

Author's response to reviews

Title: The association between low level exposures to ambient air pollution and term low birth weight: a retrospective cohort study

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The association between low level exposures to ambient air pollution and term low birth weight: a retrospective cohort study
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Response to Reviewers' Comments

Reviewer #1 (Dr. Ann Aschengrau)

Major Compulsory Revisions:

1. Comment: The authors should also conduct and present analyses that treat birth weight as a continuous variable (e.g. present mean birth weights and mean birth weight differences according to the exposure category). In this way, readers will be able to better understand the nature of the impact of pollutants on birth weight.

Response: We have inserted the following text into the Results section:

“The mean birth weight for all exposure category and for each pollutant was over 3400 grams (data not shown). The largest difference in mean birth weight between the bottom and top quartiles of exposure was seen for 1st trimester exposure to SO₂ (3467 grams for bottom quartile versus 3428 grams for those in the top quartile of exposure).”

2. Comment: The authors should also conduct and present a summary of non- parametric (e.g. spline) analyses to determine the actual shape of the pollutant-birth weight relationship. For example, it appears that there is a threshold effect for first trimester sulphur dioxide exposure above the 50th percentile, but this could be a function of the cut point selection.

Response: We plotted the results of a regression of birth weight as a continuous variable versus a natural spline function of air pollution and have added an illustrative result to the paper.

The following sentences have been added to the Results section:

“In order to further assess the shape of the concentration-response relationship, we plotted the relationship between birth weight (as a continuous variable) and a natural spline function of SO₂ exposure (Figure 3). The results indicate a linear concentration response between increasing level of SO₂ and decreasing birth weight, over most of the range of exposure. The widely divergent error bars beyond 20 ppb reflect the scarcity of observations at higher levels of exposure, as depicted by the rugplot at the bottom of the figure.”

This sentence has been added to the Discussion:

“The plot representing the natural spline function of SO₂ and birth weight was consistent with a linear concentration response between SO₂ and birth weight, over most of the range of exposure. This is in keeping with the apparent gradient of effect observed in the logistic model. The lack of statistical significance at the lower exposure quartiles may be a result of low power for observing relatively small increases in risk.”

3. Comment: The authors should state whether or not there were multiple births for a particular woman during the observational period and should take "clustering" into account, if needed, in the analysis.

Response: With our analysis dataset, we were unable to determine whether or not a particular woman had more than one delivery. Therefore, we are not able to use generalized estimating equations to take this clustering (and non-independence) into account. The following sentence has been added to the discussion to describe this limitation:

“With the existing database, it was not possible to identify multiple births during the observational period for a particular mother. Therefore clustering or co-linearity was not accounted for.”

4. Comment: The discussion of exposure misclassification should acknowledge that a dispersion model was not used, that meteorological factors were not incorporated, and that housing characteristics were not available.

Response: The following sentence in the discussion has been edited to address these limitations:

“As with previous investigations on this issue, there was an inability to adjust for some potentially important confounders such as occupational exposures, exposures to environmental tobacco smoke, maternal drug and alcohol use, or meteorological factors. Similarly, we were unable to account for indoor air exposures such as wood combustion or other housing characteristics.”

Minor Revisions:

1. Comment: Table 1: This table should include information on race and urban/rural status.

Response: The database does not capture information with respect to race. Text has been incorporated into the results section to indicate that 75% of the women in this study were urban residents. As well, Table 1 includes urban/rural status.

2. Comment: Table 2: It is unclear if these data represent all trimesters combined or a particular trimester.

Response: The title for Table 2 has been updated to clarify that the data represents mean exposures for all trimesters.

3. Comment: The authors should justify the use of inverse distance weighting.

Response: We have added the following text to justify the use of inverse distance

weighting:

“This method was chosen to assign exposure levels that give more weight to the monitors that were closer to the woman's residence.”

Reviewer #2 (Dr. Marina Lacasaña)

Major Compulsory Revisions:

1. Comment: Low birth weight prevalence in the studied population is low compared to other populations, besides, the exposure levels to different air pollutants is also low. The lack of observation of association in the lower exposure quartiles could be due to lack of statistical power. Authors should make reference to the power of the study.

Response: We agree that the lack of statistical significance at the lower exposure levels may be a result of inadequate power to detect relatively small relative risks. We have added a sentence (in conjunction with Comment 2 from Reviewer 1) to the discussion to acknowledge this issue.

2. Comment: I consider that models should adjust according to origin (rural or urban areas) because of the difference in the environmental risk factors for low birth weight; for example: there is higher exposure to pesticides in rural areas. Besides, the assigning of exposure could not be performed for 48,222 births. Was there a difference in the percentage of births to which no exposure could be assigned between rural and urban zones?

Response: There was no difference in the proportion of women living in urban and rural areas between those with exposure information and those without exposure information. This information is now in Table 1. As well, we tested the urban/rural factor for inclusion in the adjusted model, and it was not a confounding factor (e.g., it did not change the estimates pertaining to the air pollutants).

