Author's response to reviews

Title: Pre-pregnancy predictors of hypertension in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia: a prospective cohort study.

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Letter to the Editor

BMC Public Health

Dear Mr Silvestre

Re: MS ID 3112930078881025 Pre-pregnancy predictors of hypertension in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia; a prospective cohort study.

Many thanks for arranging for review of this manuscript. Please find below, our point-by-point response to the reviewers comments. We believe their contributions have greatly improved the presentation of the study.

Kind regards

Dr Sandra Campbell (on behalf of the manuscript authors)

Response to Reviewers

Reviewer: 1

Major Compulsory Revisions:

1. Did the authors obtain a written informed consent from each of the patients? At least I could not see any such mention in the manuscript, although it is absolutely essential requirement.

   Response: Yes. The women provided their consent at baseline to have their medical records reviewed and data from those records to be linked to the baseline data. This is now stated in the Methods section, under the heading Ethics.

   “The participants provided written consent to have their Queensland Health medical records reviewed and linked to their WPHC records.”

2. How was the level of physical activity in the study subjects categorized? In my opinion using GPAQ (global physical activity questionnaire) designed by WHO, would have been a better idea.

   Response: The Global Physical Activity Questionnaire (GPAQ) would have most certainly been a better idea. At the time of the study baseline data collection (1998-2000), the GPAQ had not yet been developed, however, in future research I agree it will be an appropriate tool, particularly in research that takes place in Australian Indigenous communities. Physical activity was assessed in face-to-face interview with the Well Person’s Health Check participants to assess the duration and intensity of physical activity. The participants were categorised as having adequate physical activity if they reported a minimum of 30 min of moderate to vigorous exercise on at least 5 days in the week (p.5).

3. I feel the patient inclusion methodology for this study was sound and justified, however for statistical analysis, the authors could have used Logistic Regression Analysis (Univariate/Multivariate) as the results are easy to interpret and also very reliable to test the association between study variables/predictors of the primary outcome of the study.
Response: Logistic regression models the odds ratio, a measure of association that is known to inflate risk. The robust Poisson model is used when a log binomial generalized linear model fails to converge (which was the circumstance in this analysis), and models the prevalence ratio rather than the odds ratio. Barros and Hirakata state that "poisson regression with robust variance and log-binomial regression provide correct estimates and are a better alternative for the analysis of cross-sectional studies with binary outcomes than logistic regression, since the prevalence ratio is more interpretable and easier to communicate to non-specialists than the odds ratio." BMC Med Res Methodol. 2003; 3: 21.

4. The authors have discussed that BMI is an important risk factor for preeclampsia. I sincerely agree, however to establish the association, they should have analysed dietary intake, family history of obesity, and level of physical activity in the patients, which they have not. I feel this a lost opportunity on this excellent topic they have chosen for the study.

Response:

Family history of obesity
Data on family history of obesity was not available for analysis in this study.

We have however, included data related to dietary intake (self-reported serves of fruit and vegetables consumed in the 24-h prior to the baseline health check and serum red cell folate levels) and physical activity (7-day recall was used to assess the duration and intensity of physical activity).

Dietary Intake
In Table 1, of the 220 women who had a pregnancy that resulted in birth after their health check, only 4 women (3 who developed hypertension and 1 who did not) self-reported having at least 2 serves of fruit and 5 serves of vegetables in the day before their health check. Analysis was not conducted on these data due to the small cell sizes, however, it is included to inform the reader that adequate nutrition remains a serious issue for Australian Aboriginal and Torres Strait Islander women. Red cell folate in this study is included as an additional measure of nutritional status, particularly fruit and vegetable intake (Table 1 and 2).

Physical Activity
The prevalence ratio for hypertension in pregnancy among women who reported enough physical activity, compared to women who did not was PR 1.23 (95% CI: 0.47-3.11) p = 0.691 (Table 1).

Moreover many authors have emphasized on the fact that BMI is not an accurate measure of obesity, rather body fat distribution is a good surrogate marker of obesity. The authors should have mentioned this in the limitations of the study.

