Author's response to reviews

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

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Version: 3 Date: 14 December 2011

Author's response to reviews: see over
Response to the Reviewers’ comments on revised manuscript

Reviewer: Marco Contoli

Reviewer’s report:
I thank the authors for having addressed my criticisms. From my personal point of view some concerns still remain. In particular, the authors cannot specifically characterise study population in term of asthmatic and/or COPD patients. For this reason the term COPD cannot be used in the title.

Authors’ reply. In the original title we referred to the criteria used to diagnose COPD, without having the intention to refer to our study population to consist of patients with this disease only. We agree with the Reviewer that, in order to avoid confusion on this issue among readers, it would be better to omit ‘in COPD’ from the title. The title in the revision now reads ‘Lung function decline in relation to diagnostic criteria for airflow obstruction in respiratory symptomatic subjects’.

Moreover, and even more importantly, it must be more clearly stated in the title (e.g. “Lung function decline in relation to disease severity and diagnostic criteria for airflow obstruction in respiratory symptomatic subjects”) and addressed in the manuscript that “discordant subjects” are significantly milder (in term of FEV1% predicted) compared to “obstructed patients”. Therefore it cannot be excluded that the conclusion of the study - i.e. more steeper lung function in concordant vs discordant patients - could simply reflect the severity of the underlying disease.

Authors’ reply. The aim of the study was to look at the main criterion to decide whether or not airflow obstruction is present in a subject who consults a (primary care) physician with respiratory symptoms: FEV1/FVC<0.70 or, alternatively, a LLN cut-off point for FEV1/FVC that takes age (and gender) into account. After this essential ‘Yes/No’ decision has been taken, according to all current COPD guidelines (e.g., GOLD, ERS/ATS) the next step is to assess the severity of airflow obstruction (see scheme below).

![Figure 1-2: Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV1](image)

Our point is that looking at the severity of obstruction (i.e., the level of FEV1 % predicted) in subjects who have a low (i.e., <0.70) but normal FEV1/FVC value due to their older age is a pitfall, because several previous authors have shown that, after the presence of airflow obstruction has been ‘established’ based on a FEV1/FVC value <0.70, the use of the % predicted FEV1 severity criteria will classify healthy elderly people as having mild or even moderate obstruction. Just to illustrate this: the figure and table below from a paper by
Hardie et al. (Eur Respir J 2002 20:1117–1122) shows the consequence of doing this: 35% of healthy elderly never-smokers are considered to have COPD (at least in terms of lung function) when the current (GOLD) scheme is applied (there are several other studies showing similar results).

As indicated in our previous reply, this phenomenon is further amplified by the fact that prediction equations tend to underestimate the FEV1 percentage predicted at older age (Miller, 1988; Roberts, 2006; Vaz Fragoso, 2010).

Alternatively, to provide that LLN can better predict lung function decline, the authors must reanalyse the date comparing concordant and discordant subjects matched for age.

Authors’ reply. We do not agree with the Reviewer’s view on this point, see our comment in the cover letter and the extensive motivation in our previous reply to this comment with our considerations not to correct for age (which we have pasted at the bottom of this document, for your convenience). As the schematic representation below shows, age is inextricably related to the LLN cut-off point for the FEV1/FVC and thus to the categorization of subjects, which makes ‘correction’ for age in the analysis redundant.
Copied from our previous reply:

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.