Author's response to reviews

Title: The joint influence of marital status, interpregnancy interval, and neighborhood on small for gestational age birth: a retrospective cohort study

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Author's response to reviews: see over
November 8, 2007

Dear Dr. da-Silva,

Re: MS# 2100646160143565

We are pleased to submit our revised manuscript, newly entitled “The joint influence of marital status, interpregnancy interval, and neighborhood characteristics on small for gestational age birth: a retrospective cohort study” to BMC Pregnancy and Childbirth. We would like to express our appreciation to the reviewers for their thoughtful comments. We have revised the manuscript in light of reviewer comments, and a point by point response follows. Should any questions remain, please do not hesitate to contact the corresponding author at nathalie.auger@inspq.qc.ca.

With warm regards,

Nathalie Auger

Response to reviewers

Reviewer 1: Bao-Ping Zhu

Reviewer comment: My biggest concern is the way interpregnancy interval was categorized. Based on their descriptions in the Methods section, the authors decided on the three categories based on sample size alone, whereas it is more appropriate to decided on the categories based on the actual association observed between interpregnancy interval and SGA birth, or on the accepted categories in previously published articles (such as <18, 18-23, >23 months, as was used in a recent meta-analysis published in JAMA [ref 1 in the manuscript]). The way the categories are defined in the current version of the paper renders it difficult to compare the findings of this paper with other published works.

Author response: The authors acknowledge the alternate categorization of IPI in our article compared to the JAMA article. Nevertheless, the JAMA categories are not “golden” or “standard” categories on which all future research should be based. In the JAMA article, the reference category was defined as 18-23 months. Our data set is not sufficiently large enough to permit such short intervals. We also question the clinical usefulness of defining a short 6-month interval as the reference category. Nevertheless, to address the reasons for selecting our birth categories, we have modified the following sentence in the manuscript: “We chose the <12, 12-35, 36+ month cut-offs based on sufficient sample size in each category, as well as clinical relevance. (page 8, lines 16-7)”

Reviewer comment: Consider changing “birth categories” into “interpregnancy interval categories” throughout the paper. I understand that “first-born” is not an IPI category per se; however, it can be considered as a special case. To me, “birth category” is vague, uninformative, even misleading.
Author response: We have changed the label “birth categories” into “interpregnancy interval categories” throughout the manuscript.

Reviewer comment: Title: Consider changing it to: “The joint effect of marital status, interpregnancy interval, and neighborhood characteristics on small-for-gestational-age birth,” to better reflect the content of the paper.

Author response: The title has been changed to “The joint influence of marital status, interpregnancy interval, and neighborhood on small for gestational age birth: a retrospective cohort study”

Reviewer comment: Abstract: Consider changing the last sentence in “Methods” to: “Multilevel logistic regression was employed to elucidate the associations.”

Author response: We have changed the sentence to: “We used multilevel logistic regression to assess relationships between variables. (page 4, lines 9-10)”

Reviewer comment: p. 6., 2nd paragraph (under “Data”): I wonder how gestational age is determined on the Canadian birth certificate? Is it LMP-based? If yes, how was the missing values dealt with? It would be helpful for readers to know these details.

Author response: Gestational age is based on ultrasound estimates in Québec birth certificates. There are no missing data on gestational age in the birth registry. However, implausible gestational age was present (n= 124 births), which precluded the calculation of SGA status for these births. The definition of implausible gestational age is provided in reference 21. Information on missing data and implausible gest age are provided under the “Exclusion criteria and missing data” section (page 7, bottom paragraph). To address the reviewer’s question regarding how gestational age is determined, we have modified the following sentence in the text: “The conception date was calculated by subtracting the gestational age (in weeks, based on ultrasound estimates) from the date of birth of the index child. (page 6, lines 12-14)”

Reviewer comment: In the same paragraph, did the authors use years of education as a continuous variable in the logistic regression? If yes, did the authors investigate whether it was appropriate to do so i.e., whether the relationship between years of education and SGA was log-linear? If it is not log-linear, the authors will need to categorize education, based on the shape of the curve.

