Author's response to reviews

Title: Associations of depression and depressive symptoms with preeclampsia: Results from a Peruvian case-control study

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Author's response to reviews: see over
Dear Dr. Lolu da-Silva,

Thank you for your attention to our manuscript. As requested, we have addressed each of reviewers’ concerns on a point-by-point basis. We have also made appropriate revisions to the manuscript. Our responses to the reviewer’s questions are as follows:

Response to reviewer #1 (Dr. Vilho Hiilesmaa)
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. The authors were able to collect a large number (N=339) of parturients with preeclampsia.
   -Can you classify the severity of the condition using suitable criteria, (e.g. RR over 160/100, proteinuria over 3 g/24 h. etc)?

We thank the reviewer for this interesting comment. We defined preeclampsia according to the report of National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (reference 4). Preeclampsia was defined by sustained pregnancy-induced hypertension with proteinuria. Hypertension was defined as sustained blood pressures of at least 140/90 mm Hg on or after 20 completed weeks’ gestation and on at least two occasions at least four hours apart.

In the preliminary analysis of using blood pressure cutoff 160/110 mmHg (see the following table), we found the magnitude is similar for the association between depression and mild preeclampsia or severe preeclampsia. However, we are not sure about the accuracy of this sub-classification because we did not collect the information of the severity of proteinuria; and that inaccuracy may have resulted in the finding of no difference in associations for mild versus severe preeclampsia.
<table>
<thead>
<tr>
<th>Maternal History of Depression (total score)</th>
<th>Mild Preeclampsia (N= 203)</th>
<th>Control Subjects (N = 337)</th>
<th>Unadjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal (&lt; 4)</td>
<td>113</td>
<td>213</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Mild (5–9)</td>
<td>60</td>
<td>98</td>
<td>1.2 (0.8-1.7)</td>
</tr>
<tr>
<td>Moderate (10–14)</td>
<td>22</td>
<td>18</td>
<td>2.3 (1.2-4.5)</td>
</tr>
<tr>
<td>Moderate-severe (15–19)</td>
<td>7</td>
<td>7</td>
<td>1.9 (0.6-5.5)</td>
</tr>
<tr>
<td>Severe (≥ 20)</td>
<td>1</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal History of Depression (total score)</th>
<th>Severe Preeclampsia (N = 136)</th>
<th>Control Subjects (N = 337)</th>
<th>Unadjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal (&lt; 4)</td>
<td>67</td>
<td>213</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Mild (5–9)</td>
<td>46</td>
<td>98</td>
<td>1.5 (0.96-2.3)</td>
</tr>
<tr>
<td>Moderate (10–14)</td>
<td>17</td>
<td>18</td>
<td>3.0 (1.5-6.2)</td>
</tr>
<tr>
<td>Moderate-severe (15–19)</td>
<td>5</td>
<td>7</td>
<td>2.3 (0.7-7.4)</td>
</tr>
<tr>
<td>Severe (≥ 20)</td>
<td>1</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

Since we did not collect information to allow the accurate sub-classification of mild and severe preeclampsia, we stated this as one limitation in the discussion section of the amended manuscript. (page 10, 1st paragraph)

-What was the number of cases with eclampsia?
There were 6 eclampsia cases. The text has been amended (page 5, 1st paragraph) to state this fact.

-Breakdown of preeclampsia should at least be included in the description of the material.
We did not collect information to allow the accurate sub-classification of mild and severe preeclampsia. We stated it as one limitation in the amended manuscript (page 10, 1st paragraph).

2. Please give more information on the setting of the obstetric care in Lima:
-How many deliveries per year were there in the two hospitals?
Dos de Mayo hospital: 3,600/year, Materno Perinatal Institute: 14,000/year

-Are they tertiary care/university or regional hospitals?
-Are the most difficult cases of preeclampsia treated in these two hospitals or are they referred to somewhere else?
Both institutes are operated by the Peruvian government and are primarily responsible for providing maternity services to low-income women residing in Lima (page 4, 2nd paragraph).
The Materno Perinatal Institute is the most prestigious tertiary care obstetric establishment in Peru. The Dos de Mayo Hospital is a National Hospital that is also a tertiary care hospital.

-How well the material represents all women with preeclampsia in the region?
The hospital-delivery rate in Lima, Peru is near 95%, so hospital cases are representative of women in region.