Response: We agree that BMI is not necessarily an accurate measure of obesity, rather body fat distribution is a good surrogate marker of obesity. We have therefore, included waist circumferences (measures of central obesity as a marker of visceral adiposity) as an additional measure of obesity and an indicator of body fat distribution.

5. If the authors are trying to establish these factors as pre-pregnancy predictors of preeclampsia for effective screening, then sensitivity and specificity assessment is a must, which they have not mentioned.

Response: This study did not aim to establish a screening tool for preeclampsia. Rather, its aim was to determine factors amenable to intervention that could possibly prevent preeclampsia and other hypertensive disorders of pregnancy. Measures of diagnostic accuracy were therefore not regarded as relevant in this study. This has been clarified in the Abstract and the Background section (final paragraph-p.4).
“We examined pre-pregnancy factors, potentially amenable to intervention before pregnancy, that may predict any hypertension in pregnancy (pre-existing or new onset during pregnancy) in a cohort of Aboriginal and Torres Strait Islander women in north Queensland.”

Minor Essential Revisions

6. The authors should have mentioned a sample size calculation, which would have justified the number of patients in the study.

Response: A sample size calculation has not been mentioned because there is no sample size software available for a log binomial GLM (or a robust Poisson regression). The nearest we have to it is power calculation for a logistic regression, which should provide similar results.

A logistic regression of a binary response variable (Y) on a continuous, normally distributed variable (X) with a sample size of 201 observations achieves 80% power at a 0.05 significance level to detect a change in Prob (Y=1) from the value of 0.100 at the mean of X to 0.182 when X is increased to one standard deviation above the mean. This change corresponds to an odds ratio of 2. An adjustment was made since a multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R-Squared of 1.

7. The authors should have cited the pioneering works of Powers et al. in analyzing the association of obesity and preeclampsia, in their study and compared their findings.

Response: Thank you Reviewer 1. The important work of Powers et al (Ref 12) has been included and their findings reported in the Background section (p.3).

8. Other risk factors as mentioned by the authors like previous h/o preeclampsia, nulliparity, increased maternal age etc. are well known risk factors for any population group and I feel there is no need for a separate study to establish the same.

Response: Thank you Reviewer 1. These well-established risk factors for hypertensive disorders of pregnancy are not the focus of this study, in particular, because they are not amenable to intervention. However, from a clinician’s point of view, they are important factors as possible predictors of disease.

Overall I feel that although the authors were honest in their approach, yet the final outcome is disappointing, as the study fail to introduce any new and convincing methodology regarding preeclampsia screening. However this manuscript can be improved, if the authors consider the deficiencies and rectify them accordingly, keeping in mind the following points:

a) Whether a combination of the factors mentioned is effective in screening, or they are effective individually.

As above, the study has not attempted to establish a screening tool for pre-pregnancy predictors of hypertensive disorders of pregnancy. The aim was to determine risk factors amenable to intervention before pregnancy so that the conditions may be prevented. We have made this clearer in the Background section (final paragraph, p.4).

b) They should highlight the point that these factors are more economical than any biochemical/biophysical marker to assess the risk in preeclampsia. Also this assessment does not require highly skilled personnel.

Many thanks, however, as the study does not aim to develop a screening tool for hypertension during pregnancy, it is not appropriate to highlight the cost or skill level required for detecting risk factors for hypertension in pregnancy amenable to intervention among this cohort of women. In addition, Aboriginal and Torres Strait Islander women experience an excessive burden of poor
health and low socioeconomic status in Australia; a wealthy country with a well-resourced health care system.

c) If they are showing BMI as a risk factor, then they should categorically mention which is the high risk group: overweight or obese or morbid obese?
In Table 1 we have analysed BMI as a categorical and as a continuous variable. The categorical analysis of BMI (taking normal – 18.5-25kg/m$^2$ as the referent category) showed a trend for increased risk as BMI category increased. The non-significant results of the categorical analysis are presented in Table 1. In Table 2, when BMI is analysed as a continuous variable, each unit increase in BMI demonstrated a 9% increased risk for a hypertensive disorder in pregnancy.

d) Citation of recent relevant world literature is required.
As suggested by the reviewer, the important work of Powers and colleagues (Reference 12) has been included. In the background the work has been cited to describe their findings regarding the relationship between pre-pregnancy obesity and overweight and hypertensive disorders of pregnancy.

