3 Falzon D, Jaramillo E, Schünemann HJ, *et al*. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011; 38: 516–528.
4 Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *Eur Respir J* 2005; 25: 564–569.
5 De Lorenzo S, Centis R, D'Ambrosio L, *et al*. On linezolid efficacy and tolerability. *Eur Respir J* 2012; 39: 770–772.

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Recommendations for epidemiological studies on COPD

To the Editors:

The authors of the European Respiratory Society Task Force report on recommendations for epidemiological studies on chronic obstructive pulmonary disease (COPD) are to be commended for a thorough review leading to firm and well-founded recommendations [1]. This is an important step towards harmonising the definition of COPD and better understanding the true burden of COPD around the world. However, we would like to raise two points.

In their report (p. 1263), the authors state: ''A recent report from an 11-yr follow-up study of 4,965 subjects aged $\geqslant$65 yrs at baseline, showed that subjects with an FEV1/FVC ratio $<$0.7 but above the 5th percentile still had an increased risk of death and COPD-related hospitalisation compared with asymptomatic subjects with normal lung function'' [1] (citing previous results [2]). The citation and interpretation of the findings are incorrect. First of all, MANNINO *et al*. [3] misrepresented their own findings by stating that the risk of death in that group was increased; the adjusted odds ratio (95% CI 0.96–1.3) was not significantly different from that in healthy controls [4, 5]. Secondly, the authors conceded that the ''measure of COPD-related hospitalisations was too inclusive'', which likely further overestimated the odds ratio [6].

The Task Force recommends that ''spirometric values should be post-bronchodilatory whenever possible'' [1]. We are not aware of any other field in medicine where a diagnosis of disease is rejected because a therapeutic drug moves a finding from the abnormal to the normal range. Moreover, the normal range is invariably derived from healthy individuals who were not administered that medicine. It is well known that in healthy subjects with no risk of COPD, bronchomotor tone is relieved by short-acting bronchodilators, so that forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC) may increase by up to 9%, but there are also decreases in the ratio in many individuals [7]. The recommendation to measure post-bronchodilator spirometry therefore requires the use of post-bronchodilator reference values. As bronchodilators simply move the 5th percentile for FEV1, FVC and FEV1/FVC upwards, at any age, the percentage of subjects below that percentile compared with pre-bronchodilator values is very similar in subjects at risk or without risk of COPD [7]. It seems, therefore, that administering bronchodilator drugs to healthy subjects for deriving post-bronchodilator reference values is an exercise in futility. There are also ethical issues, side-effects and contra-indications that need to be taken into account before giving healthy people a bronchodilator. The emphasis on post-bronchodilator spirometry will lead doctors to gradually adopt it routinely and disregard baseline values, putting elderly subjects particularly at risk [8, 9]. It will increase the cost of lung function testing and lead to very costly new studies to establish post-bronchodilator predicted values, which will take many years to complete. Yet, we already know which subjects are at risk of early death and morbidity: those in whom pre-bronchodilator FEV1/FVC is below the 5th percentile [10]. We therefore posit that the routine measurement of post-bronchodilator values should be discouraged.

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REFERENCES

1 Bakke PS, Rönmark E, Eagan T, *et al*. Recommendations for epidemiological studies on COPD. *Eur Respir J* 2011; 38: 1261–1277.
2 Mannino DM, Watt G, Hole D, *et al*. The natural history of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27: 627–643.
3 Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax* 2007; 62: 237–241.
4 Quanjer PH, Ruppel GL. Diagnosing COPD: high time for a paradigm shift. *Respir Care* 2011; 56: 1861–1863.
5 Quanjer PH, Furberg CD. GOLD COPD stage I is not associated with increased risk of death. *Respir Med* 2012; 106: 153.
6 Mannino DM, Buist AS, Vollmer WM. Authors' reply. *Thorax* 2007; 62: 1108–1109.
7 Pérez-Padilla R, Hallal PC, Vázquez-García JC, *et al*. Impact of bronchodilator use on the prevalence of COPD in population-based samples. *COPD* 2007; 4: 113–120.