3. In Methods/paragraph 2/end you say that 95% of those who were approached agreed to participate.
-Please provide, if possible, the total number of cases with preeclampsia in the hospitals. -How many % of them were approached by your team. How many patients with preeclampsia you did not approach?
These numbers are not known. Given that we were conducting a case control study (not a survey of all pregnancies) and that we had resources only to cover day-shifts (5 work days per week) we did not attempt to identify all preeclampsia cases in the hospitals.

-Is there any selection bias of cases with more severe vs. less severe preeclampsia being included in your study.  
We do not expect that there is any referral bias. Bias would only exist if referral was conditional on depression which was not likely in our study.

4. Table 1:
-Please sub-classify Gestational age at delivery (as you did for BMI in the same Table), e.g. number (%) of deliveries at <26, 26-28, 29-31, 32-34, 35-37, >37 weeks. Use suitable cutpoints as you prefer.  
Prematurity is the most important of perinatal problems and deserves attention in any study.
We have amended the text to include gestational age at delivery in Table 1.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
5. Classification of depression (pages 6; Table 2):
-To which category the score 20 belongs? Please clarify. The score of exactly 20 is currently not allocated in no category.
The score of exact 20 belongs to the severe depression category (≥ 20).

6. Methods, paragraph 2:
-I don’t get the significance of the sentence "Nulliparity was not a criterion for diagnosis in this investigation" Please clarify or delete.  
We have deleted this sentence in the revised manuscript.

7. I would prefer Standard Deviations (SD) instead of Standard Errors (SE) to describe the variation in a continuous variable. -SE (or SEM) gives the variation of the calculated
mean, and is highly dependent on the sample size. SD is better in that it gives to the reader an idea of the variation between the individuals (Table 1).

The SD quantifies scatter — how much the values vary from one another. The SEM quantifies the accuracy if the true mean in the population. For the purpose of giving the reader an idea of the variation of continuous variable, we have replaced SEM with SD in the revised manuscript (Table 1). We thank the reviewer for their suggestion.

Discretionary Revisions (which the author can choose to ignore)

8. It would be interesting to know whether there is a correlation between the degree of depression and severity of preeclampsia.

We thank the reviewer for this interesting suggestion. However, we could not assess the correlation due to deficits in our data collection. Specifically, we did not have information concerning the severity of proteinuria. We now we state this as one limitation in the discussion section of the amended manuscript (page 10, 1st paragraph).

9. As you say, the number of women with severe depression was very small.

-Is there any reason to keep them as a separate group? -You could merge them into the moderate-severe group. -The term moderate-severe is a bit confusing and you could consider - replacing it with another expression such as considerable, major, etc.

We appreciate the reviewer’s suggestions. However, the description of groups and the classification of groups are consistent with the methods developed by authors of the depression assessment tool we used (reference 7). Hence, we have elected to keep the table as it is.

10. Table 3 is very large. -Its impact related to its space is small. In my opinion, you could eliminate Table 3 and extend the text on page 8 as needed (last paragraph of Results describing the contents of the table).

We respectfully ask to retain Table 3. Our attempt to describe the results would lengthen the text and not provide precise results as we current present in the Table. We believe readers may want to see how different dimensions of depression and depressive symptoms are associated with preeclampsia risk. The results provide opportunities for interested reader to assess relation between suicidal thoughts and preeclampsia risk, for example. Some readers may want the specificity and precision in reported results the Table provides.

11. How about the number of Cesarean sections and deliveries with forceps/vacuum extractions? -Did you register the data? -These are important data to describe the material. They reflect obstetric practices in the hospitals.

We have added the information concerning delivery mode in Table 1. Vaginal Delivery included normal vaginal delivery and assisted vaginal delivery (in this study, no preeclamptic case but 1 control was delivered by vacuum or forceps).
Response to reviewer #2---No question:
We thank the reviewer for his/her approval of our manuscript.

Response to formatting requirement:
- Informed consent- please include a statement in your Methods section, documenting informed consent and what form it took, i.e. whether written or verbal.
We have added to the text “All participants provided written informed consent”. (page 4, 2nd paragraph)

- Please also ensure that your revised manuscript conforms to the journal style. It is important that your files are correctly formatted.
Changes have been made in the references and tables (showing the grid) according to the BMC medicine journal-authors’ checklist for manuscript formatting.

Again, thank you for your attention to our manuscript.
Yours sincerely,

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