

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Concomitant preterm birth and severe small-for-gestational age birthweight among infants of immigrant mothers in Ontario originating from the Philippines and East Asia: a population-based study
<b>AUTHORS</b>	Bartsch, Emily; Park, Alston; Jairam, Jennifer; Ray, Joel

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Olof Stephansson Karolinska Institutet, Sweden
<b>REVIEW RETURNED</b>	02-May-2017

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this manuscript. This is a study on the association between maternal country of birth and subsequent risk of SGA and preterm birth in a cohort of East Asian immigrants in Ontario, Canada between 2002-2011. The study report increased risk of preterm birth (PTB), SGA and PTB-SGA birth in women from the Philippines and Vietnam compared to women born in China. The methods used are up-to date and the data quality is of high quality.</p> <p>General comments</p> <ol style="list-style-type: none"><li>1. The main problem with the study is the lack of data on important confounders like maternal socio-economic status like educational level and occupation. Furthermore, there is no information on smoking and bmi which is likely to influence SGA and PTB risk. The important question is why women from the Philippines and Vietnam are at increased risk of adverse pregnancy outcome compared to women of Chinese origin? This has to be more highlighted in the Discussion of the manuscript.</li><li>2. Is there information on other important factors like preeclampsia which could be a mediator of PTB and SGA risk?</li><li>3. The study present stratified analysis by maternal age and parity. Was there any statistical interaction for these possible effect measure modifiers?</li><li>4. Is there any evidence that women from Vietnam and the Philippines would benefit from initiatives including preeclampsia surveillance and ultrasound for fetal growth?</li></ol> <p>Specific comments</p> <ol style="list-style-type: none"><li>1. Were there any missing data for the variables included in the study? If so, how was this treated in the multivariable analysis?</li><li>2. Could nutritional deficiencies or other life-style factors influence the difference in risk between women's origin?</li><li>3. Would it be possible to investigate preterm birth by gestational age (moderate and very preterm birth) and by spontaneous or medical onset?</li><li>4. Is there any data on attendance to antenatal care which may explain differences in risk?</li></ol>
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<b>REVIEWER</b>	Annie SY Hui The Chinese University of Hong Kong, Hong Kong SAR
<b>REVIEW RETURNED</b>	05-May-2017

<b>GENERAL COMMENTS</b>	<p>This paper is original and well written, it conveys a clear message to the audience.</p> <ol style="list-style-type: none"> <li>1. I suggest that the title should be more specific e.g. "Concomitant" preterm birth and severe small for gestation age among infants of "immigrant" mothers from the Philippines in "Ontario"</li> <li>2. Avoid using the word "countries" throughout the manuscript because Hong Kong is now a special administrative region under China. Preferably use words such as origins, east asian-born, maternal birth place etc.</li> <li>3. I understand that China was chosen as the referent group for comparison and that was fine, but it would be good to know the RRs of the primary outcome among the infants born by Ontario-born mothers so that the readers can have a rough idea whether the whole "immigrant" group per se is at risk.</li> <li>4. Under "background", it is better to use "cut-off" rather than "cut-point" which has a special meaning.</li> <li>5. Add (Figure 1) to the end of 3rd paragraph of "results" for easy reference.</li> <li>6. I suggest to incorporate the first paragraph of "interpretation" into the "results" section.</li> <li>7. Reference is missing for the last line of paragraph 1 " we were able to account for some previously noted risk factors..." under "strengths and limitations".</li> <li>8. The causes of PTB-SGA could not be identified from the dataset and should be addressed in the limitations.</li> <li>9. Please check references 8,9,13,24 and 25 are correctly cited.</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer 1

#### General comments

1. The main problem with the study is the lack of data on important confounders like maternal socio-economic status like educational level and occupation. Furthermore, there is no information on smoking and bmi which is likely to influence SGA and PTB risk. The important question is why women from the Philippines and Vietnam are at increased risk of adverse pregnancy outcome compared to women of Chinese origin? This has to be more highlighted in the Discussion of the manuscript.

