Reviewer’s report

Title: Annual decline in forced expiratory volume and airway inflammatory cells and mediators in a general population-based sample

Version: 0 Date: 22 May 2018

Reviewer: Olaf Holz

Reviewer's report:

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The authors tested the hypothesis, that the normal decline in lung function over time in the general population is related to the inflammatory status in the airways. Therefore the relationship between sputum composition, assessed between 2003 and 2005, and the decline in lung function over at least 10 years was tested. 62 subjects were available in the follow up, so the authors were able to base their results on a quite large sample size. With few exceptions, no relationship between airway inflammation and the decline in lung function was observed.

Major:

1. The ratio for this study could be better described. I miss potential epidemiological data. There are studies from Canada and Italy available about normal sputum composition. Especially sputum neutrophils seem to differ between regions. Is there evidence, that e.g. environmental factors like pollution actually lead to different declines in lung function between differently polluted areas. In our experience (unpublished) weather and temperature (potentially linked to an increased exposure to pathogens) also seems to affect neutrophil levels in sputum. There is published data on the effect of aging on sputum composition (ref 18). In this respect it seemed a bit surprising, that the authors selected a normal population sample, which was actually quite old …mean age 55 at baseline. Why not younger?

2. The authors should potentially revise the arguments provided on page 16 in paragraph 2 and 3 (line 6, 14). The interindividual variability of induced sputum cell composition was well known in 2003. The same is true for the approximate decline in lung function in the general population. Therefore it does not seem to be appropriate to argue after the end of the trial, that the study was potentially underpowered.
Minor:

1. Not being a native English speaker, I still believe that the language of the manuscript could in parts be improved.

2. Is there a major reason for the rather large number of subjects that declined to participate (n=44)?

3. "All the participants were offered a reversibility test" … how many did accept this?

4. The description of sputum induction is not clear. All participants inhaled first 0.9% and all participants then inhaled 3, 4, and 5%? Each inhalation period lasted for 7 minutes? The statement "until a sufficient amount was delivered" suggests that some subject only e.g. inhaled for 5 min others e.g. for 20 min. The danger in doing so is, that it could affect sputum composition, as the first portions produced are generally rich in neutrophils and later portions richer in macrophages.

5. Was the sputum selected from saliva prior to processing? Or was the whole exspectorate processed. This is important to interprete the biomarker levels in the supernatant.

6. Cytospins were evaluated and not smears, as stated in page 8 line 12.

7. The provided additional file shows the agreement between 2 evaluators. From the text page 8 I thought this referred to the differential cell count, but the axis in the figure appears to refer to cell numbers/ml sputum and its not clear for which cell type. Please clarify.

8. Table 1: what does Packyears refer to… the mean of all smokers (active and quitters?)

9. Table 2. Tertiles numbers do not add up to 62.

10. dFEV1 Table 2: 33.0 in abstract 32.9… should be consistent.

11. How many started smoking during the observation period? Page 12 top paragraph

12. Table 3: the levels of sputum cytokine appear to differ from the literature, which is likely to to the use of the bead multiplex assay. IL8 levels seem to be rather low, and very similar to IL6 levels, which are generally lower in sputum. IL17 subtypes on the other hand appear to be very high. In such a large sample size there should be a correlation between log IL8 levels and log number of sputum neutrophils. Did the authors see such a correlation?
13. Table 4: Comparing 5 vs 49 subjects for me is already borderline, comparing 2 vs. 49 does not seem to be appropriate. The data about these subgroups should be mentioned and discussed, however, at least for ACO the statistics should be removed.

14. I do not think that a small sample size was a limitation of the study. 62 subjects is quite a reasonable number. With this sample size it should be possible to detect a clinically relevant relationship between airway inflammation and the decline in lung function.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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I am able to assess the statistics

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