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CORRESPONDENCE

Definition of COPD: based on evidence or opinion?

To the Editors:

In 1986, the American Thoracic Society (ATS) first suggested a fixed ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) <0.75 to define airflow obstruction [1]. Subsequent ATS documents published in 1991 [2] and 1995 [3] generically defined airflow obstruction as a reduction of FEV_1/FVC, without recommending any numerical cut-off point.

By contrast, the European Respiratory Society (ERS) guidelines [4] suggested the diagnosis of airflow obstruction be based on a ratio of FEV_1 to slow vital capacity (VC) <88 and <89% of predicted in males and females, respectively. These values were not arbitrarily chosen as they roughly correspond to the lower 95th percentiles of frequency distributions of a healthy population. More importantly, they are consistent with the well-known decrease of lung elastic recoil and, by inference, of forced expiratory flow with ageing.

In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) took a step back, defining chronic obstructive pulmonary disease (COPD) by a fixed FEV_1/FVC <0.70 [5]. Since then, the enthusiasm for having new guidelines has led the scientific community to overlook the possible consequences of such a definition, even if it was already clear that it may be a source of falsely positive cases in the general population [6]. This was confirmed in a study in the USA [7] evaluating the impact of different definitions of airflow obstruction on the epidemiology of COPD. Quoting CELLI *et al.* [7], ''differences may be large, altering population prevalence estimates of COPD by >200%''. It is noteworthy that, using FEV_1/FVC <0.70, the prevalence of COPD in individuals aged ⩾70 yrs would be ⩾40%.

At variance with the GOLD guidelines, the recent ATS/ERS guidelines on lung function testing [8] stressed the use of lower limits of normality (LLN), *i.e.* the lower fifth percentile of the frequency distribution of a healthy population, to define pulmonary function abnormalities.

In a recent editorial published in the *European Respiratory Journal*, MANNINO [9] took a strong position in favour of the fixed FEV_1/FVC <0.70, claiming that it is easy to keep in mind, thus helping to remove the barriers to a widespread use of spirometry, and is more sensitive than LLN to identify patients at risk of death and COPD-related hospitalisations [10].

We would like to draw the attention of the readers to the following critical issues.

First, the fixed cut-off point indicated by GOLD guidelines may have negative consequences by misclassifying healthy elderly subjects as COPD, thus possibly causing unnecessary treatment, and by misclassifying as healthy a number of subjects aged <50 yrs already affected by COPD [9], when something could be done to limit disease progression.

Secondly, the fact that risks of death and COPD-related hospitalisation [10] are predicted by FEV_1/FVC <0.70 indicates that such an index may identify a proportion of individuals at risk [6], which has nothing to do with defining the diagnosis of the disease. Furthermore, it is an index which *per se* cannot reflect the severity of disease [8]. This is clearly apparent if one keeps in mind that two patients with FEV_1 of 20 and 100% pred may have the same FEV_1/FVC <0.70 or even <LLN, depending on the associated reduction of FVC.

Thirdly, an FEV_1/FVC >0.70 or even >LLN cannot exclude airflow obstruction with certainty because, in a minority of cases, FEV_1 and FVC may be decreased proportionally as a result of an isolated increase in residual volume [8]. This may lead to a false diagnosis of restriction instead of obstruction.

Fourthly, software and hardware have now changed the way of laboratory testing and there is no longer a need for manual, time-consuming calculations of predicted values, as even inexpensive spirometers can have predicting equations and statistically derived LLN values built in.

Finally, we understand that a fixed ratio might be useful where predicting equations are not available. However, the severity classification suggested by GOLD guidelines to tailor treatments, based on the percentage decrease from predicted FEV_1 [5], would be meaningless.

We are confident that with the world very rapidly ''going global'', the advancement of technology in the medical field will help to promote a larger use of lung function testing and, with it, the generation of reference equations for different countries and ethnicities. For the time being, however, we suggest that a definition of the pulmonary defects consistent with solid principles of lung physiology is maintained.

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STATEMENT OF INTEREST

None declared.

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Variation in the tumour necrosis factor-α gene is not associated with susceptibility to Asian COPD

To the Editors:

In a recent issue of the *European Respiratory Journal*, CHAPPELL *et al.* [1] clearly demonstrated that the lack of association with any of the tumour necrosis factor (TNF)-α single nucleotide polymorphisms or haplotypes makes it highly unlikely that polymorphisms in this gene play a major role in susceptibility to chronic obstructive pulmonary disease (COPD).

Their sample sizes were sufficient to elucidate association of TNF-α gene variations with susceptibility to COPD. However, they neglected the effect of ethnicity differences in genetic susceptibility to COPD. The frequency of the TNF-α-308*2 allele in Caucasian control populations (10–17%) is higher than that in Asians (0–8%) [1–10].

Genetic susceptibility to COPD is dependent upon the action of several gene polymorphisms, sex, age and ethnicity [2]. The TNF-α gene is known to have a polymorphic site at position -308. The TNF-α-308*2 allele, which is associated with a higher level of TNF-α production, has been associated with chronic bronchitis, a characteristic part of COPD, in a Taiwanese population [3]. However, the association of a polymorphism of TNF-α with susceptibility to COPD or to tobacco-related airway inflammation has not yet been confirmed in Asians. It was investigated whether the TNF-α-308*2 allele was associated with COPD in a Japanese population using a PCR-based genotyping assay [4]. The TNF-α-308*2 allele was found in one (1.9%) out of 53 patients with COPD and in one (1.5%) out of 65 smoker control subjects without COPD [4]. The frequency of the major allele, *i.e.* TNF-α-308*1, in the smoker control subjects (0.99) was consistent with data reported previously for other Japanese populations, suggesting that the present samples are representative of TNF-α gene polymorphism in the Japanese population [5]. However, there were no differences between COPD patients and smoker control subjects regarding the allele and genotype frequency of TNF-α. Since chronic bronchitis is not exactly the same, in terms of definition and tobacco sensitivity, as pulmonary emphysema, which is a major feature of COPD, it is possible that the TNF-α polymorphism is associated with infection-related bronchitis rather than tobacco-smoke-related alveolar wall destruction. However, most of the TNF polymorphism studies investigating COPD susceptibility revealed negative results for various Asian populations (table 1) [6–9]. Only one group of authors have insisted that the TNF-α-308*2 may be partly associated with the extent of emphysematous changes in patients with COPD [9].