3. Comment: Was the co-linearity that exists between births of the same mother, taken into account for the analysis?

Response: see Response for Reviewer 1, Comment #3

4. Comment: I consider that the models should have adjusted also for levels of other atmospheric pollutants.

Response: Unfortunately, it was not possible to adjust for other pollutants in the models as sufficient air pollution data were not available. This limitation has been described in

the discussion section (last sentence of discussion is: "In our study, data on other pollutants were not sufficiently available to include in the analysis.")

5. Comment: Although the Authors mention that one of the strengths of their study is the information regarding tobacco intake. The available information refers to the mothers smoking habits at the term of the pregnancy, and, as we know, many women stop smoking after they find out they are pregnant which usually happens after the first month of conception, this means, in the first trimester of pregnancy; and it is during this particular stage of their condition when the risk for low birth weight is higher according to this study.

Response: The following sentences have been added to the discussion to describe the limitation noted by the reviewer:

"A particular strength of this analysis was the availability of individual-level information pertaining to smoking during pregnancy. However, since the smoking information reflected smoking at the time of delivery, the smoking status for some women may have been underestimated for first (or second) trimester exposures (e.g., a woman who smoked in early pregnancy but quit during pregnancy would be considered a non-smoker)."

6. Comment: Finally, it is important to point out that these type of studies with geographical assignment of the exposure, always seem to have a non differential classification sesgo of the exposure, which tends to underestimate the magnitude of the association.

Response: We agree with this comment. The following sentence appears in the discussion:

"It is important to note that studies with exposure assignment based on geographical location may result in non-differential classification of the exposure, which can underestimate the magnitude of the association."

7. Comment: The results of different studies about prenatal exposure to environmental air pollution and low birth weight, show no consistency as to which pregnancy trimester could be most relevant and the specific pollutant which may represent a higher risk (You can read: "A Meta-analysis", published in the European Journal of Epidemiology, 2005; 20:183-199). Therefore, it is necessary to conduct follow-up studies to evaluate personal exposure using personal monitoring of different air pollutants or identifying different biomarkers of exposure, allowing the adequate evaluation of the impact of each pollutant on reproductive health at different stages of pregnancy, and, providing hypotheses of their possible action mechanisms.

Response: The authors agree that further study is required in order to determine the most relevant trimester of exposure and the relevant pollutant. Reference to the article noted above and comment about the need for further study has been incorporated into the discussion. The following sentence has been added:

"A recent review of published studies on prenatal and early childhood effects concluded

that future investigations should focus on using a more definitive means of characterizing exposures such as personal exposure monitoring to adequately evaluate the impact of each pollutant during different periods of pregnancy [23].”

Reviewer #3 (Dr. Jennifer Parker)

Major Compulsory Revisions:

1. Comment: Figure 1 and Figure 2.
 - a) Are there statistically significant trend lines?
 - b) What is the calculated trend for lbw, realizing that the authors indicated that they observed no apparent trend?

Response:

- 1a. There are significant trend lines for ozone and SO₂ but not PM₁₀ (this is now noted in the results section).
- 1b. There was a statistically significant decreasing trend in LBW among term births (p value 0 .006). This has been added to the results section.

2. Comment: Logistic regression.
 - a) Why didn't the authors adjust for year of delivery?

Response: Birth year was not included in the original analysis because it was thought that birth year could be considered a surrogate of exposure and therefore, reflect the trends in exposure. We feel that arguments could be made for adjusting for birth year, or not adjusting. We have decided to present the results with and without adjustment of birth year. Although the results are attenuated somewhat, there still is a suggestion of a dose response effect of SO₂ in the first trimester.

The abstract and conclusions have been modified to reflect these new models.

Minor Compulsory Revisions:

1. Comment: Abstract, Background. The trimester-specific objective should be mentioned.

Response: This has been added to the abstract. Last sentence of 1st paragraph of abstract has been edited to:

“The purpose of this study was to examine the association between LBW among term infants and ambient air pollution, by trimester of exposure, in a region of lower level exposures.”

2. Comment: Abstract, Results. Findings are presented with greater detail than in tables (to two decimal places rather than one).

Response: All findings are presented with two decimal places.

3. Comment: Abstract, conclusions. This study doesn't really target vulnerable populations.

Response: We have changed to the last sentence of the abstract to:
“These findings have implications for the development of effective risk management strategies to minimize the public health impacts for pregnant women.”

Discretionary Revisions:

1. Comment: Background, second paragraph. "poignant"? Does this word really fit in this context?

Response: The word “poignant” has been replaced with “relevant”.

2. Comment: Methods. Clarify study cohort creation.
 - a) How many births between Jan 1, 1988 and Dec 31, 2000? Of these, how many eligible based on study criteria (over 500 g, ≥ 37 wks gest)? How many post-term births?

Response: The database includes infants 500 grams and over. Between January 1, 1988 and December 31, 2000, there were 143,890 births. Of these, 140,663 were singleton births, and 130,863 were ≥ 37 weeks gestation. During this time period, there were 9,074 post-term singleton births (defined as ≥ 42 weeks). We have added some of these cohort numbers into the beginning of the results section.

