Reviewer’s report

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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Reviewer: Elaine Fuertes

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Summary

Using repeated data over a one-year period, the authors found that exposure to several air pollutants was associated with reduced FVC% predicted, but not with reduced FVC when measured in absolute levels, or any measurement of FEV1, in 84 COPD patients. No consistent associations were apparent in 64 healthy volunteers. Using a subset of this population (30 COPD patients), the authors also found several associations between markers of air pollution and numerous biomarkers of systemic inflammation. Again, no consistent associations appeared among healthy participants. The analysis presented is interesting, but in its current form, is rather confusing due to unclear aspects of the methods, and the huge number of tests conducted and reported.

Major points

1. There is a very large number of tests conducted and no consideration of the issue of multiple testing. Do these authors anticipate that all reported associations are "real" and independent of one another? Reporting correlations between the air pollutions, lung function measures and biomarkers might provide some insight here. Furthermore, given the large number of tests done, I would recommend not strictly looking at p-values < 0.05 to decide on which results to report - many associations for PM10 are right on the border but not mentioned.

2. Although I understand that at some point an analysis must be done on the available data, according to the text, the full study sample should have been available as of September 2018. This leaves the reader wondering, why did the authors only use one of the available two years of data in their analysis. Do the results replicate when two years of data is considered?

3. The models were not adjusted for height and weight. Have the authors tested these as potential confounders? Further, as BMI might lie in the causal pathway, an analysis removing this covariate might be of interest.

Minor points

1. When the authors report that no associations were found for the other cytokines in the results section, could they provide a list for the reader. I would also encourage the authors to provide justification for why they selected to test these particular biomarkers, and if this is hypothesis based, providing the
reader in the introduction with a clear expected direction of effect would greatly facilitate the interpretation of the results.

2. More information on how the air pollutants were assigned is required. In the abstract, this is simply described as "achieved". For example, how far were the participants on average from the monitoring data? Were there issues with missing data?

3. There is no discussion as to why %predicted FVC should show the strongest associations, especially as results were reported as null for FVC. Could the authors please expand as to why this may be?

4. Were there significant differences between the air pollution concentrations between the healthy and COPD groups?

5. In the introduction, the authors state that a limitation of previous studies is that they have only used "short follow-up periods". Could this be quantified? Providing a range of how many months/years were used in previous work would help justify the current manuscript even more.

6. The description of the selection and derivation of the study sample needs to be clarified. At the top of page 6, the authors state that all subjects 18-75 years residing in Beijing for at least 1 year were invited. Do the authors mean "eligible" here, instead of "invited"? Also, based on what criteria were 30 COPD and 30 healthy participants selected for serum cytokine detection? After applying the exclusion criteria listed, was a random selection made?

7. Table 1 should present the characteristics of the 75 COPD patients who were analyzed in this study, and the not 84 who were originally recruited.

8. It is unclear how often each sampling took place. For example, "baseline and 1-year" used for blood sampling, "each visit" used for lung function, and "baseline, half-year and 1-year" used for serum cytokine detection all in the Methods, yet "every three months" used in the abstract for serum and spirometry. The number of visits and available samples for each outcome should be made clear.

9. Was an analysis conducted looking at the impact of potential outliers in the biomarkers, as some of these can have very high (and very influential) values.

10. Can the authors clarify how those with asthma-COPD were identified in the text?

11. When the authors state that the single lag models for the biomarkers are in the Supplement, could they also briefly describe for the reader if the results were similar.
12. Very minor, but the results for IL2 are not described in the text, although this is done for all other biomarkers which show associations. Also, CO should likely also be included in the description of the results for MCP-1.

13. The statement that the effect estimates for IL2, IL17, sCD40L and MCP-1 in COPD patients were greater as the lags increased does not appear to be supported by the results, especially not for IL2 and MCP-1. Please revise, and consider whether this statement is justified in general, given the fact that the confidence intervals very largely overlap in all cases.

14. Why focus on the PM results in the conclusion, with "especially PM"?

15. Why do the authors include the description of CRP, ESR, IgE, for example, when these factors are never used in the analysis?

16. 18 smokers are listed among the COPD patients in the Results text, but 22 is given in Table 1.

Grammar/presentation

17. COPD should be defined in first sentence of abstract, not in second.

18. Some minor grammatical issues remain in the text and should be corrected. For example, "in association with air pollution" needs to be added to the sentence ...."The researchers found that RH1, TH17, INFN, IL17 were increased in COPD mice...." on page 13, or else the reader does not know how this relates to the current work that looks at air pollution effects. There are a few other points in the text when the grammar/sentences are unclear.

19. The authors could reconsider the use of "change" in the y-axis of the Figures. Is this really what is modelled, or rather a comparison of mean differences?
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