Author response: We have modified the sentence in the paragraph to address the concerns of the reviewer, as follows: “education (in continuous years, verified for log-linearity with SGA)” (page 6, lines 20-1)

Reviewer comment: p.7, 3rd paragraph (under “Exclusion criteria and missing data”): The way the education variable was imputed could cause misclassification. There are more sophisticated and better imputation methods available. However, I wonder whether the authors had considered simply creating a dummy variable representing those with missing education, and if yes, whether the results were any different?
**Author response:** Our analysis is based on a large number of births with a low percentage of missing data. Furthermore, in a different study based on these same data, we found similar results for imputed maternal education versus categories of education (manuscript currently accepted and in press with the journal Pediatric and Perinatal Epidemiology). Therefore, we did not re-run the analyses with categories of education with missing education as a separate category. Nevertheless, we have added the following sentence to the limitations section of the discussion: “We do not know how factors such as income or alternate classifications of socio-economic status could influence our results.(page 14, lines 20-1)”

**Reviewer comment:** p.8, 2nd paragraph. Since the authors pooled many years of data, there are likely biological siblings (i.e., infants born to the same mother) in the dataset, whose data are likely correlated. The authors should consider linking these infants to their biological mothers, and consider another level of intra-class correlation (in addition to neighborhood dependency). If this is impossible, they should acknowledge this as a limitation in the discussion section.

**Author response:** This analysis is not possible. We added the following to the limitations: “We also could not correct reduced precision resulting from correlation between siblings as our data do not allow the identification of siblings, although we do not suspect this effect could be substantial. (page 14, lines 21-3)”

**Reviewer comment:** As I said earlier, I have a big problem with the way interpregnancy interval was categorized.

**Author response:** Please refer to the first author response provided above. We hold strongly to the point that there is no established “gold standard” for categorising interpregnancy interval.

**Reviewer comment:** p.10, 1st paragraph, the sentence that starts with “For subsequent born infants…” is not informative. These %s are strictly determined by the cut-points the authors had chosen.

**Author response:** We are assuming the reviewer is referring to the following sentence on page 9, not page 10: “For subsequent born infants, the IPI was intermediate for the majority (44.7%), followed by long (37%), and short (18.3%) of such infants.” We agree with the reviewer that the proportions are determined by the cut-points we have chosen (this limitation is inherent to any continuous variable that is represented as categories). However, we did not cut the sentence because the point is to inform the reader about the distribution of the data.

**Reviewer comment:** p.10, 2nd paragraph. The X2 and p-values are not very informative. They are determined by the samplesize. A more appropriate way to present the data is to describe the magnitudes of the associations.

**Author response:** We are assuming the reviewer is referring to page 9 (not 10). These results refer to the descriptive characteristics of the population. We have removed the p-values. We do not show magnitude of associations because this section pertains to descriptive characteristics. The paragraph is now formulated as follows: “There was an inverse relation between births to unmarried mothers and neighborhood perceived security (Table 1), and this coincided with an increasing frequency of SGA births as perceived security diminished in neighborhoods (Table 2).
Table 3 shows that the IPI for subsequent births varied according to neighborhood characteristics. High neighborhood perceived security corresponded to a greater frequency of an intermediate IPI (49.5%), and lesser frequency of short (16.7%) or long (33.8%) IPIs relative to neighborhoods with low perceived security (41.0%, 19.7%, and 39.3%, respectively).” (page 9, lines 14-20)

Reviewer comment: p.10, 3rd paragraph. I have a problem with the statement in the 1st sentence of the paragraph. The lack of statistical significance could be simply due to the smaller sample size. I would delete this statement.

Author response: Being unmarried has an effect in both Canadian-born (discussed in previous paragraph) and foreign-born mothers (discussed in the current paragraph pointed out by the reviewer). It is important to discuss the effect of marital status in each group, particularly since we are looking at effect modification. We agree with the reviewer that sample size may have resulted in a lack of power, especially given the fewer unmarried relative to married foreign-born mothers. Nevertheless, sample size is inherently addressed in the width of confidence intervals. Figure 1, which shows the effect of marital status, shows that confidence intervals for foreign-born mothers were not unusually larger than those for Canadian-born mothers, indicating that sample size may not be the only reason for the observed differences. Therefore, we did not cut the sentence.

Reviewer comment: p.13, last paragraph. Ref. 40 is not related to the current topic under discussion. (The authors might want to investigate the other references more completely on their relevance to their study.)

Author response: Thank you for noting this mistake. We have removed the reference.

Reviewer comment: p.14, 2nd paragraph. I suspect a major reason that the attributable fraction was different between this paper and ref. 34 is that IPI was defined differently.

Author response: We agree with reviewer principally because we include firstborns as a separate IPI category. The inclusion of firstborns roughly doubles the population of interest, which then roughly decreases by half the population attributable fraction. That is to say, the attributable fractions observed in reference 34 are for the subset of subsequent-born infants, which is not a true population attributable fraction. Our population attributable fractions are for the entire population of births. Therefore, the main reason why our attributable fractions are smaller is because we included firstborns as a separate category, and not because we chose different cut-points for short, intermediate, versus long IPI. We modified the following sentence in the manuscript to clarify the above: “One study reported an attributable risk of 9.4% for short or long IPIs, but because the study was restricted to subsequent-born infants (i.e. excluded firstborns) and did not consider marriage, this estimated attributable risk cannot be directly contrasted with ours. (page 14, lines 5-8)”

Reviewer comment: p.14, 3rd paragraph. I wouldn’t characterize the lack of information about years of residency as “unavoidable” unless the data are not collected on the Canadian birth certificate.

