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
Rio de Janeiro, April 15, 2014

BMP Cover letter

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. We appreciate very much the opportunity to improve the manuscript. Sorry about the delay to send the final manuscript.

We are presenting comments for each reviewer of the manuscript.

Reviewer: Svetlana Glinianaia
Author's report based on reviewer's report
Title: Low birth weight and presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based retrospective cohort study.

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 Grosso, 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 particular place of the paper. Line numbers would be even more helpful.

R: We would like to apologize and to tell we seek to clarify all doubts and pointed accept the suggestions made by the reviewers. We are very sorry for the mistakes and we thank opportunity of being able exchange experiences with renown reviewers of this journal.

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.
   R: We would like to thank the suggestion and made the necessary changes in the Article.
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.
R: We would like to thank the suggestion and made the necessary changes in the Table 1.

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.
R: We apologize and would like to say that we rewrite the end of the eighth paragraph of the methods again in order to make it more clearer: "First, we conducted a univariable analysis between LBW and adjustment variables. At this stage, we also calculated chi squared tests for linear trend analysis, according to each case. We tested each variable in the model individually and selected those whose descriptive level of significance scored 0.20 or lower in the univariable analysis (education, mother’s age and number of prenatal appointments), except for the variable gender, which was kept in the model because of its significance in relation to the outcome variable (newborn weight). The variable type of delivery was not included in the multivariable analysis method because its statistical significance in univariable analysis was greater than 0.20."

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.
R: We apologize for not being clear in our writing because we did not pay attention that in other countries this classification could be made differently. Aiming to clarify the doubts, we would like to inform you that in Brazil the levels of education and teaching are classified into basic education in fundamental levels (≤7 years) and medium (≥8anos). In order to facilitate easier understanding of all, we fit the categories used in this study will use the International Standard Classification of Education, better known by its acronym in English ISCED (International Standard of Classification of Education). This is a classification of educational levels to enable the comparison of statistics and educational policies enters different educational systems. The classification was developed by the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1970, then taking aim expressed as serve as a tool to enable the collection, compilation and processing of education statistics at national level and international. The ISCED was adopted by the International Conference of Education, which met in Geneva in 1975, and was subsequently adopted by the General Conference of UNESCO.
So appreciate your suggestions and advise that the categorization of maternal education in the paper was adapted to international standards as follows: primary education (≤ 7 years) and secondary education (≥ 8anos). This was changed in the text and in the Table 2.

Minor Essential Revisions

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.
R: We are very grateful for your suggestions, as these greatly enriched this work. We adjust the text and excluded the results of no significant associations that it are shown in Table 2 (second paragraph of results). Also we adjust the description of Table 3 in the third paragraph of the results.

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).

R: Thanks for your suggestion. We adjust your suggestions in the abstract, methods, results and discussion of the present paper.

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.

R: We appreciate your suggestion and included the additional table containing the results of the explanatory variables analyzed in this study.

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.

R: We would like to clarify that this is an option 'a priori' regrouping these two categories, less than 20 or 40 or more. This is because the literature emphasize that older mothers and younger mothers, including adolescents, have higher risk for LBW. This form of dichotomization allowed clarity and simplicity in the presentation of data in the table. Finally we would like to emphasize that these variables were only used to adjust the model does not explain LBW.

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 Brazil and adequacy of this method of exposure estimation needs to be explained and justified in more detail.