We appreciate the reviewer's point, but believe that we have handled some aspects of what is raised above. Please allow us to address some of the points above, as follows:

- Background, paragraph 2. We do rationalize why women from the Phillipines might be especially at higher risk of PTB + SGA: "Chronic hypertension<sup>7</sup> and preterm onset of preeclampsia<sup>8</sup> are each risk factors for provider-initiated ("iatrogenic") PTB and SGA, and they are significantly more likely to present in Filipina women than Caucasian or other East Asian women".

- We did, in fact, control for socioeconomic status, probably the best overall reflector of social tendencies within our cohort. However, we see no reason to believe that educational level can alter the likelihood above and beyond income? How does being more educated alter one's risk of having

fetal growth restriction or preterm birth? It probably does not.

- Limitations: We now state: “We also did not possess information on parental height or weight – which may influence newborn weight – or conditions such as maternal chronic hypertension and diabetes mellitus, or maternal behavioural risk factors (e.g. smoking, drug or substance use). However, Filipina women of reproductive age living in Canada have a rate of smoking under 6.0%, comparable to that of their East Asian counterparts<sup>7</sup>, and the corresponding rate in pregnancy would be expected to be even lower. The body mass index (BMI) of Filipina women of reproductive age tends to be higher than that of other East Asians<sup>7</sup>.”

- Implications, we state: “Chronic hypertension is one important risk factor for both PTB<sup>18</sup> and SGA<sup>19</sup> 20, and also for preeclampsia<sup>21</sup>, which can give rise to PTB-SGA<sup>22</sup>. Chronic hypertension is highly prevalent among Filipina women in Ontario<sup>7</sup>; therefore, efforts to regulate blood pressure and prevent preeclampsia may help reduce the risk of SGA-PTB among Filipina women, and also those from Vietnam.”

- Conclusion: “Specifically, it would be worthwhile to evaluate whether the rates of smoking, high BMI, or other socioeconomic indicators differ widely between pregnant Filipina women and those women from other East Asian birthplaces.”

2. Is there information on other important factors like preeclampsia which could be a mediator of PTB and SGA risk?

Our response:

- Background, paragraph 2: “Chronic hypertension<sup>7</sup> and preterm onset of preeclampsia<sup>8</sup> are each risk factors for provider-initiated (“iatrogenic”) PTB and SGA, and they are significantly more likely to present in Filipina women than Caucasian or other East Asian women.”

- The focus of this study was to identify whether women from the Philippines are at higher risk for PTB-SGA than are women from other East Asian birthplaces. Performing mediation analyses might be better suited to a future study, in which the focus would be identifying those factors such as preeclampsia, in addition to socioeconomic, nutritional, and lifestyle factors, that strongly mediate the relationship between Filipina ethnicity and high rates of PTB-SGA. However, such a dataset would require detailed individual assessments, such as dietary (e.g., salt intake) and activity questionnaires, physical measures of adiposity, etc.

3. The study present stratified analysis by maternal age and parity. Was there any statistical interaction for these possible effect measure modifiers?

A priori, we chose to stratify by these factors, as we were not interested in the expression of a statistical P-value for the interaction, but an outright expression of the relative risks and outcome event rates but these conventional maternal demographic factors.

4. Is there any evidence that women from Vietnam and the Philippines would benefit from initiatives including preeclampsia surveillance and ultrasound for fetal growth?

Great point. We have now changed the final sentence of the Implications paragraph to: “By the third trimester of pregnancy, periodic sonographic assessment of fetal growth and well-being should be considered, as there is evidence that this helps the clinician identify SGA infants and balance the risks of prematurity against a worsening intrauterine environment<sup>27 28</sup>.” Reference 28 is newly added, which is a study in which Vietnamese caregivers effectively used ultrasound for fetal growth to identify SGA infants.

Specific comments

1. Were there any missing data for the variables included in the study? If so, how was this treated in the multivariable analysis?

In the multivariable models, for a covariate that was categorized as “unknown”, we included that “unknown” category when we adjusted for income quintile and marital status. For maternal age and parity, because “unknown” was so rare for each (mentioned in the Results section, first paragraph), we excluded those pregnancies with unknown maternal age or parity, to enable model convergence. We now clarify this in the Data analysis section: “The “unknown” categories of marital status and residential income quintile were included in the multivariable models. However, for maternal age and parity, we excluded those pregnancies with “unknown” status, given the rarity of this situation and the need to allow model convergence, accordingly.”