3. Comment: Are pollutant monitors co-located? That is, does one monitoring station collect data for O₃, SO₂, and PM₁₀?

Response: Only three monitoring stations collect data on more than one pollutant (see response to Comment 5 below).

4. Comment: It's surprising that only 60% of mothers within 25 km of the monitor have sufficient trimester-level data.
 - a) Is this because one or more trimesters are missing data? Is there a particular pollutant missing? Can you elaborate on this a little more?
 - b) Is there a whole pregnancy (that is, nine months rather than trimester) effect using the full sample of 108,399 mothers within 25km of a monitor?

Response:

4a. We have revised the text to indicate that 83% of the women had adequate air monitoring data available (the 69% we previously reported also counted, as missing, those women who did not have a singleton, term birth). The reason that we do not have complete exposure data is because not all of the monitors were operational every year. As well, some of the monitors were missing data for some of the days/weeks. We required that pollutant data was available for 75% of the total days of a woman's trimester in order for her to be included in the analysis.

4b. Our primary objective was to evaluate trimester effect, so we did not analyze the relationship between exposure during the entire pregnancy and low birth weight. The numbers would have been quite reduced from the full sample, since we would have required that exposure information was available for 75% of the total days of the pregnancy.

5. Comment: How many monitors were used in the study?

Response: There were eighteen monitors available for this study. The following sentence has been added to the Methods section:

“Eighteen monitoring stations provided the ambient air pollution data for the study; only three stations monitored more than one pollutant.”

6. Comment: Methods. Logistic regression.

a) Why were the particular covariates chosen? Is there rationale for thinking that, say weight change, would influence the association between pollution exposure and term LBW?

b) How did income change over the 13 year data period; how reasonable is it to assign 1996 levels to 1988 or 2000 births?

Response: The covariates were selected because they had been used in previous studies of low birth weight and air pollutants. The income variable that we used was based on quintiles of the average neighborhood income level. Although some neighborhoods may have shifted from one income quintile to another, it is not likely that there was a great deal of change in the neighborhood income levels over the study period.

7. Comment: Results. Logistic regression.

a) Why are RR presented with one decimal place but the CI with two?

b) Did adjustment for the covariates change the associations? Show unadjusted associations.

c) Given that a lot of studies talk about smoking, did adjustment for smoking change the associations?

d) For the continuous exposure model, the results could be expressed in terms of the interquartile range or simply 5 units.

e) Although not the express purpose of the study, given the long length of time being considered, testing for effect modification/interaction between year of delivery and the exposure might be informative, that is, has the association between lbw and exposure changed over time.

Response:

7a. Results for RR and CI have been edited so that all have two decimal places.

7b. Unadjusted RRs have now been presented.

7c. For first trimester exposure to SO₂, the relative risk for the highest quartile changed from 1.20 to 1.19 with, and without, smoking in the model.

7d. Results for the continuous analysis are now presented for the interquartile range.

7e. Effect modification was not observed between the air pollutants and birth year.

8. Comment: Results. Figure 1 and Figure 2.

a) Why are these on two graphs and not one or three?

b) Is there a footnote describing the missing SO₂ data for 1997?

c) Can you add lines around the bars indicating the range (say 25th and 75th percentiles) or note in the text that the variation in exposure for births each year has increase/decreased/stayed the same over time?

Response:

8a. The units for the gaseous pollutants and PM differ, hence 2 separate Figures are required.

8b. A footnote has been added with respect to the SO₂ missing data.

8c. Bar charts now include ranges to provide more illustrative data.

Reviewer #4 (Dr. Radim Sram)

Minor Essential Revisions:

1. Comment: p. 7 and others - units used should be the same, it means metric! ug/m³ and not ppb. Add PAHs to the list of abbreviations.

Response: The standard units for Canadian ambient air quality monitoring are µg/m³ for PM₁₀, and ppb for SO₂ and O₃. PAHs have been added to the list of abbreviations.

Discretionary Revisions:

1. Comment: It is of interest that the first trimester exposures in the highest quartile for SO₂ and PM₁₀ were associated with increased risks of delivering a LBW infant. You should add to discussion how these concentrations correspond with results of other authors analyzing the impact of SO₂ and PM₁₀ to LBW and IUGR.

Response: We have added the following sentence to the discussion to compare our exposure concentrations with those of other authors:

“Among the studies that observed a relationship between early pregnancy exposure to air pollutants and IUGR, our exposure levels were not consistently lower or higher than those reported in other studies. For instance, the high exposure group for PM₁₀ was ≥ 50 ug/m³ in a study conducted in the Czech Republic [9], whereas the top quartile of PM₁₀ in our study was ≥ 19 ug/m³. In Vancouver, British Columbia, the top quartile exposure level for SO₂ was ≥ 6.3 ppb [13], which was a lower level than our top quartile.”