R: We would like to clarify that the CATT-BRAMS incorporating various parameters such as wind direction, relative humidity, CO, anthropogenic burning, burning resulting crop management (burning of sugar cane for example), among others. Further information may be obtained from the article recently published by Hyder and colleagues in 2014, and this was included in this version of the article. Which was in press at the time he submitted the article. Below is the complete reference: Hyder A1, Lee HJ,
Ebisu K, Koutrakis P, Belanger K, Bell ML. PM2.5 exposure and birth outcomes: use of satellite- and monitor-based data. Epidemiology. 2014 Jan;25(1):58-67. However, it's important to clarify that the concentrations of PM2.5 and CO were derived from a simulation using the Coupled Aerosol and Trace Gas Transport model for the Brazilian development of the Regional Atmospheric Modeling System Model (CATTBRAMS). CATTBRAMS is an atmospheric emission and transport model that takes into account atmospheric dynamics. The emissions from biomass burning for several trace gases and aerosol particles were obtained from satellite observations of fires, using the 3BEM (Brazilian Biomass Burning Model). The aerosol mass concentration predicted by the CATTBRAMS model accounts for advection, turbulent motion in the planetary boundary layer, convective transport by shallow and deep cumulus, wet and dry deposition and plume rise, among other effects. The spatial model domain was set up to encompass the entire South American continent. The horizontal model resolution was 48 km by 48 km over all of South America, with reference to the seat of the municipality (city where the mother lived during pregnancy) as centroid of the grid cell. The CATT-BRAMS model framework provided ground-based estimates of pollutants from anthropogenic sources concentrations for each microregion in the Amazon region, for details see: Ignotti E, Valente JG, Longo KM, Freitas SR, Hacon SS, Artaxo Netto P. Impact on human health of particulate matter emitted from burnings in the Brazilian Amazon region. Rev Saúde Pública 2010;44(1):121-30 and Freitas SR, Longo KM, Silva Dias MAF, Chatfield R, Silva Dias P, Artaxo P, Andreae MO, Grell G, Rodrigues LF, Fazenda A and Panetta J. The Coupled Aerosol and Tracer Transport model to the Brazilian developments on the Regional Atmospheric Modeling System (CATT-BRAMS) – Part 1: Model description and evaluation Atmos. Chem. Phys., 9, 2843–2861, 2009.

Additionally, we would like to emphasize that the time series of this study were calculated daily by the model 3BEM (Brazilian Biomass Burning Emission Model - CPTEC) based on hotspots identified by remote sensing. A model is made through a computer system that simulates emissions and atmospheric transport of products originating from biomass burning in Amazonia, using parameters of horizontal and vertical diffusion of solar radiation, humidity and temperature, and predicts with good precision, concentration these atmospheric pollutants in the study area. The CATT-BRAMS is able to estimate these concentrations for all municipalities in the Brazilian Amazon. Additionally, please note that the regions studied in this article are areas that are under development and have low power consumption per capita. Thus, it is unlikely that population growth regions could justify possible changes that change the way the relevant standards of anthropogenic emissions. In addition, biomass burning Amazon accounts for about 70% of all emissions of particulate matter throughout Brazil. Therefore, it does not seem logical that these emissions are capable of influencing the total values of particulate material from the region analyzed.

We would like to clarify that additional information about the model were added in the paper, along with references describing the model in detail. However, it is extremely important to remember that this is an ecological study and thus measurements at the individual level could not be applied.

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…”.

R: We adjust your suggestions in the present paper.

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

R: The final number of births used for the analysis was added in the methods of the abstract (N=6147).

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”.
R: We adjust the paper according to your suggestion.

4) I suggest changing “Data were analyzed 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 analyzed by multiple logistic regression adjusting for infant’s sex, mother’s age, education and prenatal care.” This is more informative and accurate.
R: We changed the phrase “Data were analyzed 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 analyzed by multiple logistic regression adjusting for infant’s sex, mother’s age, education and prenatal care”, according your suggestion.

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=...)”.
R: We would like to clarify that the results were rewritten.

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’. Page 5, para 3: the last two sentences are not clear.
R: We adjust the paper according to your suggestion.

2. Reword the following sentence at it does not make much sense as is: “Ha and colleagues[10] also observed an association between daily PM10 variations during pregnancy and the number of live births with low birth weight in the 1st and 2nd trimesters.”
R: We rephrase the sentence to better understanding of the reader.

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.
R: The Background were shortened and made more succinct.

R: We adjust the paper according to your suggestion.
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…”.
R: We are very grateful for your suggestions. We changed the phrase “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…”, according your suggestion.

6. Ref 12 published in Portuguese language can be omitted as reference 29 describes a similar study in São Paulo in the international journal.
R: Thanks so much. We changed the reference 12 published in Portuguese language with to reference 29 that 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.
R: We would like to thank the suggestion. We opted to move this paragraph to the discussion.

Methods:
1) See comment on the design above.
R: Thanks so much for yours suggestions.

2) Page 6, para 3, line 3: Please clarify whether you mean multiple pregnancies or individuals in your exclusions.
R: We change the term "multiple pregnancy" to "twin pregnancy" in order to make this paragraph more clearer.

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).
R: We try to describe more clearly in Article type of delivery (normal and caesarean section), since this is one of the co-variate analysis.

4) Please describe the method of gestational age estimation, i.e. based on the last normal menstrual period (LMP) or early ultrasound measurements.
R: We would like to clarify that the data of this study are of secondary origin and they are available in aggregated form according to weeks of gestation reported in the database SINASC.

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.
R: We we change the phrase " We assigned a level of exposure to each interquartile range of PM2.5 using the first interquartile range as a reference." to " Levels of PM2.5 and CO were divided into quartiles and the lowest quartile (<25th, Q1) was used as the reference group" in order to make this paragraph more clearer.
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.

R: It was replaced in the manuscript the terms ‘bivariate’ with ‘univariable’ and ‘multivariate’ with ‘multivariable’ because these are the more accurate statistical terms.

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.

R: We apologize and would like to say that we rewrite the paragraph again in order to make it more clearer: "First, we conducted a univariable analysis between LBW and adjustment variables. At this stage, we also calculated chi squared tests for linear trend analysis, according to each case. We tested each variable in the model individually and selected those whose descriptive level of significance scored 0.20 or lower in the univariable analysis (education, mother’s age and number of prenatal appointments)[23], except for the variable gender, which was kept in the model because of its significance in relation to the outcome variables: LBW (<2500g) versus no LBW (≥2500g). The variable type of delivery was not included in multivariable analysis method because its statistical significance in univariate analysis was greater than 0.20."

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.

R: We rewrite the paragraph in order to make it more clearer: "We chose not to analyze the models with both pollutants included simultaneously, since there was collinearity between PM2.5 and CO (exposure variables) in all periods we analyzed. To perform multivariable analysis we built eight two models, one for each type of pollutant (PM2.5 and CO). We tested possible interactions between maternal age (risk versus no risk) and burning pollutants (PM2.5 and CO)."

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.

R: We made the necessary changes in the Article.

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).

R: The title of this table was changed.

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

R: The mean of this term was added in the article. So the page 10, paragraph 2: "In the final adjusted analysis, the associations between exposure to air pollutants (PM 2.5 and CO) and risk of LBW were statistically significant for the fourth quartile of PM2.5 concentrations in the second trimester (OR=1.51;
95% CI = 1.04- 2.17) and in the third trimester (OR= 1,50; 95% CI = 1.06 - 2.15) and for the fourth quartile of CO concentrations in the second trimester only (OR= 1,49; 95% CI 1.03 - 2.14). "

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 page 1, comment 2) and my comments on the description of the results in the abstract. Start the description of the results in Table 3 by referring to this table.
R: The changes in the manuscript were made.

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.
R: We made the necessary changes in the manuscript.

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.
R: The changes were carried out in the manuscript.

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.
R: We would like to clarify that this is an option ‘a priori’ regrouping these two categories, less than 20 or 40 or more. This is because the literature emphasize that older mothers and younger mothers, including adolescents, have higher risk for LBW. This form of dichotomization allowed clarity and simplicity in the presentation of data in the table. Finally we would like to emphasis that these variables were only used to adjust the model does not explain LBW.
We made the changes in the manuscript.

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.
R: We made the necessary changes in the manuscript to clarify this paragraph.

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).
R: We rewrite this part of discussion again in order to make it more clearer.

Typos/minor corrections:
P.4, line 1: change ‘with’ to ‘about’.
R: We change the word ‘with’ to ‘about’ in the line 1 of the first paragraph.

P.5, line 4: correct ‘Gouveia’.
R: We corrected ‘Gouveia’.

P. 6, para 3, line 7: change ‘losses’ to ‘missing’.
R: We changed ‘losses’ to ‘missing’ in the line 7 of the third paragraph of the six page.

P. 6, para 3, line 3: change “n=71” to ‘n=71’.
R: We made the necessary changes in the manuscript.
P. 7, para 4: change ‘Fetal’ to ‘Maternal’ exposure to studied pollutants ‘by’ trimester…
R: We change the word ‘Fetal’ to ‘Maternal’ in the fourth paragraph of the seven page.

P. 8, line 1: change from ‘on’ to ‘from’.
R: We made the necessary changes in the manuscript.

P.9, line 8, change ‘…was 0.05’ to ‘…p<0.05’.
R: We changed ‘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.
R: We made the necessary changes in the manuscript on page 7.

P. 12, para 3: increase font size in the last sentence to make it consistent with the rest of the text.
R: We think the authors mean ‘maternal age a risk’ rather than ‘gestational age at risk’.
R: We change the word ‘maternal age a risk’ to ‘gestational age at risk’ in the second paragraph of the thirteenth page.

