Reviewer’s report

Title: Does the oxidative stress play a role in the associations between outdoor air pollution and persistent asthma in adults? Findings from the EGEA study.

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Reviewer: Maribel Casas

Reviewer's report:

This study of Havet et al uses the EGEA study to examine whether oxidative stress explains the association between residential air pollution exposure and persistent asthma in adults. The study is of interest because there are not many studies assessing this relationship. Hereby I include some comments:

Abstract:

- In the abstract, please include the year when air pollution levels were estimated and also the years of EGEA2 and EGEA3 follow-ups.

- The results section of the abstract needs to be rewritten. The last two sentences are not clear. Also, I think it would be nice to first show the total effect of O3 on persistent asthma (OR=2,16) and then the effect of FiOPs on this association. The results of PM10 in relation to asthma and FiOPS should be shown in the abstract as well as that no association was found with NO2 and PM2.5.

Introduction:

- I miss some explanation in the introduction on the public health implications of the present study. Filling a gap in knowledge is enough to justify it but it would be nice to describe the potential future interventions. Also, it would be nice to mention the different mechanisms linking air pollution and persistent asthma (a part of oxidative stress).

Methods:

- The years between EGEA follow-ups differ between the abstract (11 years) and methods (12 years) - please revise.

- Please, report only one number here; it is confusing: 1602 participants (n=1571 adults aged ≥16 years) - also in the supplementary material.
- In methods, indicate when blood sample was collected (in EGEA-2 follow-up between 2003 and 2006) in the main text and not in the supplementary material; otherwise, is not clear the temporality of exposure - mediator - outcome.

- A brief explanation of the other covariates such as familial dependence and smoking will be thankful.

- In the mediation analysis, models did or did not include random effects on center and familial dependence?

Results:

- "At EGEA2, the mean age of the 204 adults was 39 years, 48 % were men, 24 % were current smoker, 79 % had persistent asthma": since persistent asthma is defined based on whether subjects in EGEA3 had current asthmatics or not, should not be EGEA3 instead of EGEA2?

- Line 253: "and were lower in non-smokers".

- Overall, I prefer the terms "increase/decrease" rather than "positive/negative" because they can confuse the reader.

- Line 266: here the authors should describe the association between PM10 and persistent asthma.

- It is strange that the authors only present the results for O3 and not for PM10 even they observed an association between PM10 and Flops and persistent asthma.

Discussion:

- Line 318: in the present study no association is observed with PM2.5. Authors should explain the reasons of these null findings although this pollutant has more capacity to induce oxidative stress than PM10, as the authors point out.

- Lines 322 and 324: authors need to justify why they explain these findings here (i.e. why PM2.5 has been associated with 8-isoprostane and not with FlOPS).

- Not necessary to repeat "for the first time" so many times.

- Lines 354-357: I would remove this sentence.

- It would be nice to describe difference between FlOPS and other oxidative stress markers such as telomere length, which has also been associated with persistent asthma in adults (Belsky et al Am J Respir Crit Care Med. 2014 Aug 15;190(4):384-91).
- Table 3 heading needs to indicate that this analysis is for O3 exposure.

Supplementary material:

- The EGEA3 follow-up is not described in the respiratory symptoms section.

- The flowchart is difficult to follow - I would try to simplify it by grouping some of the exclusion criteria (i.e. plasma Flops dosages with variation coefficient >20% and missing data on plasma Flops).

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