**Reviewer's report**

**Title:** Air pollution, fetal and infant tobacco smoke exposure, and wheezing in preschool children. The Generation R Study: a population-based prospective birth cohort.

**Version:** 2  Date: 16 October 2012

**Reviewer:** Chris Carlsten

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Most of the following are major compulsory

1. In response to our concerns about the definition of smoking, the authors still do not clearly define "fetal smoking" and "infant smoking". They have added the following "At enrolment, mothers received the first questionnaire containing data about their active smoking habits [15, 16]. Information about maternal smoking during other periods of pregnancy was obtained by postal questionnaires sent in second and third trimester of pregnancy. Based on the first questionnaire, we grouped mothers smoking habits during pregnancy into „no# (never smoked during pregnancy or until first trimester only) and „yes# (smoked continuously during pregnancy). Reported smoking habits in second and third trimester of pregnancy were used to reclassify the maternal smoking habits where appropriate [15].” However, this does not clearly define "fetal smoking" and "infant smoking". Please revise with the following clearly filled in: "Fetal smoking was defined as XXXXX. Infant smoking was defined as YYYY". Without this, the paper is profoundly flawed. Table 1 to me does not help fundamentally in this matter.

2. Furthermore, why would "until first trimester only" be considered "no" given the clear knowledge that the 1st trimester is a very sensitive time for fetal development?

3. Pg. 9: The authors state that “To increase power, we additionally assessed the modifying effect of tobacco smoke exposure by interaction terms which were all significant”, but then the majority of p-values that they report are >0.05? Then on page 10, the authors state that "We observed in our annual analyses that the associations between air pollution and wheezing among children exposed to fetal and infant tobacco smoke was significant at age 3 years only." I believe the authors mean to say that the interaction was significant here, and not the association which I don't believe is significant (according to the results in Table S2). This is confusing and indicates sloppiness which decreases confidence in the overall findings.

4. Authors have added "increased levels of air pollutants exposure during the previous 1 month were associated with increased risks of wheezing (odds ratios 1.25 (0.98, 1.58))" --> since OR crosses 1, "increased risks" is inappropriate. The authors should demonstrate diligence when interpreting their results. In this case, indicating that the OR was elevated but that it did not reach statistical
significance, would be more appropriate.

5. The authors have added "The correlation between fetal and infant smoke exposure was poor (kappa 0.409)". Why use the kappa (typically reserved for assessing correlation between 2 observers of assessment of the same measure [at the same point in time]) here?

6. The author's hypothesis that “short exposure duration to air pollutants might be more important for developing respiratory symptoms, whereas in the presence of environmental smoke exposure, long exposure duration to air pollutants might be more important” seems strange. There are many articles that suggest that long-term exposure to air pollutants is important for the development of respiratory symptoms, especially long-term respiratory symptoms. To speculate otherwise based on your results alone is problematic.

7. The authors have added "If children who were lost to follow up would have had more wheezing episodes, this could have led to an underestimation of the observed effect of air pollution and tobacco smoke exposure on wheezing as well". It is often argued that those with more health symptoms are LESS likely lost to followup. Why argue otherwise?

8. “per 10mg/m3 PM10” is still written twice in the results section of the abstract (this was mentioned in the previous review but not addressed)

9. The grammar in the new sections should be improved in several places before publication.

10. SD in the results section has been added, but not defined in the text (pg 8). This abbreviation should also be added to the abbreviation list.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests