Reviewer’s report

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

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Reviewer: Wassim Labaki

Reviewer's report:

In this manuscript, Kononova and colleagues found that markers of inflammation in the blood and the sputum do not predict decline in FEV1 over 10 years of follow-up in a population-based sample of healthy participants. Although the objectives and hypotheses of the study are interesting, many concerns must be noted regarding data analysis:

The reported mean decline in FEV1 was 32.9 ml/year for the cohort. This decline could be mostly due to the effect of advancing age. If we consider a Caucasian man with the mean age reported in the study (55 years) and the mean height reported in the study (1.74 m), his expected FEV1 is 3.58L based on the NHANES spirometry reference equations. The expected FEV1 of the same man 10 years later (i.e. at age 65) is 3.25L. His decline in FEV1 over 10 years is 3.58 - 3.25 = 0.33L = 330 mL which equates to a decline of 33 mL per year, the same mean decline observed in the cohort. This overall relatively small decline in FEV1 is not surprising as the recruited participants were reportedly healthy at baseline with a limited smoking history. Along the same lines, categorizing the decline in FEV1 by tertiles may not be physiologically accurate. If we look at the highest tertile (> 38 mL/year), such a decline may be expected for a tall man but may be indicative of disease in a short woman. Therefore, given the aforementioned observations, to more accurately assess the effect of inflammatory markers on FEV1 decline, it may be better to analyze it while controlling for other factors that can influence spirometry results such as age, sex, height and smoking history (e.g. in a multivariable model).

Additional comments:

- Although a positive reversibility test is a common feature of ACO, it may not be enough alone to diagnose it.

- On page 9, lines 8-9, the authors state that "there were no significant differences between total, follow-up and not follow-up groups." I recommend just directly comparing the characteristics of the follow-up and not-follow-up groups (while still showing the total in the table).
- For comparisons in Table 2, unless the authors are working with normally distributed data, I recommend using a Kruskal-Wallis test instead of a one-way ANOVA test to compare characteristics across the three groups given the small number of subjects in each group.

- There seems to be a number of discrepancies in the raw data shown in Table 2 of which I will point out a few: a) the number of participants in the groups (20, 22 and 19) add up to 61 (not to the 62 subjects with follow-up data), b) the number of reported males is 61 (should be 35?), c) the mean monocyte count for the total group is reported as 0, which is unlikely given that two of the tertiles have mean monocyte counts of 0.4 each.

- In Table 4, only two subjects have post-BD FEV1/FVC ratio < 0.7 with reversibility, which makes it hard to draw any definitive conclusions regarding this subgroup.

- Furthermore, in Table 4, given the low number of subjects being compared in each group, a non-parametric test such as Mann-Whitney test would be recommended instead of a two-sample student t-test.

- Again, there seems to be a number of discrepancies in the raw data in Table 4 of which I will point out a few: a) the number of participants in the groups (49, 5 and 2) add up to 56 (not to the 62 subjects with follow-up data), b) the percentages of females between parentheses (on the last line of the table) may be incorrect.

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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.

No

**Are the conclusions drawn adequately supported by the data shown?**
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No

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