Author’s response to reviews

Title: Lung function decline in relation to diagnostic criteria for airflow obstruction in COPD in respiratory symptomatic subjects

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Author’s response to reviews: see over
Response to the Reviewers’ comments (in italic typeface)

Reviewer: Marco Contoli

Reviewer’s report:

The aim of the study was to evaluate lung function decline in symptomatic middle-aged and elderly subjects identified as ‘obstructive’ according to either the fixed 0.70 FEV1/FVC cutpoint or an age-and gender-specific LLN cutpoint for this ratio. The study is of interest however I have major concerns to address to the authors.

Major Compulsory Revisions

The authors found that the annual postbronchodilator FEV1 decline in obstructed subjects based on FEV1/FVC ratio but with a normal FEV1/FVC in term of age and gender-specific LLN (discordant subjects) were very similar to subjects who were non-obstructive according to both definitions, but also that it was less than half the rate of the decline observed in subjects with airflow obstruction base on both definition (obstructed patients). However discordant and obstructed patients were not matched for several variables that can influence lung function decline. Indeed, according to table 1, discordant patients were significantly milder (postBD FEV1 71.3%) compared to obstructed patients (postBD FEV1 58.1%) and smoking habit was different between the two groups with more current smokers in the “obstructed” group compared to “discordant” patients (55% vs. 36% respectively).

Authors’ reply: We subdivided the study population into three categories based on the presence of airflow obstruction at baseline as defined by the fixed post-BD 0.70 FEV1/FVC cut-off point and gender and age specific LLN cut-off points. It is inevitable that if one takes certain individual characteristics into account when classifying subjects in categories (in this case gender and age, as these two factors determine the LLN cut-off point for each subject) the respective subgroups will differ on these particular characteristics. Because older subjects are more likely to be in the discordant subgroup than younger subjects are, subjects in the discordant subgroup will on average be older than subjects in the other two subgroups. Thus, matching or other ways to adjust for differences between the subgroups in our regression models is not appropriate in this case, because – for the reason mentioned above – age and gender cannot be considered as ‘confounders’ when these characteristics have deliberately been used to categorize subjects. The same line of reasoning should be applied to the difference in FEV1 % predicted between the discordant and obstructive subgroups, because the current prediction equations tend to underestimate the FEV1 percentage predicted at older age – which particularly applies to the discordant subgroup (Miller, 1988; Roberts, 2006; Vaz Fragoso, 2010).

We fully agree with the Reviewer that some other patient characteristics that are not directly related to the way the cut-off points are defined (e.g., smoking, medication use) can influence lung function decline and therefore we took these characteristics into account in the analyses of our primary and secondary outcomes: separate analyses were performed for smokers and non-smokers to avoid possible confounding through the different distribution of smokers in the three subgroups, and for the same reason we adjusted our analyses for the different proportions of inhaled corticosteroid users by including a covariate in the regression models. We have added a few lines of text to the Methods (page 10) and Discussion (page 18) sections to explain and discuss this.
Moreover, was the proportion of asthmatic and COPD patients similar in the two groups?

Authors’ reply: In this study we used routine data from subjects with respiratory symptoms in whom a GP suspected a possible underlying chronic respiratory condition (COPD, asthma) and referred the subject to the primary care diagnostic centre for pre- and post-BD spirometry testing and standardized medical history taking. Respiratory consultants routinely assess the combined spirometry and medical history information, but because the consultants do not actually see the subject and do not have the possibility to request additional diagnostic tests (e.g., advanced pulmonary function testing, bronchial provocation test etc.) and/or further follow-up, their assessment is mainly limited to interpretation of the spirometry results in terms of presence or absence of obstruction, possible restriction, and reversibility. This is not sufficient to base a clinical diagnosis of COPD or asthma on and therefore we (unfortunately) cannot compare the groups in terms of proportions of patients with formal diagnoses of asthma or COPD. On consideration, we have deleted a sentence in the Discussion section to avoid confusion on this point (page 14: “Analysis of the non-obstructed subjects in whom a diagnostic advice was given showed that the majority (76%) had (probable) asthma and ~2% (probable) restriction” was omitted).

Finally, was the follow-up period during which the lung function decline was evaluated similar between study groups?

Authors’ reply: There were no differences in follow-up time between the study groups, which was 3.4 (SD 1.4) years for the subjects in the non-obstructed, 3.2 (1.4) years for the subject in the discordant, and 3.4 (1.5) years for the subjects in the obstructed group (p=0.592). This information is included in the manuscript in the first line of table 1.

The authors must adequately address these issues.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Reviewer: Ronald Halbert

Reviewer’s report:

This is a well-done study addressing an important issue: discordance between different definitions of COPD. Unlike many papers, the authors present new data to help shed light on the issue. Particular strengths include:

1) clear study question, appropriate design

2) nice dataset --representative of patients seen in primary care (but subject to issues well-discussed in the paper)

3) good analysis, with excellent sensitivity analyses addressing potential criticisms
I have one criticism -- actually a disagreement with the authors' interpretation of the results of alternate prediction equations (Tables 3a & 3b). The authors state on p. 14 that these alternative equations "generally showed the same picture...." However, Table 3a shows only 1 of 5 alternate equations showed significant differences in FEV1 decline (col 8). In Table 3b, 2 of 5 alternate equations show significance in the primary relationship at issue. These results do NOT in my mind show "...generally the same picture...", and are better interpreted as "...the principal effect described by the authors is highly dependent on which prediction equation one uses." Given the strength of the paper otherwise, I must consider this a discretionary revision.

Authors' reply: We agree with the Reviewer that the way we have formulated our interpretation of the results regarding the use of alternative prediction equations in tables 3a & 3b in the original submission is not entirely appropriate. The results show that using different prediction equations leads to different numbers of subjects (especially) in the discordant subgroup (ranging from n=14 to n=138 in discordant smokers and n=46 to n=251 in discordant non-smokers) which leads to different estimates and standard errors of the FEV1 decline. The estimated FEV1 decline is consistently larger in the obstructed subgroup compared with the discordant subgroup for all prediction equations in smokers (table 3a) as well as in non-smokers (table 3b), but the Reviewer is right in that this difference is not always statistically significant (which also depends on the number of patients in the discordant group). In line with the above we have rephrased our interpretation into:

"Use of alternative FEV1/FVC prediction equations generally showed that the annual postbronchodilator FEV1 decline in discordant subjects was lower compared with obstructed subjects. However, the use of different prediction equations lead to variable numbers of subjects in the respective categories, resulting in different estimates of FEV1 decline, variances and levels of statistical significance. It is therefore important that the most appropriate prediction equations for the study population are used to provide unbiased estimates of FEV1 decline and correct conclusions." We have also added this to the conclusion on page 18 ("....although the result is dependent on which FEV1/FVC prediction equation is used.").

Also, there are some minor necessary English revisions required.

Authors' reply: the revised manuscript has been read by a native speaker, which has resulted in some minor textual corrections.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.