8 Bellia V, Battaglia S, Matera MG, *et al.* The use of bronchodilators in the treatment of airway obstruction in elderly patients. *Pulm Pharmacol Ther* 2006; 19: 311–319.
9 Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008; 300: 1439–1450.
10 Vaz Fragoso CA, Concato J, McAvay G, *et al.* Chronic obstructive pulmonary disease in older persons: a comparison of two spirometric definitions. *Respir Med* 2010; 104: 1189–1196.

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From the authors:

We thank P.H. Quanjer and co-workers for their valuable comments to our paper [1]. Chronic obstructive lung disease (COPD) is a syndrome and we welcome a debate on how to define it in an epidemiological setting.

First of all, we should state that we are in favour of forced expiratory volume in 1 s (FEV_1)/(forced) vital capacity ((F)VC) ratio lower than the 5th percentile of the normal distribution as the diagnostic criterion for COPD. That is why our paper recommends this criterion for COPD in epidemiological studies [1]. However, we should acknowledge that there are controversies on this topic. For the sake of completeness, the study by MANNINO *et al.* [2] was cited. We agree that MANNINO *et al.* [2] showed that the age-adjusted hazard ratio of mortality of those with an $FEV_1/FVC < 0.7$ and greater than the 5th percentile of the FEV_1/FVC ratio did not reach the level of significance when compared to those with an $FEV_1/FVC > 0.7$. However, they also showed that there is a clear dose–response relationship, with increasing hazard ratios of mortality with decreasing FEV_1/FVC, the reference being an $FEV_1/FVC > 0.7$. An $FEV_1/FVC < 0.70$ may be considered a risk factor for the development of COPD as diagnosed by an FEV_1/VC less than the lower limit of normal [3].

As to the question of using a bronchodilator prior to spirometry in epidemiological studies, we think that the criteria for COPD used in epidemiological studies should be the same as in the clinical setting, in which post-bronchodilator spirometry is recommended. This will enhance interpretation and comparison between studies as well as communication with politicians and healthcare providers. Spirometric reference values based on post-bronchodilator values are already available [4].

If the research question also relates to reversibility, then both pre- and post-bronchodilatory spirometry should be performed. Studies show that it is not only the level of FEV_1/(F)VC that may differ between pre- and post-bronchodilator values of the ratio, but also the observed risk factor–disease relationships, especially those related to age and smoking [5]. The potential risks of inhaling a β-agonist in the recommended doses are negligible [6].

We acknowledge that there is the possibility that some subjects choose to abstain from participating in an epidemiological study because they do not want to inhale the medication. However, in a Norwegian community sample aged 18–73 yrs, this figure was only 3%. The characteristics of the nonresponders in this study did not differ overtly from those seen in other studies [5, 7, 8]. As to the cost, our experience is that the cost, in both time and money, of using a short-acting bronchodilator is very modest compared with the total cost of running a community study on COPD.

As shown by both our report and the comments of P.H. Quanjer and co-workers, there are several methodological questions related to the diagnostic criteria of COPD. This clearly points to the need for further epidemiological surveys on COPD.

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REFERENCES

1 Bakke PS, Rönmark E, Eagan T, *et al.* Recommendations for epidemiological studies on COPD. *Eur Respir J* 2011; 38: 1261–1277.
2 Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax* 2007; 62: 237–241.
3 Viegi G, Pedreschi M, Pistelli F, *et al.* Prevalence of airways obstruction in a general population: European Respiratory Society *vs* American Thoracic Society definition. *Chest* 2000; 117: Suppl. 2, 339S–345S.
4 Johannessen A, Lehmann S, Omenaas ER, *et al.* Post-bronchodilator spirometry reference values in adults and implications for disease management. *Am J Respir Crit Care Med* 2006; 173: 1316–1325.
5 Johannessen A, Omenaas ER, Bakke PS, *et al.* Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. *Thorax* 2005; 60: 842–847.