Author’s response to reviews

Title: Lung function and systemic inflammation associated with short-term air pollution exposure in chronic obstructive pulmonary disease patients in Beijing, China

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Author’s response to reviews:

Because there are table and figure in our responses. We uploaded the response to reviewers in Personal Cover.

Response to Reviewers

Reviewer #1: The authors have largely responded to my comments, although a few remaining minor suggestions remain, mostly related to the results.

1. In line 8 page 10, it is probably more informative to say that there was a difference in the distribution of ozone only (rather than list all the pollutants for which there was no difference).
Response: Thanks a lot for your valuable suggestion. According to another reviewer’s suggestion, we deleted the dataset of the health population in our study. So, we deleted the sentence in the revised manuscript.

2. On line 11 page 11, associations with IL2 were not observed for SO2 (Figure 5, S5). I think the authors meant to say PM10 instead of SO2 here, as PM10 is not mentioned but probably should be. Similarly, why is CO not included in the multilag results for MCP-1 (Figure 6)? For Figure 6 MCP-1,
the authors also say that associations with PM2.5 are observed, but this does not appear to be strictly true in the Figure, given that all other results are judged based on the presence/absence of formal statistical significance.

Response: Thanks for pointing these out. Associations with IL-2 were observed for PM2.5, PM10, NO2 and CO (see page 10, line 12-13). For MCP-1, similar correlations were observed with exposure to PM10, NO2 and CO (Figure 5 and Figure S5) (see page 10, line 20-21).

3. If the authors only presented results that are significant for the biomarkers in Table S3, why are graphs for IL5, VEGF-A and GM-CSF not shown, as from Table S3, significant associations were observed for these outcomes?

Response: Thanks a lot. In our results, IL5, VEGF-A and GM-CSF only correlated with few air pollutants. So, we didn’t show the results in the initial manuscript. We had added the figures about IL-5, VEGF-A and GM-CSF in the revised results (see page 10, line 22; page 11, line 1-3).

4. Finally, there continues to be some examples of grammatical errors throughout. Some of which are minor: e.g "was" should be "are" on line 11, page 4, the term "miss rate" is incorrect (line 21, page 8). However, in some cases, these grammar issues make the results difficult to interpret. Eg. Lines 14 - 15 page 10, saying that there is no reverse association between air pollution and FEV1 and FEV1% (as compared to FVC). Why would a reverse association be expected? I think what the authors are suggesting is that they did not observe "similar" associations as for FVC. Another example is in line 1 on page 11, the authors state that "an inverse trend was noted" for certain biomakers. What is meant by "inverse". I think the use of increasing levels and decreasing levels would be easier to understand rather than "inverse, positive, negative" which are currently frequently used to describe the results. In some cases, no direction is stated, such as in line 22 page 11 in which associations are referred to as only "significant". I suppose, if accepted, the journal editorial team will consider these issues, but this will likely require some input from the co-authors.

Response: Thanks a lot. We have carefully revised the manuscript and tried to improve the language in the revised manuscript. We also requested professional support from the Springer Nature Author Services.

Reviewer #2: The authors have addressed adequacy most of the reviewers' comments. However, there is still one aspect that remains confusing to me.

Indeed, the authors' reply to the comment regarding the reason for including a healthy group, reinforces my initial concern.(1) If a direct comparison between the two groups is not feasible, in particular if the models applied in COPD patients and healthy individuals are not comparable (importantly, something not stated in the manuscript), then I do not see the real added value of the observations in healthy individuals (In that case direct, but also indirect comparisons, cannot be made). In the methods section it is stated that "The model was adjusted for age, sex, marital status, educational level, smoking history, body mass index and daily temperature and humidity. Therefore readers understand that it is the fully adjusted model used both in COPD and healthy individuals since all these potential confounders are relevant in both groups. But from the answer provided I understand it is actually not exact and I have no idea which factors were not included (or coded differently?) in the analysis among the healthy individuals, and to which extent it might explain differences in association observed between the 2 groups (No additional information on the confounders included in the models was provided in the legends/notes of figures and tables).

Overall, I'm still not convinced that data provided in the healthy group is highly relevant given the
methodological limitations that prevent any comparison between observations in cases and healthy groups (except if the authors can provide sufficient information to indicate that differences in models cannot explain differences in association results).

(1) "We want to observe the effects of air pollution on both COPD and healthy participants because scarce studies explored the effects of air pollution on circulating cytokines both in COPD and healthy participants. However, many covariables did not matched between two groups in the study, direct comparison is not appropriate. We took the results of healthy population as indirect reference to COPD patients."

Response: Thank you for your insightful suggestion. In this study, COPD and health group were adjusted for the same confounders (age, sex, marital status, educational level, smoking history, body mass index and daily temperature and humidity). However, some factors are quite different between COPD and health group (see table below), for example: (1) the health participants are all non-current smokers; (2) COPD patients were older than health participants. Although these confounders were adjusted in the model, we cannot ensure those factors had no effects on the differences between the 2 groups. Adjustment of those factors helps to control the confounding effect. However, these factors may have effect of modification. This was the reason why we did not make a direct comparison between the two groups. As you pointed out, this study was focused on the effects of air pollution on COPD patients. Your concerns are critical for the interpretations of our analysis. After careful consideration of your suggestions, we agree that it is inappropriate to include health group in this study. We decided, as you suggested, to remove the health group in the revised manuscript. This is the most important modification of the current version. Please review our current version and we wish it will be much straightforward.

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<th>COPD (n=84)</th>
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<td>Current smokers</td>
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