Abbreviations:
PAHs: remove ‘maternal inhalation of’.
R: We removed ‘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.
R: We removed extra dots after the paper title in many references and corrected others references.

Discretionary revisions
1. I wonder whether it was possible to analyze 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).
R: Unfortunately we could not analyze the birth weight as a continuous variable for a few reasons. There was a strong non-parametric distribution of exposure variables requiring transformation into normally distributed variable. Sadly not all the parameters of PM2.5 and CO were liable to be parameterized. Additionally, it is important to emphasize that the logistic regression is a universally known epidemiological method, which allows a simplification of the presentation of the results.

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).”
R: We rewrite the paragraph again in order to make it more clearer, according your suggestion.

3. I wonder whether ‘parity’ could also be used in the adjusted analysis.
R: Indeed it could, but in Mato Grosso had many records without this information (missing data), thus preventing Their use in the adjusted analysis.

Reviewer: Melanie Bannister-Tyrrell

Author's report based on reviewer's report

Major Compulsory Revisions

1. The study title describes the study design as a population-based case control study, which is inaccurate. The study is better described as a cohort study, as defined in the Methods.

   R: We made the necessary changes in the Article.

2. The authors should incorporate discussion of a recent systematic review of the association between air pollution and low birth weight in nine countries into the introduction and conclusion: Dadvand et al, Maternal Exposure to Particulate Air Pollution and Term Birth Weight: A Multi-Country Evaluation of Effect and Heterogeneity. Environmental Health Perspectives 2013; 121(3): 267-373.

   Please also see previous publications by this consortium. This meta-analysis presents similar analyses to the current manuscript, by investigating low birth weight at term as the primary outcome and exposure to PM10 and PM2.5 throughout pregnancy and in each trimester and using maternal education as the primary measure of socioeconomic status. Discussion of how the submitted manuscript aligns with this international meta-analysis would strengthen the article.

   R: We are very grateful for your suggestions, as these greatly enriched this work. These in turn were incorporated in the fifth line of the second paragraph of the Introduction of this article and in the eleventh line of the first paragraph of the discussion.

   So, we point out that the references were included:1) Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, Nieuwenhuijsen M. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect. 2011. May;119(5):598-606.


3. The authors should provide data on the seasonality of biomass burning and seasonal variation in PM2.5 and CO, as several important confounders that have not been included in this study also vary seasonally. For example, malaria infection varies seasonally and is associated with low birth weight, similarly other infections and nutrition are also likely to vary seasonally and be associated with low birth weight. In the absence of data on these variables, at minimum the authors should include an indicator variable for season or month in the logistic regression model.

R: The seasonal variation in PM2.5 and CO derived from biomass burning seasonal are important confounders for LBW. Therefore, the variable denominated “month of birth” was used as indicator variable in the exploratory analysis, being that its association with LBW was evaluated in the univariate analysis. However it was not found significant results (p-value less than 0.20) that could justify its inclusion the regression model. The description of this information was included in the eleventh paragraph of the discussion evaluate.

4. Air pollution due to other sources such as traffic-related emissions and domestic fuel stove use is also likely to be a confounder and may vary with temperature/season. The authors should clarify whether the modeled pollutant dispersion estimates the prevalence of all pollutants from all sources, or just the pollutants estimated to be emitted from biomass burning.

R: We would like to clarify that the CATT-BRAMS incorporating various parameters such as wind direction, relative humidity, CO, anthropogenic burning, burning resulting crop management (burning of sugar cane for example), among others. Further information may be obtained from the article recently published by Hyder and colleagues in 2014, and this was included in this version of the article. Which was in press at the time he submitted the article. Below is the complete reference: Hyder A1, Lee HJ, Ebisu K, Koutrakis P, Belanger K, Bell ML. PM2.5 exposure and birth outcomes: use of satellite- and monitor-based data. Epidemiology. 2014 Jan;25(1):58-67.

5. The authors state that the years 2004-2005 were periods of particularly intense biomass burning. Was there a large increase in biomass burning in 2004-2005 compared to 2002-2003, for example? To overcome several of the limitations in terms of seasonal confounding and air pollution due to traffic emissions, indoor fuel stoves and other sources, the authors could also investigate the prevalence of low birth weight in the study municipalities in the years before the period of intense biomass burning, as a historical control period.

