Reviewer's report

Title: Low birth weight and presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based case-control

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Reviewer: Svetlana Glinianaia

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BMC Pregnancy and Childbirth manuscript entitled "Low birth weight and presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based case-control" by Ageo M C Silva, Gisele P Moi, Inês E Mattos and Sandra S Hacon

There is accumulating evidence of the association between maternal exposure to ambient air pollution and adverse birth outcomes, including low birth weight. This area of research is of public health importance because the exposure to air pollution is widespread and low birth weight is an important determinant of infant mortality and further child and adult health. Despite the growing epidemiological evidence, it is mainly based on the data from developed countries, and the data from developing countries are lacking. This study examined the association of ambient PM2.5 and CO with low birth weight (LBW) in term births in selected cities of the area Mato Grossso, the Brazilian Amazon.

I have a number of concerns in relation to the interpretation and presentation of the results (clarity and consistency between the description in the Methods and the Results sections). There are also many inaccuracies and discrepancies between different parts of the manuscript which need to be sorted out.

First of all, I do not understand why this manuscript has been submitted as 'case report'. It looks like a research article to me.

Editorial comment: I feel that it is inconsiderate towards the reviewers to submit a paper without page numbers, which makes it difficult to refer to a particulate place of the paper. Line numbers would be even more helpful.

Major Compulsory Revisions

1. The paper contains a number of inconsistencies that need to be corrected throughout the paper:

   1) Study design needs to be consistently described throughout the study. It is named a population-based case-control study in the paper title (the word ‘study’ is lacking in the title) and in the abstract, but ‘population-based retrospective cohort study in the Methods. If it is a case-control study it needs to be explained how cases and controls were selected. Based on the description of the study population, it looks like they used a population-based retrospective cohort.

   2) PM exposure – everywhere in the paper it is referred to PM2.5 as a particulate
matter exposure examined in this study, except Table 1, where in both the Table title and in the table itself PM10 has been used, and in Abbreviations where PM10 term has been explained, but not PM2.5. Please correct as appropriate.

3) It has been stated in the Methods that type of delivery was not included in the multivariate analysis as the p value in the univariate analysis was >0.20, while according to Table 2, it was part of the adjusted model. Please amend as appropriate.

4) It has been stated in the Methods (p. 7, para 3) that mother’s education was categorised as <4 years and #4 years of study, whilst in Table 2 the categories 0-7 and #8 are given and in the abstract and the Results the latter categories have been described.

2. The general comment in relation to the interpretation of the results is that if no statistically significant result is found, one cannot conclude that there is a higher risk of LBW associated with a certain factor (for example, maternal education or age in Table 2). The same refers to the interpretation of the findings on the association between exposure to air pollutants and LBW, e.g. according to Table 3, the association between higher exposure to PM2.5 (4th quartile) and LBW was significant for the second and 3rd trimester of pregnancy compared to the 1st exposure quartile. For CO, the association with LBW was only significant for the exposure in the highest quartile in the 2nd trimester of pregnancy. This needs to be corrected throughout the paper and in the abstract.

3. The authors need to make sure that everywhere in the paper (the abstract, Methods, Results and Discussion) it is stated that they examine LBW in term births (births at gestational age #37 weeks). Currently, it is just mentioned in the Methods that births at <37 weeks were excluded. It is important to emphasize as LBW can be a result of different biologic mechanisms; it can be a consequence of either preterm birth (appropriate-for-gestational-age babies born prematurely) or retarded fetal growth (small-for-gestational-age babies born at term).

4. It would have been more demonstrative to include an additional table or to add to Table 1 the descriptive statistics for the examined explanatory variables, i.e. newborn’s sex, maternal age and education, type of delivery, number of prenatal care visits in relation to LBW, instead of giving the incomplete description in the first paragraph of the Results (p. 10, para 1). Without this table and without seeing the absolute numbers, it is difficult to have a clear idea about the characteristics of the population and the LBW prevalence in different groups.

5. It needs to be justified why such a wide maternal age group (20-39 years) was used as a reference group and why mothers aged <20 and #40 years old were combined for the analyses. It was shown earlier, that ORs for LBW were significantly higher for mothers in 30-34 and 35-39 year-old groups as well, and younger mothers (<20 years) were not at higher risk of LBW baby (e.g. ref. 29 - Gouveia, 2004 and ref. 30 - Ritz, 1999). Age groups 20-29 or 25-29 are commonly used as a reference.

6. The method of maternal exposure estimation is not ideal as it is not based on individual-level information, but according to the authors, the predictions of the concentration of atmospheric pollutants in the studied region by the
CATTBRAMS Model are fairly accurate. However, the limitations of exposure estimation provided by the computational modeling and potential bias resulting from lack of individual-level information, including maternal mobility during pregnancy and differences in exposure depending on the place of residence, if any, between different cities included in the study area should be discussed in more detail. The readers are not familiar with the specific characteristics of this region of Brasil and adequacy of this method of exposure estimation needs to be explained and justified in more detail.

Minor Essential Revisions

Abstract

1) As suggested above, please amend the following: “This … study assessed the association between exposure to particulate matter (PM2.5) and carbon monoxide (CO) from biomass burning in the Amazon and LBW in term (#37 gestational weeks) singleton live births in cities of Mato Grosso, Brazil…”.

2) Give the final number of births used for the analysis in the methods of the abstract.

3) Methods: Reword the following sentence: “Maternal exposure was estimated through the medium of pollutants for each trimester and for the entire period of gestation.” to clarify how maternal exposure was estimated. It is not clear as is. It needs to be clarified where the PM2.5 and CO concentrations were measured and what was used (the mean or the median for each trimester and over the entire pregnancy period) for estimating exposure in women who lived in the studied area. For example, “maternal exposure was assigned as the average municipality-level concentration (or average concentration in selected cities of Mato Grosso) over gestation and each trimester based on mother’s residence”.

4) I suggest changing “Data were analysed by logistic regression and multivariate method and the adjusted odds ratios were calculated for exposure variables associated with LBW…” to “The association between air pollutants and LBW was analysed by multiple logistic regression adjusting for infant’s sex, mother’s age, education and prenatal care.” This is more informative and accurate.

5) Results: The results are not described correctly. For example, the first sentence reports about the higher risk of LBW for women with education of eight years and more (and does not specify the direction of the association with the number of prenatal care visits), while Table 2 shows that shorter period of study (0-7 years) had a higher OR for LBW (significant in the unadjusted and non-significant in adjusted analysis) and the lower number of prenatal care visits were significantly associated with increased odds of LBW.

The second sentence of the Results also should be reworded as it does not correctly describe the association between exposure to air pollutants and LBW. The ‘forth interquartile range’ should be changed to the ‘fourth quartile. For example, “In the adjusted analysis, the associations between exposure to air pollutants and risk of LBW were statistically significant for the fourth quartile of PM2.5 concentrations in the second trimester (OR=…) and in the third trimester
(OR=...) and for the fourth quartile of CO concentrations in the second trimester only (OR=...)."

Background:
1. The text of the Background needs grammatical and stylistic editing as in other sections of the paper.
   For example, change 'pollutants for the atmosphere' to 'air pollutants'; change 'pregnancy side effects' to 'adverse pregnancy outcomes'; change 'greater exposure to PM10 by mothers' to 'greater maternal exposure to PM10'; reword 'even if the biological mechanism involved in air pollution and low birth weight'; reword 'producing a lower fetal development'.
2. Page 5, para 3: the last two sentences are not clear.
3. Overall in the Background, the text can be shortened and made more succinct. I suggest giving a summary of the published evidence in a couple of short paragraphs, instead of describing each individual study, and describing what this study can add to the evidence.
4. Page 5, para 2, line 1: use consistently 'LBW' after introducing it on page 4.
5. Page 5, para 4, aim: change “to assess the impact of exposure to particulate matter and carbon monoxide from biomass burning in the Amazon and Cerrado (Brazilian savanna) biomes on live birth weights in cities…” to ‘to assess the association between maternal exposure to particulate matter and carbon monoxide from biomass burning in the Amazon and Cerrado (Brazilian savanna) biomes and LBW in term singleton live births in cities...”.
6. Ref 12 published in Portuguese language can be omitted as reference 29 describes a similar study in São Paulo in the international journal.
7. I am not sure that the added paragraph on the biological mechanism should be in the Introduction as this paper does not explore this aspect. It can be moved to the Discussion.

Methods:
1) See comment on the design above.
2) Page 6, para 3, line 3: Please clarify whether you mean multiple pregnancies or individuals in your exclusions.
3) Type of delivery as one of the covariates examined in relation to LBW needs to be described in the Methods (p. 7, para 3).
4) Please describe the method of gestational age estimation, i.e. based on the last normal menstrual period (LMP) or early ultrasound measurements.
5) p. 8, para 1: The sentence below needs rewording as it does not accurately explains how the exposure was grouped into quartiles: “We assigned a level of exposure to each interquartile range of PM2.5 using the first interquartile range as a reference.” The first quartile, not interquartile range, was used as a reference. The interquartile range is the range from the 25th to the 75th percentile, or in other words, the difference between the third and the first quartile.

I suggest amending to: “Levels of PM2.5 and CO were divided into quartiles and the lowest quartile (<25th, Q1) was used as the reference group.”

Change this also in the description of the interaction tests on page 9.

6) P. 8, para 3 (and in other instances): change ‘bivariate’ into ‘univariate’ analysis meaning that an association between one of the explanatory variables and the outcome variable (LBW vs no LBW) was tested in this analysis.

7) Outcome variable is not ‘newborn weight’ as stated in the Methods (P. 8, para 3, line 7) but a dichotomous variable LBW (<2500g) vs no LBW (#2500g). Please correct.

8) P. 9, para 1: It is stated that two models were built, one for PM2.5 and one for CO.

There must have run at least 4 models for each pollutant: one for each trimester of pregnancy and for the entire pregnancy, eight models altogether, which is shown in Table 3.

Results:

See the suggestion for an additional table above.

1. Table 1: units for PM2.5 and CO should be added. Also, it would be useful to present the descriptive statistics by season to give an idea about seasonal variations (see Gouveia, 2004). The authors state in the Conclusions (P. 14, para 3) that “greatest concentrations pollutants from biomass burning come from acute emissions that occur between July and October, the Amazon’s dry season” indicating that there must be significant seasonal variations in air pollutant concentrations.

As there is a big difference between the mean and the median, normal distribution of data is unlikely. Therefore, it would be useful to present interquartile range together with the median.

Taking into account a remarkable variation in concentrations, a description of the spatial variation would be useful as well.

2. Table 2: change the title of the table to:

Association of maternal and infant factors with low birth weight in term singleton live births (results of univariate and multivariate logistic regression).

3. Page 10, para 2, line 2: it is not clear what is meant by ‘exposure categories’.

4. Page 10: the description of the results shown in tables 2 and 3 needs rewording according to my earlier comments on the statistical significance (see
Discussion:

1. P. 11, summary of the main results: amend the description according to the earlier comments and make it consistent with the description in the abstract and the Results sections.

2. P. 11, para 3: I do not agree with the description of findings by Gouveia et al, 2004. They found an inverse association with continuous birth weight, i.e. a reduction in birth weight was found for higher pollutant concentrations, but they found a positive association with low birth weight, i.e. an increased risk of LBW was found for higher exposures to air pollutants; for example, the association was significant for the fourth quartile of PM10 in the 2nd trimester of pregnancy.

3. Page 13, para 2: The authors discuss the association between maternal age and LBW referring to a ‘risk-free’ maternal age (18 to 35), however, they used a different wide age group as a reference (which I questioned earlier), 20-39 years. The last sentence in this paragraph is not convincing.

4. Page 13, para 3: I do not feel that this statement is correct. Exclusion of preterm births did not allow the analysis of LBW “exclusively as an outcome of exposure to pollution” as there are other factors (for example, smoking) that affect birth weight and for which the analysis could not be adjusted.

5. I feel that the discussion of the study limitations, including the exposure estimation, and their potential effect on the results should be more extensive (see my earlier comments).

Typos/minor corrections:

P.4, line 1: change ‘with’ to ‘about’.

P.5, line 4: correct ‘Gouveia’.

P. 6, para 3, line 7: change ‘losses’ to ‘missing’.

P. 6, para 3, line 3: change “n-=71” to ‘n=71’.

P. 7, para 4: change ‘Fetal’ to ‘Maternal’ exposure to studied pollutants ‘by’ trimester…

P. 8, line 1: change from ‘on’ to ‘from’.

P.9, line 8, change ‘…was 0.05’ to “…p<0.05’.

P. 12, para 2: Use ‘CO’ here but spell it out (carbon monoxide) when is has been first used I the Methods on page 7.

P. 12, para 3: increase font size in the last sentence to make it consistent with the rest of the text.

Page 13, para 2: I think the authors mean ‘maternal age a risk’ rather than ‘gestational age at risk’.

Abbreviations:
PAHs: remove ‘maternal inhalation of’.

References:
Refs 2, 17 - incomplete references.
Make the format in all references consistent. Remove extra dots after the paper title in many references, e.g. refs 8, 11, 12, 15, 16, 22 etc.

Discretionary revisions
1. I wonder whether it was possible to analyse birth weight as a continuous variable, i.e, was birth weight available at individual level as a continuous variable. If yes, why the authors have chosen not to do that. It would have been possible to compare their results with the findings from another paper from Brazil by Gouveia, 2004 (ref 29).
2. P. 6, para3, lines 7-8: I suggest to reword the following sentence “We considered as losses records which did not inform the child’s sex (n=1) and those that did not provide information on any of those variables (n=2).” to “We excluded records with missing information on child’s sex (n=1) and any of the variables listed above (n=2)”.
3. I wonder whether ‘parity’ could also be used in the adjusted analysis.

Level of interest: An article of importance in its field

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

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

Declaration of competing interests:
I declare that I have no competing interests.