

Author's response to reviews

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

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Author's response to reviews: see over

RESPONSE TO THE REFEREES' COMMENTS

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

Ferran Ballester, Marisa Estarlich, Carmen Iñiguez, Sabrina Llop, Rosa Ramón, Ana Esplugues, Marina Lacasaña and Marisa Rebagliato

Following the reviewers' and editor's comments, changes have been made in our manuscript. Below we present an answer (*in italics*) to each referee's comment along with an indication of the changes made.

We sincerely thank the editor and the reviewers and editorial assistant for the helpful comments and suggestions that contributed to the improvement of the manuscript.

Sincerely yours,

Ferran Ballester on behalf of the authors

Date: 12 December 2009

Referee 1. Svetana Glinianaia

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.

Following the referee's comment, we have taken great pains to sharply reduce the length of the Discussion section, cutting it by more than 750 words. Regarding table 6 (table 5 in the original version) and taking into account the journal format, we would prefer to keep it in. We consider it to be useful for the readers as it summarizes recent reports on the relationship between fetal development and air pollution in studies that included NO₂ as an exposure marker. In the case of lack of space or editing difficulties, a possible solution would be to place it as a complementary file. In any case, we leave this for the editor to decide.

Minor essential revisions 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".

We agree with the referee about the usefulness of this information for readers of this manuscript. We have therefore included the information on preterm births in the methods section. We have also made the recommended changes specifying that we included only single live term births.

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.

We thank the referee for the detailed revision; we have corrected the typos both in the abstract and in the results section.

3) Abstract methods, line 1 of the methods: I suggest adding 'exposure to' "ambient nitrogen dioxide..."

We made the proposed change as it clarifies the meaning of the sentence.

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.

*We have added one of the references we used to apply the residual methods for standardization of anthropometric measures for gestational age:
Lindsay RS, Hanson RL, Bennett PH, Knowler WC. Secular trends in birth weight, BMI, and diabetes in the offspring of diabetic mothers. Diabetes Care. 2000 Sep;23(9):1249-54*

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.

The text is correct, but there was an error in the table. The rows for low and normal gestational weight gain had been erroneously interchanged in table 1 in the original manuscript. They are now correct.

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?

As stated in the previous point, the figures in the rows for normal and low gestational weight gain were erroneously interchanged. This may explain the referee's question.

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.

We have corrected this typo in Table 1.

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 ..."

Following the referee's comment, a table with the descriptive statistics and the correlations between periods of exposure to NO₂ has been created, thus allowing for an important reduction in the length of the text.

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

This change has been made.

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

This change has been made.

11) Page 9, para 2, line5: "...was associated with the risk of SGA-weight"...

As suggested by the referee, "the risk of" has been added to the sentence.

12) Discussion, page 12, para 1, line 3: I suggest replacing "...the clearest relationship..." with the "...strongest relationship"....

Following the reviewer's comment, this change has been made.

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.

This sentence has been reworded.

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).

Titles of all tables have been revised.

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.

We have changed this sentence.

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

The amendment has been made.

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.

As indicated above (minor revisions 8) and following the reviewer's comment, a table with the descriptive statistics for exposure to NO2 has been included in the manuscript.

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.

We thank the reviewer for this observation; after additional consultation with a native speaker, we have changed the spelling accordingly.

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: 11.1 µg/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 from the bottom).

We have revised and corrected all these typos as well as others we detected. For example, we have changed "correspondent period" to "corresponding period" in the titles of former tables 2, 3, and 4.

Referee 2. Francesco Forastiere

Minor Essential Revisions.

1. A clarification should be made about the fact that in building the exposure variable, kriging was used first and then the LUR. The meaning of that is unclear.

We have reworded the first paragraph on the assessment of air pollution exposure in the Methods section so as to better clarify the procedure used for estimating the NO₂ spatial distribution.

2. The method to derive NO₂ specific values for trimester should be better explained.

We have added information on the method for deriving NO₂ specific values for the entire period as well as for each trimester in the paragraph on assessment of air pollution exposure in the Methods section.

3. The distribution of estimated NO₂ should be reported.

We have added a new table (Table 2) in the revised version with the descriptive estimations for estimated NO₂.

Editors' comments

In particular, the title should include the study design, for example: A versus B in the treatment of C: a randomized controlled trial.

We have included the study design in the title of the revised version.

On the title page, please remove the phrase "authors" and the colon before the authors' names; format the email addresses in paragraph style separating the terms

with semi-colons; change the phrase Author for correspondence to Corresponding author with a symbol following it which should also be placed after the number superscript, and remove all the other information about the author entered.

We have made these changes.

Please remove the page numbers, bolding and italics in the manuscript.

All suggested changes have been made.

In the Methods section of the abstract, numbers that begin a sentence should be written out and "The" should be placed before association in the fifth sentence.

We have made the suggested changes.

Please remove the key words at the bottom of the abstract on page 3.

We have done this.

Please proof read the entire manuscript and check the spacing e.g. on page 4, the period should come after the square brackets and there should be a space between the period and "On"; on page 5 the percent symbol should be next to the number and there should be a space between the period and "We". On page 5, there should be a comma after (in grams) in the first sentence of the second paragraph and the "and" should be removed. On page 6, please remove some of the extra return carriages. On page 8 in the paragraph at the bottom, there should be a dash between non and linear i.e. non-linear. =20

The entire manuscript has been proofread thoroughly, including an in deep revision of the English Language

The list of abbreviations should be in sentence format with the terms separated by semi-colons.

We have done this.

At the end of the Authors' contributions section please include a statement that all authors have read and given final approval of the version to be published.

We have added this.

Please be sure that all references are aligned.

The references have been revised.

The table should have all horizontal lines visible and whenever possible, it is best if tables are formatted to fit on one (portrait) page.

We have done this whenever possible.