleagues assessed COPD-related hospitalisations and mortality among 5201 individuals aged 65 years and older who had participated in the Cardiovascular Health Study.[6] The authors concluded that study participants they termed "potentially overdiagnosed" (those with FEV_1/FVC <0.70 who also had an FEV_1/FVC ratio above or equal to the lower limit of normal (LLN)) were more likely to die and to have COPD-related hospitalisations during the 11 year follow-up period than "normals" (those with FEV_1/FVC ⩾0.70 and FVC >80% predicted who were asymptomatic). Based on

this finding, the authors suggested that using the LLN criterion may miss some older individuals who could benefit from intervention.

This conclusion was based on the analysis where all "potentially overdiagnosed" participants classified as GOLD stages I–IV were grouped together and compared with the "normals", with a resulting mortality hazard ratio (HR) of 1.3 (95% CI 1.1 to 1.5). However, as noted above, the controversy focuses on individuals classified in GOLD stage I. Persons with $FEV_1/FVC < 0.70$ and $FEV_1/FVC \geqslant LLN$ within GOLD stage I represent the majority (72%) of the "potentially overdiagnosed" individuals[2] who would theoretically benefit from further clinical evaluation and treatment through adherence to the GOLD criteria. The adjusted mortality HR for this subgroup was 1.1 (95% CI 0.96 to 1.3) compared with the "normal" group.[6] The magnitude of the HR is quite small and the confidence interval includes 1.0. This contrasts with the significantly raised adjusted mortality HR of 1.4 (95% CI 1.1 to 1.7) for the GOLD stage I subgroup with $FEV_1/FVC < LLN$. The study results therefore do not substantiate a significant increase in all-cause mortality among the GOLD stage I subgroup that is "potentially overdiagnosed".

The authors report a small but statistically significant increase in the risk of hospitalisation with mention of COPD in the GOLD stage I subgroup of "potentially overdiagnosed" individuals compared with the "normal" group. However, individuals with respiratory symptoms but normal lung function (ie, GOLD stage 0 in the paper) had a similar increase in hospitalisations, both before and after adjustments. Because the "potentially overdiagnosed" subgroup included individuals with symptoms consistent with COPD, the observed increases in hospitalisations with mention of COPD could be attributable to the presence of respiratory symptoms rather than to any lung function abnormalities. The authors could address this confounding of lung function differences by symptoms by re-analysing the hospitalisations after excluding individuals with symptoms in the "potentially overdiagnosed" subgroups.

An additional concern with the study relates to the potential for diagnostic bias. The authors indicate that they analysed hospitalisations "with mention of COPD" but do not indicate whether or not these hospitalisations were attributable to COPD. Because the entire study population underwent initial spirometric testing, it is possible that some of the treating physicians were aware of the spirometry report and may therefore have been more likely to have mentioned COPD on discharge for those patients with an FEV_1/FVC ratio < 0.70, even if COPD did not actually contribute to the hospitalisation. The authors could address this potential for diagnostic bias by re-analysing the results, restricting the outcome of interest to hospitalisations for which COPD or other respiratory illness was the primary discharge diagnosis.

Adherence to the $FEV_1/FVC < 0.70$ criterion in GOLD stage I will potentially identify an additional 5.4 million individuals (58%) in the US population as having COPD compared with use of the LLN criterion.[2] This large group of individuals will experience anxiety as well as financial costs, but we do not believe there is sufficient documentation of a potential benefit.[6] We agree with others who recommend reconsideration of the FEV_1/FVC ratio < 0.70 as a criterion for identifying mild COPD.[2–5]

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Authors' reply

We thank Drs Enright, Miller and Petsonk *et al* for their insightful comments regarding our recently published paper.[1] Their concerns can be summarised as follows: (1) use of the fixed forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio of 0.70 rather than a lower limit of normal greatly "overdiagnoses" chronic obstructive pulmonary disease (COPD) and is thus detrimental to both public health and the psychological health of patients; (2) GOLD stage I COPD does not represent disease but is, in most people, simply normal ageing; and (3) our measure of "COPD-related hospitalisations" probably included many hospitalisations not caused by COPD.

While we recognise the potential for overdiagnosis posed by use of the GOLD fixed ratio criterion, historically the greater public health problem has been the underdiagnosis (and corresponding undertreatment) of COPD, especially lung function impairment that clinicians would consider clinically relevant (GOLD stage II or more severe).[2 3] We have seen many patients with misdiagnosed lung disease, and the misdiagnosis is almost always a result of either not having performed spirometric tests or having poorly done spirometric tests. We therefore believe that the lack of spirometric testing in clinical practice is the larger threat to misdiagnosis and hence that, from a public health and educational perspective, the emphasis should probably be on underdiagnosis rather than on overdiagnosis. The problem of underdiagnosis is further exacerbated by poor quality spirometry and underestimation of FVC owing to inadequate emptying of the lungs. This is not to say that we should ignore the problem of potential overdiagnosis. The debate that is going on at present about the different criteria for airflow obstruction is a healthy one that can best be informed by analyses such as ours and the subsequent discussion that such analyses generate. This is how knowledge advances, and we are happy to have stimulated a lively discussion and anticipate that it will lead to further studies and analyses.

The question of whether the GOLD stage I classification really just represents "normal" ageing in most people is another area of ongoing debate. Although we do not dispute that the FEV_1/FVC decreases with ageing and that not everyone meeting GOLD stage I criteria has "disease", we also know that, on average, older individuals with better lung function tend to live longer and are more healthy than those with worse lung function.[4] We also know that those with respiratory symptoms fare worse than do those without such symptoms. Finally, while we acknowledge the potentially negative psychological consequences of labelling someone as having a chronic disease, patients understand the concept of disease staging, and telling someone that they have potentially early stage COPD may in fact have some positive public health consequences. For instance, one study has noted that patients who underwent spirometric tests and were found to have "mild" disease were more likely than subjects with "normal" lung function to stop smoking, and that cessation rates were even higher in those who were told they have "moderate" and "severe" disease.[5] Again, we anticipate that trying to address the questions surrounding normal ageing versus the development of early disease will lead to further studies and analyses of longitudinal data.

As to whether our measure of COPD-related hospitalisations was too inclusive, we agree that not all of these hospitalisations were for COPD exacerbations per se. The link between COPD and other diseases (such as pneumonia, congestive heart failure and lung cancer) has been well established, and many hospitalisations in patients with COPD are for these co-morbid conditions.[6] However, lung function impairment does consistently seem to increase the risk of such hospitalisations.

In conclusion, the letters published here raise some important issues at the intersection of how we define disease (particularly in epidemiological studies) and how we treat it. In practice, while we use the GOLD criteria to classify the severity of disease in our patients with respiratory disease, we use clinical criteria such as the presence of symptoms or quality of life impairment to guide treatment. This is particularly true in mild disease where the best interventions are smoking cessation, weight loss and exercise.

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