Author's response to reviews

Title: Up-to-date on mortality in COPD - report from the OLIN COPD study

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Author's response to reviews: see over
To
The Editor-in-Chief, Tim Shipely, PhD
BMC Pulmonary Medicine

Re: Manuscript ID 7960221535366772
Up-to-date on mortality in COPD - report from the OLIN COPD study
By Anne Lindberg, Lars-Gunnar Larsson, Hana Mullerova, Eva Rönmark, and Bo Lundbäck

Dear Editor,

We thank very much for the encouraging letter from the journal and for the comments, remarks, constructive criticism and useful suggestions made by the referees, Dr Mannino and Dr de Marco, and we have rewritten the manuscript by following them. We have answered the questions and comments given by the referees point by point following the advice given and made appropriate changes.

The revised manuscript is hereby submitted. We believe the paper has improved considerably, and we now hope that the paper can be published in BMC Pulmonary Medicine.

Yours sincerely,

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Responses to the reviewers;
Reviewer: Dr David Mannino

1. It is unclear why Table 3 does not include smoking. Also both age and FEV$_1$ for the next table would make more sense if reported in 10 years (or 10% for FEV$_1$) intervals.

We thank Dr Mannino for this comment and agree that smoking habits is of great importance when discussing COPD, heart disease and mortality. When smoking habits not are included in the table 3, heart disease is (besides age, male gender and COPD) a significant risk factor for death, however, when smoking habits are included heart disease is no longer a significant risk factor. The tables 3 and 4 have been revised as suggested by Dr Mannino and smoking habits (the categories non-smoker, ex-smoker and smoker) are added as co-variates in both models, using non-smokers as reference group. The tables have been commented on in the section results (page 9) as well as in the section discussion (page 13). The abstract and the conclusion have been revised accordingly.

The presentation of age and FEV$_1$ as continuous variables could, as Dr Mannino wisely points out, be replaced by intervals of ages as well as FEV$_1$. We have looked into the data and thoroughly discussed the presentation of results. Even though the study population is large (993 cases of COPD and 993 non-COPD subjects matched by age and gender) the age distribution is skewed, and also the distribution of FEV$_1$ (as expected, fully comparable to the results from other general population studies within the area of COPD epidemiology) and this is one of the reasons why we would like to keep the current presentation of these variables as continuous.

2. The risk of heart disease barely changes from Table 3 to Table 4 (from 1.43 to 1.38). Thus, I believe saying that heart disease as a risk factor is “replaced” is over interpreting the data.

We respectfully take part of this comment and understand the importance of correct interpretation of data. Considering Dr Manninos comment, and also the results of the new tables 3 and 4, we have revised the conclusion in the abstract and also the wording in the section discussion (page 12, 13).

We have also made a test for interaction between heart disease and COPD, the result was negative, i.e. the risk for mortality associated to COPD is independent of presence of heart disease or not.

3. What proportion of the population (control) – was restricted? i.e- a normal ratio but a low FEV$_1$? This is a group that is also at increased risk of death over time

Restrictive lung function impairment is, as Dr Mannino clearly points out, a group with increased mortality and we understand that this should be commented on. In the population without COPD (i.e. FEV$_1$/FVC>70%) approximately 20% had a restricted lung function (FEV$_1$<80% of predicted) if we base the classification of restrictive lung function on the dynamic spirometry data. Even though the aim of this paper was not to analyse the properties of the restricted group, we have, after dr Manninos remark, added comments in which this
subject field is discussed (section discussion, page 12). The problems of using dynamic spirometry for classification of restrictive lung function are also discussed.
Responses to the reviewers;
Reviewer: Dr Roberto de Marco

1. The authors say in the introduction that “within the OLIN studies, cross-sectional and longitudinal data on respiratory diseases, including lung function, have been collected in several cohorts recruited from the general population since 1985”. However, they start the follow-up study only in 2002-2004. They should at least justify their choice and clarify the design of the study in the Methods section.

We thank Dr Marco for this comment and understand the need of clarification. The epidemiological research program the OLIN studies (Obstructive Lung Disease in Northern Sweden studies) started in 1985. Several cohorts, adult as well as children, have been recruited from the general population at different occasions since the start. All participants in previous examinations of the four adult cohorts recruited during the eighties and the nineties were invited to re-examination (spirometry and structured interview) starting in autumn 2002 and the re-examinations were completed during 2004.

The current COPD-population (n=993) was recruited from the examinations in 2002-2004; all subjects fulfilling the spirometric criteria according to GOLD (FEV₁/FVC<0.70) were identified together with a similar size age- and gender matched population without COPD.

The last part of the section introduction (page 4) and first part of the section Methods (Study design and Study population, page 5) has been revised accordingly.

2. It is not clear to me, why smoking is present as a risk factor in table 4 but not in table 3. In my opinion smoking should be present in both tables. In fact, table 3 suggests that people with “spirometric COPD” have a risk of dying double with respect to non-COPD subjects, after adjusting for other potential risk factors/confounders. However this estimate is not adjusted for smoking habits. Furthermore the interaction n between COPD and smoking habits should be evaluated in order to test if the effect of smoking on mortality is the same in COPD and non COPD subjects.

We thank Dr Marco for this remark and agree that the presentation of data needs to be considered. When smoking habits not are included in the table 3, heart disease is (besides age, male gender and COPD) a significant risk factor for death, however, when smoking habits are included in the model heart disease is no longer a significant risk factor. The tables 3 and 4 have been revised as suggested by Dr Marco and smoking habits (the categories non-smoker, ex-smoker and smoker) are added as co-variates in both models. The results have also been commented on in the section results (page 9) as well as in the section discussion (page 12, 13). Further, the abstract as well as the general conclusions are revised in accordance with the results.

In a multivariate model including age, gender, COPD and smoking, male gender and COPD significantly increased the risk for death (besides age). However, testing for interaction between smoking and COPD was negative, i.e. COPD was associated with an increased risk for death irrespectively if smoking or not. According to Dr de Marco suggestion these results are commented on in the section results (page 9).
3. There are two international cohort studies (de Marco et al AJRCCM 2009, Brideveaux et al Thorax 2008) showing that asymptomatic and non smokers subjects classified at baseline as mild/moderate COPD (spirometric GOLD criterion= had, after a 10-year follow up, a FEV1 decline and a rate of hospitalization for respiratory diseases similar to that of non COPD subjects. From the analyses presented, is not clear whether non smokers with spirometric COPD had a greater mortality than non COPD subjects. This should be analysed and discussed in a better way.

We thank Dr Marco for this remark and agree that presentation of data and discussion of the results could be improved, also in relation to other publications. The crude mortality data (Table 2) show that the mortality was higher in non-smoking subjects with COPD (8.3%) compared to in non-smoking non-COPD subjects (5.3%) but the difference did not reach statistical significance. The crude mortality was significantly higher in ex-smoking as well as in smoking COPD compared to in ex-smoking and smoking non-COPD subjects respectively. However, in the multivariate models (presented in the revised tables 3 and 4) show that non-smoking and ex-smoking is not related to an increased mortality in our study.

A limitation of the current study is that the definition of COPD is strictly made by spirometric criteria without regard to respiratory symptoms. The results are further discussed in relation to previous publications (page 11, 13) and a new reference has been added (de Marco et al, reference number 23). In the current manuscript we can not satisfactory answer to these questions; however, further follow-up of the cohort will give us data on the impact of respiratory symptoms on the disease progress in mild/moderate COPD in middle aged and elderly subjects.