2. Could nutritional deficiencies or other life-style factors influence the difference in risk between women’s origin?

Please see response to general comment #2. Overall, in a country like Canada, where nutrition is replete among women, it is doubtful that any experience under-nutrition. Rather, there may be a tendency for over-nutrition in Canada, no matter where a woman comes from, and women from the Phillipines are no exception (see 2nd paragraph, on page 10, at <https://glas.uic.edu/docs/librariesprovider11/asam-expo/john-capua-thesis.pdf?sfvrsn=2>).

3. Would it be possible to investigate preterm birth by gestational age (moderate and very preterm birth) and by spontaneous or medical onset?

This would be difficult, in that we have used severe SGA a < 5th percentile cut-off, which means that we have a generally smaller number of births, and then we cross that with PTB < 37 weeks, and the outcome counts drop further. To then further assign a breakdown of PTB to < 32 weeks (for very PTB) would create cell sizes that would likely have to be suppressed for some maternal birthplace groups.

4. Is there any data on attendance to antenatal care which may explain differences in risk?

According to a 2015 retrospective cohort study of women in Ontario, evidence suggests that immigrant women have higher rates of prenatal screening (see <http://cmajopen.ca/content/3/2/E236.full>)

In our prior study of Canadian women of reproductive age, Filipina women had higher rates of visits to a doctor than other East Asians. In the Limitations section we added: “It is unlikely that access to prenatal care explains the current findings, as 88% of Filipina women and 85% of other East Asian women in Canada have a regular medical doctor<sup>7</sup>.”

Reviewer 2

1. I suggest that the title should be more specific e.g. "Concomitant" preterm birth and severe small for gestation age among infants of "immigrant" mothers from the Phillipines in "Ontario"

Changed to “Concomitant preterm birth and severe small-for-gestational age birthweight among infants of immigrant mothers in Ontario originating from the Phillipines and East Asia”

2. Avoid using the word "countries" throughout the manuscript because Hong Kong is now a special administrative region under China. Preferably use words such as origins, east Asian-born, maternal birth place etc.

We replaced “countries” with more appropriate terms, such as Birthplace.

3. I understand that China was chosen as the referent group for comparison and that was fine, but it would be good to know the RRs of the primary outcome among the infants born by Ontario-born mothers so that the readers can have a rough idea whether the whole "immigrant" group per se is at risk.

We ran an additional analysis, now in Supplementary file 2. We present, in the Results section, last paragraph, the following: "Re-running the main model of PTB-SGA, with Canadian-born mothers as the referent, showed that only the offspring of Filipina mothers were at higher risk of PTB-SGA (Supplementary file 2)."

4. Under "background", it is better to use "cut-off" rather than "cut-point" which has a special meaning.

We have replaced "cut-point" with "cut-off"

5. Add (Figure 1) to the end of 3rd paragraph of "results" for easy reference.

We added "(Figure 1)" to the end of both the second and third sentence in this paragraph.

6. I suggest to incorporate the first paragraph of "interpretation" into the "results" section.

We prefer to leave as is. We think this paragraph serves as an introduction to the Discussion. This is in keeping with a structured Discussion section, as preferred by the BMJ editors (see <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1115625/pdf/1224.pdf>)

7. Reference is missing for the last line of paragraph 1 " we were able to account for some previously noted risk factors..." under "strengths and limitations".

This was referring to the fact that we had included these variables in our analysis. We have added "Through our analysis," to clarify.

8. The causes of PTB-SGA could not be identified from the dataset and should be addressed in the limitations.

We have now added this as a sentence in the limitations paragraph.

9. Please check references 8,9,13,24 and 25 are correctly cited. Citations have now been properly formatted.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Olof Stephansson Karolinska Institutet Sweden
<b>REVIEW RETURNED</b>	18-May-2017

<b>GENERAL COMMENTS</b>	The authors have revised the manuscript according to my comments. No further comments.
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<b>REVIEWER</b>	Annie Hui The Chinese University of Hong Kong Hong Kong SAR
<b>REVIEW RETURNED</b>	24-May-2017

<b>GENERAL COMMENTS</b>	I have no further comments regarding the changes on the manuscript.
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