Reviewer 2.

Major compulsory revisions:

Background

1. The authors built a case for examining risk factors that promote the increased prevalence preeclampsia in their population. Among these risk factors, hypertension is mentioned in the third paragraph and the authors’ data support this notion. However, diabetes is also mentioned, which is not the focus of this manuscript, and in fact, the data from the authors’ population do not support this statement. Please add information to the background regarding obesity as a risk factor for the development of preeclampsia, which is a main focus of this study.

Response: Reference to diabetes has been removed from the introduction as suggested. The focus is now on hypertension and obesity as risk factors for the development of preeclampsia. The following has been included in the Background section. Para 4.

“Pre-pregnancy overweight and obesity have been identified as risk factors for hypertensive disorders of pregnancy [10, 15]. In the United States, obesity is the leading risk factor for preeclampsia; it confers a 3-fold increased risk and is present in 30% of cases [12]. Now a major epidemic in developed countries including Australia, obesity is impacting on the health and well-being of Indigenous Australians. With the change from traditional carbohydrate based diets to energy dense high fat diets, combined with lower levels of physical activity [16], Aboriginal and Torres Strait Islander women of childbearing age are at increasing risk of pregnancies complicated by hypertensive disorders.”

2. Last paragraph, sentence 3: remove the word ‘among’.

Response: ‘among’ has been removed.

3. Please use your background statements, which should focus around hypertension and obesity as risk factors for preeclampsia, to generate a hypothesis statement.

Response: The following hypothesis statement has been added to the Background, final sentence.
"We hypothesised that abnormal pre-pregnancy blood pressure levels and maternal adiposity would increase the risk of hypertensive disorders during pregnancy."

Methods

1. In the first sentence, please define what these ‘factors’. Also, it is unclear what ‘hypertension in the next pregnancy’ means. This just means those individuals who became pregnant after their baseline health check from the three data sets, correct? How many of these patients had multiparous pregnancies?

Response: The first sentence has been amended to enhance clarity.

"Three datasets were linked to bring together information on maternal pre-pregnancy factors gathered at a baseline health check (anthropometric, biochemical and lifestyle) and the presence or absence of a hypertensive disorder during the next pregnancy following the health check."

Of 220 women who gave birth, 47 women were primiparous (21.4%) and 173 had a previous birth. This has been included in the Results section under the sub-heading ‘Prevalence of hypertension in pregnancy among the women who had a baby’.

2. Statistical analysis section: please state that data will be presented as both unadjusted and adjusted. What statistical tests were used?

Response: The analysis has calculated prevalence ratios and 95% confidence intervals with 2 sided p-values of 0.05 for baseline characteristics associated with hypertension during pregnancy to test the direction and strength of associations. The following has been included in the Methods section, under the subheading ‘Statistical analysis’.

"Data are presented as both unadjusted and adjusted analyses."

Results

1. Please move paragraph two to the first paragraph position. Please provide a heading for this paragraph, something like ‘study sample at health check’ or something along these lines.

Response: The second paragraph has been moved to the first paragraph position and a paragraph heading has been added – “Study sample at the baseline health check”.

The paragraph has been amended to include a brief description of the cohort characteristics at the baseline health check.

“Study sample at the baseline health check

At baseline, there were 1009 women of childbearing age (15-44 years) in the study sample. We excluded 48 women because they were pregnant at the time of their health check. Of the remaining 961 women, 61.2% identified as Aboriginal, 30.7% as Torres Strait Islander, and 8.1% identified as both Aboriginal and Torres Strait Islander. Pre-pregnancy characteristics of the cohort are reported in detail elsewhere[28]. Briefly, abdominal obesity (waist circumference ≥88 cm) was found in 60.5% of women, and 37.1% had a BMI > 30. Fruit and vegetable intake and adequate physical activity were low (1.5 and 21% respectively, and self-reported rates of tobacco smoking and risky drinking in the week before the baseline health check were high (60.8% and 41.9%, respectively)."
2. Move your first paragraph to the second paragraph position. Please provide a heading for this paragraph highlighting that this data is specifically about the prevalence in the study sample that development hypertension in pregnancy. Place the '22 had hypertension in the next pregnancy' as the last sentence and please do not start the sentence with a number.

