Reviewer's report

Title: Air pollution exposure during pregnancy and reduced birth size in a mother and child cohort in Valencia, Spain.

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Reviewer: Svetlana Glinianaia

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Manuscript 1903277862317924 “Air pollution exposure during pregnancy and reduced birth size in a mother and child cohort in Valencia, Spain” by Ferran Ballester, Marisa Estarlich, Carmen Iñiguez, Sabrina Llop, Rosa Ramón, Ana Esplugues, Marina Lacasaña and Marisa Rebagliato”

General comments

There is a growing body of evidence suggesting that exposure to particulate air pollution can adversely affect the growth and development of the fetus. This research is of great public health importance as the exposure to air pollution is widespread and birth outcomes are important determinants of future child and adult health. Although the number of studies on the adverse effect of exposure to ambient air pollution on birth outcomes is increasing, there is still substantial inconsistency in the findings in relation to critical exposure windows and type of air pollutants. This study examining the relationship between maternal exposure to air pollution (specifically NO2) and size at birth (birth weight and length, small weight for gestational age and head circumference) in a prospective cohort of pregnant women and their children provides some additional evidence for the effects of air pollution on some birth measures of fetal growth.

The abstract is concise and informative, and is a good summary of the main findings of the study (see minor comments on the abstract). The introduction reflects good knowledge of existing literature and puts the current study into the context of evidence available to date.

The objective of the study and the study design are clearly defined. The methods are appropriate and are described in great detail (see the comment below on inclusion criteria for the mothers), or the appropriate references are given to the more detailed description of the cohort or exposure estimation. The results are satisfactorily interpreted (see minor comment 5).

The authors are aware of the limitations of their study and acknowledged them in the Discussion. Overall, the paper is clearly written and well presented.

Specific comments

Major compulsory revisions

Discussion:
I think that the Discussion is too verbose and could be reduced, e.g. strengths of the study given on page 12 (para 2) can be combined with the description of strengths on page 14, before the Conclusions. Information on previous studies on the effect of NO2 on birth outcomes is nicely summarised in Table 5. However, I am not sure whether the journal would be happy to accept this table in addition to essential tables on the study findings, as this would require more space. If the authors find it possible I suggest taking it out.

Minor essential revisions (the added or changed words are underlined) or questions

1) I wonder whether there were any preterm births in the studied cohort. If yes, it would be useful to know the percentage of preterm births. If the cohort was restricted to singleton live term births, it has to be specified in the Methods. From the reference 19 describing the INMA cohort it is clear that ‘a singleton pregnancy’ was one of the inclusion criteria. However, I would recommend repeating the inclusion criteria in this paper or at least specify this in the Abstract methods and Methods of the paper (Study design and population) that this cohort was restricted to singleton pregnancies, e.g. in the abstract it could read: 785 pregnant women and their singleton newborns... In the Methods, this could be added on page 5, line 5: …” and 787 delivered a live singleton infant”.

2) Abstract results, page 3, line 4 of the results: reduction in birth weight should be changed to ‘-40.3’g based on the results presented in Table 3, and according to Table 3 this reduction was observed for the first trimester, not the second, as given in the abstract. In the second trimester the corresponding reduction in birthweight was -37.5g. The same correction should be made in the Results section on page 9, end of the first paragraph.

3) Abstract methods, line 1 of the methods: I suggest adding ‘exposure to’ “ambient nitrogen dioxide…”

4) Methods, para 2, line 4-5: It would be useful for the readers if the authors could give a reference to the residuals methods they used for standardisation of anthropometric measures for gestational age.

5) Results, page 7, sentence 3: see my next comment. In contrast to description of the results in this sentence: “…those with low weight gain …had infants with a lower birth weight and a higher proportion of SGA (in weight) babies,” Table 1 shows that women with low weight gain had the lowest percentage of SGA infants (9.4% vs 18.0% in women with normal weight gain) and mean birth weight of their infants was higher (3320.2g) than that of infants born to women with normal weight gain - 3234.1g. - needs correction in the text.

6) Table 1: footnote, page 25: under f the author refer to 1990 Institute of Medicine guidelines for the definition of gestational weight gain. However, in the methods I would give the definitions for low, normal and high weight gain during pregnancy and explain whether the recommendations for weight gain during pregnancy depended on the pre-pregnancy BMI or weight. For example, I am surprised to see the highest percentage of SGA infants (and lowest mean birth weight) for pregnancies with the normal gestational weight gain and the lowest
percentage for pregnancies with the low weight gain. Could this be explained that the low weight gain was mainly observed in overweight or obese women, if this was the case?

7) Table 1: footnote, page 25: under a it is written: “Number may not sum up 755”… I believe the authors meant ‘785’, the total number of women in their cohort.

8) Results, page 8, paragraphs 2&3 (see discretionary comment 3): If the authors prefer to keep the text, I would recommend rewording of the last sentence of the 2nd paragraph: “For 43.2% of women, the outdoor NO2 level at their residences during the pregnancy period was above 40µg/m3, the World …”

9) Page 8, Air pollution exposure and anthropometric measures, 1st sentence: I suggest changing “Simple analysis…” to “Unadjusted analysis….”.

10) Page 8, Air pollution exposure and anthropometric measures, line 6: ‘reject the null hypothesis’ instead of ‘rule out’

11) Page 9, para 2, line5: “…was associated with the risk of SGA-weight”…

12) Discussion, page 12, para 1, line 3: I suggest replacing “…the clearest relationship…” with the “…strongest relationship”…

13) Discussion, page 12, para 1, line 6: “… in the case of growth retardation of HC…” needs rewording, e.g. This may indicate that exposure during the whole pregnancy plays the most important role for reduction in growth of infant head.

14) Discussion, page 10, para 2, line 10 from the bottom: I suggest adding “…found an association between LBW in term births and NO2…”

15) Table 3: please make the column titles look consistent across the columns: either (n=785) or (n:785).

Discretionary revisions:

1) Introduction, last para, last sentence: As this paper is a part of the INMA study I suggest changing “Our objective is”… to “The objective of this report (or paper) is”…to make it clearer that this is the objective of the presented analysis.

2) Results, page 7, line 3: suggest to amend to “…higher pre-pregnancy weight and/or BMI…”

3) Results, page 8, paragraphs 2&3: The authors could consider presenting a table on NO2 levels (mean, IOR) for the whole pregnancy and by trimester together with correlation coefficients for different periods of exposure instead of giving a two-paragraph description.

4) I believe spelling ‘fetal’ or ‘fetus’ is preferred nowadays to ‘foetal’ or ’foetus’ even in the British journals, unless Environmental Health requires the spelling used by the authors.

Typos:

Abstract, background, page 3, line 3: comma should be removed after ‘air pollution'
Table 3 title, line 4: corresponding period.

Page 8, lines 4 and 5 from the bottom: …” an increase in…” and “… a decrease in head circumference by -0.07cm…”.

Page 9, para 2: “In bivariate analysis…”

Page 11, para 2, line 9 from the bottom and Table 5, ref 35, last column: crown-heel length

Table 5, ref 35, last column: correct units of NO2: 11.1µg/m3

Table 5, ref 27, 2nd column: Seoul

Page 11, para 2, line 8 from the bottom: omit ‘in NO2’ at the end of sentence as it does not make sense.

In some places of the manuscript a space is missed (e.g. between sentences on page 11, para 2, line 4) or there is a space between the last word and the dot where it is not needed (e.g. page 4, line 4 or page 5, second line form the bottom.

Conclusion: After addressing the issues raised in this review and taking into account the comments, this manuscript can be recommended for publication in Environmental Health.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**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