Author response: We have modified the sentence to read as follows: “Similarly, we categorized foreign-born mothers as one group when in fact differences may exist based on nationality or length of residence in Canada, but this was unavoidable because data on duration of residence is
not available in the birth registry. (page 14, lines 13-6)"

**Reviewer comment:** References: Check the references to ensure uniformity (e.g., ref. 27).

**Author response:** Thank you, we have corrected this mistake which was due to our referencing software.

**Reviewer comment:** Tables and graphs: All captions should contain information about what, who, where, when.

**Author response:** Thank you, we have made these changes.

**Reviewer comment:** Figures 1-2. The vertical axis should be on log-scale. Otherwise the graph will give misleading impressions.

**Author response:** Because our ORs and CIs are located between 0.4 and 2, re-scaling on a log scale (i.e. y-axis 0.1, 1, 10) makes the figure difficult to read. We have therefore chosen to keep the figures in their original form.

**Reviewer comment:** Discretionary Revisions (which the author can choose to ignore)
I was curious as to why the authors chose to investigate these three variables, not the other important risk factors, such as education, income, and employment?

**Author response:** Although we agree with the reviewer, this was not the study question for the present study. On a side note, we do not have information on mother’s income or employment in the birth registry. Maternal education was available and adjusted for.

**Reviewer 2:** Jose M Belizan

**Reviewer comment:** I consider that the manuscript do not provide original information on the subject.

**Author response:** In the introduction, we indicate the gaps in the literature concerning IPI and social factors associated with the IPI such as marital status. We also point out the growing role of neighborhood effects in the literature, and how such effects have never been studied in relation to the IPI. Our statistical approach is furthermore based on up-to-date methods for the analysis of neighbourhood data. Further, our finding concerning interaction between IPI and marital status has not been documented in the literature thus far. Therefore, we strongly disagree with the reviewer that the study is not novel. Further, the reviewer does not give us evidence for the basis of his/her position, hence we cannot respond in any detail greater than the above.
Reviewer comment: Furthermore, instead of being a publication that can show Canadian information on the issue of interpregnancy interval, analysis to assess the role of marriage and neighborhood complicate the interpretation of the results.

Author response: Although, our study question was not to assess the effect of IPI per se, we acknowledge that this is a valid, but different, research question, suitable for a different study.

Reviewer comment: Also, major conclusions and recommendations are based on the finding that the odds ratio in intermediate IPIs are lower for married (OR 0.50, 95% CI 0.47-0.54) than unmarried women (OR 0.65, CI 0.56-0.76). I wonder the biological implications of such small differences in odds ratios.

Author response: We acknowledge that the differences between categories are not large, and may possibly be due to large sample size. We also acknowledge that such differences do not necessarily imply biologic or clinical significance. Nevertheless, trends were consistent, and we address potential biologic mechanisms in the discussion.

Reviewer comment: Authors could make a contribution to the subject if they analyze the association of IPI to SGA and then design a hierarchical model to assess a series of variables that could be linked to such association.

Author response: The study design proposed by the reviewer, while valid, does not address the research question we began with.

What next?: Reject because scientifically unsound

Author response: The reviewer does not provide supporting evidence for the claim that the study is scientifically unsound.

Reviewer 3: Judith Lumley

Reviewer's report:

Discretionary Revisions (which the author can choose to ignore)

Reviewer comment: Include in the introduction: -a brief summary about health care in Quebec

Author response: We modified the following sentence in the introduction “Although research on the IPI has been performed in many countries, relatively few studies have been conducted in developed nations characterized by low rates of adverse birth outcomes and comprehensive health insurance such as Canada (page 5, lines 7-9)”
**Reviewer comment:** -the quality of the perinatal data collection

**Author response:** We are not certain how to incorporate this comment. The birth registry in Quebec is complete, but like any data collection instrument, misclassification and missing data are possible. Missing data is addressed on page 7 of the manuscript. If the reviewer can clarify the statement he/she would like us to add to the text, we would be happy to comply.

**Reviewer comment:** assessment of the relative homogeneity of neighbourhoods

**Author response:** On page 7, we state in the methods that the neighbourhood level examined in this study was developed based on its relative homogeneity, as follows: “We used Montreal police districts because they were created based on functionality, spatial homogeneity, and historic socio-demographic similarity of residents (page 7, lines 5-7)”