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

Version: 0 Date: 11 Oct 2019

Reviewer: Valérie Siroux

Reviewer's report:

Gao N and co-authors investigated the acute effects of air pollution exposure in lung function parameters and serum cytokines in a group of COPD patients (n=75) and a group of healthy individuals (n=64) in China. The analysis is based on lung function and cytokines measured each 3 months in the first-year follow-up. Results indicate that 4 pollutants (NO2, PM2.5, SO2 and CO) were statistically significantly associated with a lower FVC in COPD patients although only SO2 was inversely associated with lower FVC and FEV1 in healthy subjects. The study further show that short-term air pollutants enhances systemic inflammation in COPD patients, by aggravating the Th1/Th2 and Th17 cytokines imbalance. Overall the manuscript is well written and provide interesting results in the field. Nevertheless, I have some concerns detailed below.

1) Overall strategy: This paper is aimed to address effects of air pollution on lung function and systemic inflammation among COPD patients. The reason for including a healthy group is not clearly stated (neither in the introduction, nor in the methods) and by providing results from a large set of associations independently in each group makes the interpretation uneasy. If the authors wish to show that COPD patients are more vulnerable to air pollution then it needs to be explicitly stated (including in the aims) and statistical tests of interaction (disease*air pollutant exposures) are warranted.

2) Population: It is unclear why the study is based only on the first-year follow-up (p.6 line 15-16) although data up-to the 2-year visit have not been recorded and are available according the flow-chart. This needs to be explained and scientifically supported.

3) Population: The number of subjects retained for the analysis is unclear and inconsistent through the manuscript: from Table 1 (which should be presented for the population on which the analysis is based), 84 COPD vs. 64 healthy individuals; from the flow chart, 69 COPD and 60 healthy individuals; From the Results first paragraph 135 participants, from the Abstract, 75 COPD and 64 healthy individuals. Similarly, the number of spirometry test does not fully converge with the number of subjects (shouldn't it be 135*5-16= 659, rather than 691?).

4) Population: most of the COPD patients were former or current smokers (almost 90%) although inversely most of the healthy individuals were never smokers (92%). Therefore, differences in the associations observed between COPD and healthy individuals could be attributed to smoking status (that could enhance the harmful effects of air pollutants exposure) and not to COPD disease. This is a major weakness in the interpretation of the results in this
study. Ideally, a healthy group mainly composed of smokers would have been appropriate. A sensitivity analysis investigating the robustness of the association in COPD patients after excluding current smokers (if former smokers is defined by no smoking for at least several months) can help to address this issue. This limitation requires discussion.

5) Statistical analysis: multiple comparisons have been tested in this study (&gt;250 tests without considering the different lags for exposure assessment). Although correcting for multiple comparison is not straightforward given the high level of correlation between tests (Bonferroni correction would not be appropriate here), not taking it into account in the analysis makes the interpretation of the results quite difficult. Methods relying on the effective number of independent tests as proposed in the genomic field (ex: Li et al. Hum Genet 2011) could be used here. Also, this multiple comparison issue needs to be addressed in the discussion.

6) Statistical analysis: Wouldn't it be possible and relevant to address the mediation effect of cytokines in the association between air pollutants exposures and lung function parameters in COPD patients?

7) Results _Table S1_: Value of 0 for the min PM10 seems incorrect. How many daily PM10 concentration was observed at 0? If it is related to measurement errors, shouldn't it be corrected to the expected minimum value? In addition, did the authors checked that the distribution of air pollutant concentrations was similar between COPD patients and Healthy individuals? This information could be added to the manuscript (Tables S1 presented for each group separately).

8) Conclusion: The authors concluded on the role of air pollution on aggravating the Th1/Th2 cytokine imbalance. I agree that results observed on individual cytokines indicate this, but I think it could be relevant to further investigate this by analyzing ratio between Th1/Th2 cytokines to further document the Th1/Th2 imbalance.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

**Quality of written English**
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal