Author's response to reviews

Title: Low birth weight and presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based retrospective cohort study.

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Author's response to reviews: see over
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BMP Cover letter

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Dear Dr. Peter O'Donovan, BioMed Central Executive Editor of BMC Pregnancy and Childbirth

Many thanks for your comments and suggestions about the manuscript in annex. Sorry about the delay to send the final revision.

We are presenting comments without mention the reviewer, because we noticed that the suggestions and corrections are very similar. Please find attached our manuscript revised to be evaluated by BMC Pregnancy and Childbirth after we have made all the corrections.

In case of any questions, please do not hesitate to contact us anytime.

Sincerely,

Sandra Hacon

If you have any questions, please don't hesitate to contact us.

**Title:** Low birth weight and the presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based retrospective cohort study.

**Author’s report based on editor’s report**

Dear Editor Mr. Tacbobo

We would like to thank for your important considerations regarding our manuscript. We have attempted to respond to your concerns and the reviewer’s comments in detail.

Editor's Requests:

We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language
editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.

R: We thank the editor for the comments, and have had the manuscript edited by a native English speaker from a professional editing company, as suggested.

Issues that specifically need to be addressed are as follows:

In the abstract and introduction acronyms are used but never defined - do no assume the reader knows what HPA, PM2.5, PM10, CO, SO2 etc mean

R: We have defined the abbreviations used in the Abstract and Background sections.

Abstract
lines 27-31 (and also page 5 lines 105-106) - needs to be 2 sentences. It is too complicated to read as it is. It is unclear from the abstract that LBW is the main outcome (currently states live birth weight). Also LBW needs to be defined as <2500 gm. Results need to start with a description - move from methods eg Of 6147 full term, singleton, live births includes in the study, 193 (3.1%) were LBW. (This could also be added to the results section of the paper.)

R: We apologize for the lack of clarity. We have rewritten the Abstract (lines 26–29 and 39–40), Background (lines 104–108), and Methods (lines 195-197) to clarify these issues.

Introduction
Define acronyms, as above.

R: We have defined all of the acronyms used in the Background as suggested.

Lines 94-96 doesn't make sense - perhaps?: Ha and colleagues[12] showed that air pollution in the first trimester of pregnancy was a risk factors for LBW. ?

Lines 100-101 doesn't make sense - what assumption. Please rewrite this
sentence Lines 105-106 - needs to be 2 sentences. It is too complicated to read as it is.

R: We apologize for the confusing text. We have made the suggested changes in the Background (lines 92–98, 99–102, and 103–107).

Methods
Para 1- please respond to the reviewer (Bannister-Tyrrell, #4&5 Compulsory revisions) - by adding a comment about the potential confounding by seasonal effects on air pollution. This is reported in the response but not in the paper.

R: This information has been added to the text (line 186).

Para 2 needs to be reorganized as it does not flow well. There were 6147 births and when records with missing data were excluded there were still 6147 births. Lines 132-135 are unclear and need to be revised - exclusion of preterm births is an important point. Delete 'or otherwise'.

R: We appreciate these suggestions and have made the suggested changes. However, we believe that the editor meant paragraph 3 and not paragraph 2 with regard to reorganization. We have also clarified the information on lines 128–131 of the original manuscript.

CATT-BRAMS - please respond to Bannister-Tyrrell #7 - how was exposure allocated to women? Was this based on their residence or the place where they gave birth? Is it possible for women to give birth in one municipality but reside in another and so get an incorrect exposure? If so, this needs to be added as a potential limitation of the study. Perhaps there is information about residential mobility (or lack of it) in Brazil.

R: We have added information on how exposure was allocated to women to the revised text in the methods (line 149-167).

Line 159 - what variable?

R: We appreciate suggestions and made changes in line 157-158: "which was also categorized into 0-3 ou 4 or more".

Line 161 - delete "for trimester" as it is redundant
R: We have deleted the phrase “for trimester”.

Add that method of gestational age determination is unknown as requested by reviewer Glinianaia.

This information has been added to lines 177–180.

Line 192 - state that grouping <20 and >40 year old women was an a priori decision (as requested by reviewer Glinianaia) - as it makes no sense to most readers.

R: We appreciate the editor’s comment and have clarified this grouping decision (lines 187–191).

Bannister-Tyrell comment #3 - is not addressed in the text - issues of seasonality are largely ignored - perhaps month of birth (or conception) should have been included in the models? Nowhere is it mentioned that season has been examined so it needs to be added. Season of birth could be included in Tables 2 and 3 using the same month groupings Table 1.

R: We would like to emphasize that matters of seasonality were not ignored. Since the variable "month of birth" was included in the univariate analysis, whereas no association was found with statistically bpn. Thus, we opted for parsimony of presentation of tables and their inclusion in the table include only two and three related to pregnancy and childbirth variables. The seasonality considerations were included in lines 181-186, as follows: “The seasonal variation in PM2.5 and CO derived from biomass burning is an important confounder for LBW. Therefore, the variable of “month of birth” was used as an indicator variable in the exploratory analysis because its association with LBW was evaluated in univariable analysis and it was not found to be significant (p<0.20), which could justify its inclusion in the regression model”. Results

Please add a sentence or two of description about Table 1 - this appears to show seasonal variation? What are the seasons and burning patterns?

R: We have added the requested information on what table 1 shows and information on seasons and burning to the revised manuscript (lines 210-212).
Table 1: add rows for the median and IQR for each pollutant in each year - as requested by reviewer Glinianaia.

*R: These rows have been added to Table 1 as suggested.

Revise paragraph 1 by Adding:
Of 6147 full term, singleton, live births includes in the study, 193 (3.1%) were LBW. Of these, 52% were male infants, 40% of mothers had >=8 years of education...... (Table 2).

*R: We have added this information to paragraph 2 (lines 213-216) of the Results.

Table 3 - education is still inconsistently reported, use <7 years and >=8 years throughout There is an ongoing issue about the multivariable analysis - Table 3 clearly shows that all factors are included (including type of delivery) in at least one model (all have adjusted ORs) - the methods need to be revised to make this clear.

*R: We have ensured that the definition of education is consistent throughout the manuscript (in the text and Tables 2 and 3). We have revised the Methods to clarify that all of the variables shown in Table 3 were included in multivariable analysis. (Tables 2-3, in the lines 152–158 and 209-218).

**Discussion**

The discussion needs to be reduced and made more succinct, including removal of duplicate information. Line 234 ‘and’ not ‘e’

*R: We appreciate the editor's suggestions and have made the suggested change.

Lines 235-240 - these 2 sentences should be removed. This information is mentioned in the introduction and congenital anomalies are NOT an outcome of this paper. It can be mentioned as a strength that congenital anomalies were excluded to reduce confounding, citing Vrijeid.
R: We have removed these two sentences as suggested and it was added in discussion: "another strength point of this study is that the congenital anomalies diagnosed at birth were considered an exclusion criterion database analyzed, citing Vrijeid (Lines: 336-338).

From line 242 - finish this sentence at ‘9 countries’. Then delete from there to line 246 - begin the next sentence at 'LBW at term.....
R: We appreciate the editor’s suggestions and have made these changes (lines 232 and 238).

Line 259-261 doesn't make sense - perhaps: This could be explained by differences in methods employed in these studies, by assessing different levels of exposure or by different ethnic populations in each region. ??
R: We thank the editor for the suggestion and have revised the text accordingly (lines 255–260).

It is unnecessary to go over every association with LBW like prenatal care, education, maternal age. It is enough to say that you observed associations with the established risk factors for LBW and cite the supporting papers.
R: We have briefly listed our observed associations in context with previous literature as suggested (lines 286–293).

Lines 298-310 should be deleted from the discussion. Either delete the interaction analysis or report it in the results with enough information so that it can be understood. It is completely unclear as it is and confuses maternal and gestational age (line 305).
R: We appreciate the editor’s suggestions and have deleted these lines from the revised manuscript.

Lines 311-313 - this sentence doesn't make sense. A strength of the study is restriction to term births - removing the confounding effect of LBW due to preterm birth which has a different pathological pathway to fetal growth restriction (see comment #3 by reviewer Glinianaia).
The necessary changes were made (lines 302–314). So: "The fact that we excluded newborns at term who were less than 37 weeks’ gestation, which is etiologically associated with restricted uterine growth and LBW[29, 43], enabled us to analyze LBW as an outcome of exposure to pollution, without the influence of this confounding variable. Our study found evidence that maternal exposure to air pollution during the second and third trimesters of pregnancy is associated with LBW. In the final adjusted model, an increase in LBW of approximately 50% occurred when the fourth quartile was compared with the first quartile range of PM2.5 and CO. However, there may be other confounding factors that could be associated with LBW, such as exposure to tobacco or use of wood stoves, among others. Additionally, the method of estimation of maternal exposure may not have been ideal because it was not based on individual-level information. Furthermore, potential bias resulting from a lack of information and possible maternal mobility during pregnancy could lead to differences in exposure not measured in this study."

Lines 314-318 repeats paragraph 1 of the discussion and should be deleted.
R: We have deleted these lines in the revised manuscript as suggested.

The limitation of lack of individual information on the main exposure variable (comment #6 reviewer Glinianaia) is not clearly articulated - line 321 mentions tobacco and stoves but this is also the an issue for the air pollution exposure.
R: We appreciate suggestions and the necessary changes were made in the line 315-330. So: Smoking remains a major public health problem in Brazil. Over the time, the prevalence of smoking among women in the developing world has been very low, being This is partly driven by cultural constraints against women’s smoking; around approximately 50% of men in developing nations smoke cigarettes, compared with 9% of women. Specifically in Brazil, about 9% of women aged 18 years or more 9.2% have smoking and 11% of women are exposed to passive smoking. Data on smoking and other individual exposures of pregnant women have not been measured investigated. This may compromise the construct validity of the models we analyzed . Ecological studies analyze global data, that which include whole populations. Their main limitation is the fact that it is impossible to controlling the confounding factors
regarding exposure at the individual level is impossible. Nevertheless, a few observational studies have indicated a strong correlation between smoking and the level of education, and they have suggested that maternal education is a proxy variable of smoking habits. This justifies the importance of including maternal education as an adjustment in the logistic regression models. The seasonal variation in PM2.5 and CO derived from biomass burning seasonal could be pointed out as a limitation of this our study. However, his influence was not statistically significant when analyzing the variable “month of birth” and was not significantly associated with LBW in the univariable model. In addition, the lack of information on parity is also noted as a limitation of the study.

Re smoking - please report an overall smoking rate for Brazilian women of reproductive age or note that it is unknown if that is the case.

R: We appreciate suggestions and inserted this information in the lines 315-3218.

So: "Smoking remains a major public health problem in Brazil[44]. Over the time, the prevalence of smoking among women in the developing world has been very low, being driven by cultural constraints against women’s smoking; around approximately 50% of men in developing nations smoke cigarettes, compared with 9% of women[45]. Specifically in Brazil, about 9% of women aged 18 years or more have smoking and 11% of women are exposed to passive smoking[46].

Lack of information on parity should also be noted as a limitation of the study.

R: We have added to the Discussion that a lack of information on parity is a limitation (line 329-330).

It might be better to have one paragraph on strengths of the study and then another that reports all the limitations.

R: We appreciate the editor’s suggestion and have separated these paragraphs (lines 315–338).

Inability to examine seasonal factors is a limitation of the study.
R: The inability to examine seasonal factors has been added as a limitation of the study (lines 315–338).

Thanks again for your suggestions and hope to have answered to the satisfaction of all the observations made by the editorial.

Sincerely,
Sandra Hacon