Response: A heading for this paragraph is now provided – “Prevalence of hypertension in pregnancy among the women who had a baby”.

The last sentence in the paragraph is now as follows:
“Overall, 22 women (10%) had a hypertensive disorder in their first pregnancy following the baseline health check."

3. In the third paragraph, place a heading indicating that the data in this paragraph is unadjusted. It is not clear what ‘subsequent pregnancy’ means. Please define

Response: The following heading has been included – “Unadjusted analysis of baseline characteristics, by hypertension in pregnancy”.

The term 'subsequent pregnancy' has been removed and replaced by 'in the first pregnancy after the health check'.

4. For the last paragraph, please place a heading indicating that the data in this paragraph is adjusted for age and ethnicity. Begin this section by moving the second half of the last sentence from the second paragraph (’Adjustment for ethnicity and age greatly diminished many protective...’). Also, rephrase this sentence because it is confusing, ie, ‘diminished many protective’. Next, state the hypertension data and albuminuria data. Then start a new paragraph stating the obesity and metabolic syndrome (you need to define what is meant by metabolic syndrome) data. I don’t think you should mention central obesity in this paragraph because you did not examine this directly; however this should be mentioned in the discussion. End the paragraph with a sentence detailing the glutamyl transferase activity.

Response: The heading “Analysis adjusted for age and ethnicity” has been included for this paragraph. The paragraph has been re-formatted according to the Reviewers suggestions and the term central obesity has been removed.

The second half of the last sentence from the second paragraph (adjustment for ethnicity and age greatly diminished many protective...) has been removed from the manuscript. It has not been included in this paragraph, as it does not apply to Table 2. The sentence originally applied to risk of pregnancy among the whole cohort of non-pregnant women of childbearing age(n=961), rather than risk of hypertension in pregnancy among the 220 women who had a baby.

5. Is it possible to get blood levels of the adipokines leptin and adiponectin?

Response: Unfortunately it is not possible to get blood levels of the adipokines leptin and adiponectin for this cohort. Tests for these inflammatory markers were not undertaken at the baseline health check.

Discussion

1. The discussion need to be totally rewritten. The first paragraph should detail the main findings as they relate to what was written in the background section and follow the order of the results section. Is BMI representative of central adiposity or obesity as a whole? Please remove the transferase data from this first paragraph; this data should be discussed later. End this paragraph with a sentence summarizing what your main findings mean in the big picture; this sentence should represent what will be presented in the remainder of the discussion.

Discussion
2. The second paragraph starts of nicely. However, this paragraph should state why it was important for the authors’ to conduct this study. From the way the authors have written this paragraph, it seems that these authors’ data are not novel.

3. For the third and fifth paragraphs, the authors should not focus on physical activity because the data presented in this manuscript do not warrant a lengthy discussion of this.

4. A new third paragraph should discuss hypertension as a risk factor for preeclampsia.

5. The next paragraph should discuss obesity as a risk factor for preeclampsia.

6. The next paragraph should combine paragraphs 3 and 4.

7. Paragraph 6 should be the limitations paragraph.

8. Paragraph 7 should be the conclusions paragraph.

Response: The Discussion section has been re-written according to the reviewers’ recommendations.

Figure

1. Figure 1 should be numbered.
   Response: Figure 1 has been numbered.

Additional editorial requirements:

1. Formatting changes:

   Please remove the ‘Aims’ heading in the abstract.

   Response: The ‘Aims’ heading has been removed.

   Include a ‘Conclusion’ section after ‘Discussion’

   Response: The conclusion section has been headed.

   Kindly separate the ‘Acknowledgments’ and the ‘Authors’ contributions’ sections.

   Response: Acknowledgments and Authors’ contributions sections have been separated.

   Please include a ‘Competing interest’ section after the Conclusions/Abbreviations. If there are none to declare, please write ‘The authors declare that they have no competing interests’.

   Response: A Competing interest section has been included.