R: We would like to clarify that the data from this study are of secondary source and were kindly provided by Center for Weather Forecasting and Climate Studies, National Institute for Space Research (INPE - CPTEC) through the Coupled Model aerosol and trace gas transport model to the developments of the Brazilian Regional Atmospheric Modeling System (CATT-BRAMS Model). We’re very sorry, but currently we would have great difficulty in obtaining data from other periods. However we would like to emphasize that the time series of this study were calculated daily by the model 3BEM (Brazilian Biomass Burning Emission Model - CPTEC) based on hotspots identified by remote sensing. A model is made through a computer system that simulates emissions
and atmospheric transport of products originating from biomass burning in Amazonia, using parameters of horizontal and vertical diffusion of solar radiation, humidity and temperature, and predicts with good precision, concentration these atmospheric pollutants in the study area. The CATT-BRAMS is able to estimate these concentrations for all municipalities in the Brazilian Amazon. Additionally, please note that the regions studied in this article are areas that are under development and have low power consumption per capita. Thus, it is unlikely that population growth regions could justify possible changes that change the way the relevant standards of anthropogenic emissions. In addition, biomass burning Amazon accounts for about 70% of all emissions of particulate matter throughout Brazil. Therefore, it does not seem logical that these emissions are capable of influencing the total values of particulate material from the region analyzed.

6. Categorization of maternal education is inconsistent in the Methods and Results. In the Methods (5th paragraph), mother's education is “categorized as up to three years of study and four years or more of study” – is this primary or secondary study? In the Results in text and in tables, mother’s education is classified as 0-7 years versus 8+ years. Is this primary or secondary study? The categorization must be consistent throughout.

R: We apologize for not being clear in our writing because we did not pay attention that in other countries this classification could be made differently. Aiming to clarify the doubts, we would like to inform you that in Brazil the levels of education and teaching are classified into basic education in fundamental levels (≤7 years) and medium (≥8anos). In order to facilitate easier understanding of all, we fit the categories used in this study will use the International Standard Classification of Education, better known by its acronym in English ISCED (International Standard of Classification of Education). This is a classification of educational levels to enable the comparison of statistics and educational policies enters different educational systems. The classification was developed by the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1970, then taking aim expressed as serve as a tool to enable the collection, compilation and processing of education statistics at national level and international. The ISCED was adopted by the International Conference of Education, which met in Geneva in 1975, and was subsequently adopted by the General Conference of UNESCO.

So appreciate your suggestions and advise that the categorization of maternal education in the paper was adapted to international standards as follows: primary education (≤ 7 years) and secondary education (≥ 8anos).

7. Please provide more information on how exposure level was classified for each municipality. Does the CATT-BRAMS model output exposure levels for each town and city, or over a defined area? How were the exposure data allocated to women - based on primary residence or birth location?

R: The concentrations of PM$_{2.5}$ and CO was derived from a simulation using the Coupled aerosol and trace gas transport model for the Brazilian development of the
Regional Atmospheric Modeling System 7 Model (CATTBRAMS). CATTBRAMS is an atmospheric emission and transport model that takes into account atmospheric dynamics. The emissions from biomass burning for several trace gases and aerosol particles were obtained from satellite observations of fires, using the 3BEM (Brazilian Biomass Burning Model). The aerosol mass concentration predicted by the CATTBRAMS model accounts for advection, turbulent motion in the planetary boundary layer, convective transport by shallow and deep cumulus, wet and dry deposition and plume rise, among other effects. The spatial model domain was set up to encompass the entire South American continent. The horizontal model resolution was 48 km by 48 km over all of South America, with reference to the seat of the municipality (city where the mother lived during pregnancy) as centroid of the grid cell. The CATT-BRAMS model framework provided ground-based estimates of pollutants from anthropogenic sources concentrations for each microregion in the Amazon region, for details see: Ignotti E, Valente JG, Longo KM, Freitas SR, Hacon SS, Artaxo Netto P. Impact on human health of particulate matter emitted from burnings in the Brazilian Amazon region. Rev Saúde Pública 2010;44(1):121-30 and Freitas SR, Longo KM, Silva Dias MAF, Chatfield R, Silva Dias P, Artaxo P, Andreae MO, Grell G, Rodrigues LF, Fazenda A and Panetta J. The Coupled Aerosol and Tracer Transport model to the Brazilian developments on the Regional Atmospheric Modeling System (CATT-BRAMS) – Part 1: Model description and evaluation Atmos. Chem. Phys., 9, 2843–2861, 2009.

