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Reviewer: Chris Carlsten

Reviewer's report:

Summary

Using data from 4,634 children, the authors found an increased risk of wheezing during early-life associated with air pollution exposure, but only among children exposed to tobacco during both fetal life and infancy. This association was not observed in the cross-sectional yearly analyses. The hypothesis of this study is clearly stated, and it is novel in examining the effect of air pollutants at different exposure windows during early life. The detailed assessment of health outcomes and exposures at several time points is an important strength of this study. Weaknesses included the current description of the tobacco smoke variables, and the discussion of relevant results.

Major Compulsory Revisions

• How infant and fetal smoking was defined is poorly explained, and no descriptive statistics are given for these variables in Table 1. Was fetal smoking defined as yes if a mother answered yes to smoking during any of the three time points assessed, or all three? Was infant smoking related to both the mother and the partner smoking, or only one of the two? Providing descriptive statistics for these variables would also help the reader understand how many observations were included in each smoking category in the models. This information is currently lacking.

• Why did the authors also not examine the effects of PM2.5? This air pollutant is commonly monitored and may have different effects, (potentially more or less pronounced than those associated with PM10).

• Of the eligible children, only 61% participated. The potential for bias therein must be carefully explored and analyzed to the extent possible.

• The authors do not clearly explain why a positive association is only found using the GEE modelling approach, but not in the cross-sectional yearly examinations. Some comment or suggestions as to why these results differ should be given.

• The authors should comment on how many children moved during each year. A major strength of this study is the detailed information on moving during early life,
but no data are provided. It would also be useful if the authors provided summary information on the differences in air pollution levels across the years per child. Did most children have very similar air pollution exposures each year, or was the variable per child large? Moving behaviour may be especially interesting as the overall temporal variation in the air pollutants seems relatively low (Table S1).

- A major concern is the authors’ apparent misunderstanding of the relevance of the Rabinovitch study and it’s comparison to the present manuscript. In Rabinovitch, albuterol usage and LTE4 were related to PM2.5 concentrations on days when urine cotinine levels were low (<10 ng/ml per mg creatinine); on these days, mean albuterol usage and LTE4 increased up to 5 or 6% per 10µg/m3 increase in mmPM2.5. As far as this reviewer can appreciate, this is in sharp distinct to the results of the present manuscript, in which ETS and traffic-related pollution seem to be reinforcing (or create ‘vulnerability’ as suggested by the authors). These divergent results need be reconciled and the authors need to demonstrate a reasonable interpretation of the existing literature or argue why this reviewer’s posited contradiction is not reasonable. This is critical to the success of this manuscript as it represents, in the mind of this reviewer, the most novel contribution that this manuscript has to offer to the literature. This reviewer appreciates that you studied ETS at a different timepoint relative to the health endpoint, and different health endpoint, than did Rabinovitch, but nonetheless to say that “this effect modification has been previously assessed by Rabinovitch” (your page 1) is easily misleading.

- A further discussion as to why both fetal and infant smoke exposures are needed to increase the risk is required. This is interesting as the associations for the fetal smoking group are very close to null, and thus suggest that this exposure may not be as important as smoke exposure during infancy.

- If the results are the same between the imputed data and the complete cases, why not only show the data based on the complete cases, especially as the authors imputed for the outcome variable as well as the covariates (the former of which is less advisable).

- The results for the sensitivity analysis should likely be presented in the results section. Introducing a new Table and results in the discussion section is unusual. Also, Table S3 does not show that a larger variation in exposure levels of air pollutants were measured in the previous month at the age of 1 year, as is indicated in the text (odds ratios are presented in this table). In fact, this information does not appear to be presented at all.

- Where the GEE models adjusted for respiratory infections at any age, or only in the previous year as is indicated in the legend of Figure 2? Also, given the high rate of missing values for this covariate (46%), are the results similar when the models are not adjusted for respiratory infections?

- Page 10 says “confirms the earlier results that air pollution is associated with doctor diagnosed asthma and not with wheezing due to infectious mechanisms”. This statement is problematic for 2 reasons: a) Morgenstern did not look for
infection, and since the 2 mechanisms are not mutually exclusive both could have been at play; b) adjusting for such infections is not the same as a design/analysis focused on whether or not such infections are caused by air pollution and then lead to wheezing; this is especially true when looking at complex interaction dynamics such as you posit (ETS and ambient pollution # wheeze)

• Why do the authors believe that exposure misclassification (e.g. indoor air pollutants or commuting) would lead to an underestimation of the associations?

• The third sentence of the introduction is confusing. Do the authors want to suggest that children are more exposed to air pollutants than adults (which I suspect) or less exposed. The current sentence suggests the latter.

• Not all environmental exposures negatively influence the risk of asthma and symptoms, as is suggested by the authors in the introduction. For example, farming exposures are believed to be protective. Possibly adding “some environmental exposures” would help clarify this point.

• There appears to be a significant interaction between air pollution and tobacco smoke exposure at age 3 for both PM10 and NO2. This is mentioned in the legend of Table S2, but may be of some importance and could be discussed in the results

• Page 7 say “... (95% range 37.0-42.1)”. What does that mean? I suspect this is either 95% CI or range, but this is unclear and perhaps sloppy.

Minor Essential Revisions

• There is a mistake in abstract: “per 10 mg/m3 PM10” is written twice in the last sentence of the results section
• First sentence of results: the authors should indicate what (556) is (the standard deviation?).
• In the list of abbreviations, “Matter” should not be capitalized.
• Reference 14 is not formatted like the others (capitals used in title)
• In Table S2: * and ** do not appear in the table, and thus should be deleted from the legend.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

No perceived conflicts