8. The first paragraph of the results states that the prevalence of LBW was higher among male newborns, but the second paragraph and Table 2 shows that female newborns have higher odds of LBW. Please check.
R: The suggestions were accepted and the writing of the first and second paragraph were altered so that there is no danger any more confusion in interpreting the results.

9. Add numbers for each category in Table 2.
R: Thanks for your suggestion. We added numbers for each category in Table 2.

10. Discussion, paragraph 3: Explain why studies of the effects of air pollution on LBW are controversial in Brazil.
R: We appreciate your suggestion and try writing the paragraph again in order to make it more clearer:” In Brazil, studies on the effects of air pollution on LBW are still scarce and often not consistent, while some exhibit statistically significant associations between air pollution and low birth weight, other studies did not show statistical significance in this association. This could be explained by differences in methods employed in these studies or by assessing different levels of exposure or even ethnic populations or peculiar to each region.”

11. Report the stratum-specific estimates for the interaction between maternal age and pollutant exposure in a separate table, along with the overall p-values for interaction (not the stratum-specific p-values).
R: Unfortunately, the analysis of pollutants and LBW, stratified by maternal age did not show p-values for statistically significant interaction, although the p-value was less than
0.20. These statistically significant associations between pollutants (PM 2.5, CO) and LBW were only possible to be observed only when we included the interaction term "age * air pollutants" as an explanatory variable in the multivariate models.

Minor Essential Revisions

1. Last sentence of first paragraph in Background: The second half of this sentence is misleading. “Pollutants released in the process of incomplete combustion” includes particles (PM10, PM2.5) as well as carbon monoxide (CO), not carbon dioxide (CO2). Particle pollutants (aerosols) have a cooling effect on the atmosphere, and carbon monoxide has very weak direct effects on atmospheric temperature. The products of incomplete combustion cause poor air quality but not rising temperatures – so delete the second half of the sentence after the comma.
   R: We complied in the manuscript.

2. Paragraph 4 of Background: The sentence “This is due mainly to the fact that there are no measurements of atmosphere pollutants”. What does this mean? Are there no stationary monitors in regions with high biomass burning? Please clarify this sentence to explain the lack of data more explicitly.
   R: We rewrite the paragraph in order to make it more clearer: "Although there are studies that have shown an association between air pollutants from anthropogenic sources and pregnancy outcomes, there is still little understanding of the association between LBW and exposure to products of biomass burning and few studies have been conducted on the subject[12, 15]. This is due mainly to the fact that there are no measurements of atmosphere pollutants in most cities of the Brazilian Amazon. This restricts quantification of an exposure dose for different groups. This is due mainly to the lack of direct measurements of these pollutants in the most exposed to intense biomass burning populations, as is the case in many municipalities of these region."

3. Second paragraph of methods: Replace the words ‘specific coefficients’ with ‘variables’.
   R: We would like to say that the words ‘specific coefficients’ was replaced with ‘variables’ in the second paragraph of methods.

4. Throughout methods and results: Replace ‘bivariate’ with ‘univariable’ and ‘multivariate’ with ‘multivariable’ as these are the more accurate statistical terms (occurs several times).
   R: We would like to inform that it was replaced in the paper the terms ‘bivariate’ with ‘univariable’ and ‘multivariate’ with ‘multivariable’ because these are the more accurate statistical terms.

5. Paragraph 8 of methods: Replace ‘chi-squares’ with ‘chi squared tests’.
   R: We replaced chi-squares’ with ‘chi squared tests’ in the eighth paragraph.
6. Paragraph 8 of methods: Authors state that the variable ‘type of delivery’ was not included in the adjusted model but results for ‘type of delivery’ are presented in Table 2.
R: We rewrite the paragraph in order to make it more clearer: "We also obtained from SINASC information on possible confounding variables. We considered the following: the newborn’s gender; the mother's education in number of years that was categorized as primary education (up to 7 years) and secondary education (eight years or more); the mother’s age (categorized as up to 19, 20-39 and 40 or over); the number of prenatal visits (categorized as none, 1 to 3, 4 to 6 and 7 or more); and type of delivery (normal and cesarean section). This variable was also categorized as 0-3 or 4 or more."

7. Paragraph 9 of method: The authors state “We were able to use this method (logistic regression) because the outcome is a rare event...”. This isn't true – what you mean is that when the outcome is a rare event, the odds ratio approximates the risk ratio. Also delete the following sentence (“Also, there is evidence if similarity between prevalence ratios and odds ratios in bivariate analysis”).
R: We deleted the sentence (“Also, there is evidence if similarity between prevalence ratios and odds ratios in bivariate analysis”).

8. Second paragraph of Results, last sentence – “In the adjusted analysis, only the number of prenatal visits was associated with LBW (NOT “with statistical significance”)”
R: We removed this part of the text in order to avoid misinterpretations of this study.

9. Identify the reference category of PM2.5 or CO exposure that was used in the model producing the adjusted results for Table 2, in text and in the Table information.
R: We would like to clarify that in Table 2 is the only results of the analysis of variables associated with LBW. The variables were then selected for inclusion in the multiple adjusted from including analysis model. For better understanding, we take the liberty of changing the title of Table 2. Therefore, we removed: " according exposure categories...".

Discretionary revisions

1. Last paragraph of methods: the sentence ‘Interaction terms we used were...’ is unnecessary and may be deleted, as the interaction is sufficiently described in the previous sentence.
R: We appreciate your suggestion and the sentence (“‘Interaction terms we used were...”) was deleted in the Last paragraph of methods.

2. Last line of Methods - the plural for software is not softwares – perhaps say ‘software packages’ or just ‘software’.
R: We apologize for the error in writing and we would like to report that the error was gone in the text.

3. First paragraph of Results – it is confusing to read the prevalence of LBW was 3.1% and then read that among pregnancies of mothers with 8-11 years of education it is 39.9%. It would be better to give absolute prevalence percentages in the different groups.
R: We rewrite the paragraph in order to make it more clearer: "A descriptive analysis of daily observations of PM2.5 and CO are shown in table 1. The prevalence of LBW was 3.1%. Among infants with LBW, the occurrence was higher in males (52.0%) and among those born of pregnancies derived from mothers with secondary education (39.9%). It is also observed that most of the women were aged 20-29 years (56.6%) and held consultations 7 or more (56.4%) of prenatal care."

4. Second paragraph of Results – delete “we noticed that” and just state that in univariable analysis (see point 4 of minor essential revisions) LBW was associated with…
R: We deleted in the second paragraph of results ("we noticed that").

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.

R: We would like to clarify all doubts and pointed accept the suggestions made by the reviewers. We thank opportunity of being able exchange experiences with renown reviewers of this journal.

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.

R: We made the necessary changes in the manuscript.
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.

R: We made the necessary changes in the Table 1.

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.

R: We rewrite the end of eighth paragraph of the methods again in order to make it more clearer: "First, we conducted a univariable analysis between LBW and adjustment variables. At this stage, we also calculated chi squared tests for linear trend analysis, according to each case. We tested each variable in the model individually and selected those whose descriptive level of significance scored 0.20 or lower in the univariable analysis (education, mother’s age and number of prenatal appointments), except for the variable gender, which was kept in the model because of its significance in relation to the outcome variable (newborn weight). The variable type of delivery was not included in multivariable analysis method because its statistical significance in univariate analysis was greater than 0.20."

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.

R: Aiming to clarify the doubts, we would like to inform you that in Brazil the levels of education and teaching are classified into basic education in fundamental levels (≤7 years) and medium (≥8anos). In order to facilitate easier understanding of all, we fit the categories used in this study will use the International Standard Classification of Education, better known by its acronym in English ISCED (International Standard of Classification of Education). This is a classification of educational levels to enable the comparison of statistics and educational policies enters different educational systems. The classification was developed by the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1970, then taking aim expressed as serve as a tool to enable the collection, compilation and processing of education statistics at national level and international. The ISCED was adopted by the International Conference of Education, which met in Geneva in 1975, and was subsequently adopted by the General Conference of UNESCO.

We provided the categorization of maternal education in the paper was adapted to international standards as follows: primary education (≤ 7 years) and secondary education (≥ 8anos). This was changed in the text and in the table 2.
Declaration of competing interests:
We declare that we have no competing interests.

We hope we have answered all your suggestions and corrections. Please find attached our manuscript to be evaluated by BMC Pregnancy and Childbirth after to have answered your corrections and suggestions.

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

Sincerely,

Sandra Hacon