Author’s response to reviews

Title: Associations of sociodemographic and clinical factors with perinatal depression among Israeli women: a cross-sectional study

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Author’s response to reviews:

Elizabeth Camacho
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Re: manuscript BPSY-D-19-00434

Dear Dr. Camacho,

Dear Dr. Harrison,

Together with my collaborators, I am pleased to have the opportunity to submit a revised version of our manuscript, entitled, “Associations of sociodemographic and clinical factors with perinatal depression among Israeli women: a cross-sectional study“.

Following the Reviewers’ comments, we made substantial changes to the manuscript, which we believe have clarified and improved the presentation of our findings. We note that we have now changed the criteria for depression for the purpose of this study. Specifically, in the Israeli protocol for the EPDS, a score of “yes” to question 10 (regarding thoughts of suicide) automatically determines depression. However, since this criterion does not appear in the literature, we decided to remove it from the criteria of depression used in the current study. This change makes our findings more easily comparable to those of other studies. Following the described change, the prevalence of depression decreased somewhat and age was no longer statistically significant in the multivariate analysis.
Below are our point-by-point responses to the Reviewers’ comments.

We hope you will find the revised version of our manuscript suitable for publication in BMC Psychiatry.

Sincerely,

Dr. Limor Adler

Reviewer reports:

Elizabeth Camacho, PhD (Reviewer 1): The authors have made a good start to exploring the associations between EPDS score and other factors. However there is still some work to be done to strengthen the quality of the paper. I have made some suggestions for the authors to consider.

1. Background - a few points could be made clearer in the background

   a. you state that "Identifying risk factors of perinatal depression is important for encouraging women with depressive symptoms to seek help". I would suggest rather that it may potentially help healthcare professionals to better identify those with depression if they are extra-vigilant with mothers with many risk factors; encouraging those who develop depression (which will not only be those with the risk factors) to seek help is a separate issue.

   Thank you for this very helpful suggestion. The sentence was changed to “Identifying risk factors of perinatal depression may potentially help healthcare professionals better identify women with depression, by increasing vigilance regarding women who have these risk factors.” P3, 59-61.

   b. in the second paragraph you state that "the EPDS showed considerable heterogeneity“ and go on to describe a figure with a very tight 95% confidence interval, so should this perhaps be homogeneity instead? If not then perhaps describe in more detail what the heterogeneity relates to. In the same paragraph, it would be useful for readers to know what the prevalence was in the Hahn-Holbrook study.

   We now clarified: “Heterogeneity was substantial across the 56 countries included (Q = 16,823, p = 0.000, I² = 98%); depression ranged from 3% (2-5%) in Singapore to 38% (35-41%) in Chile. The rates for the Israeli studies included in the review ranged from 5.2% to 43.0% “. P3, 51-53.

   c. it would be useful to have a sentence or two in the background about the Israeli health system and what healthcare funds are (e.g. is this a private insurance plan or more like
medicaid?) and so whether the sample from this healthcare fund are likely to be representative of the general population or biased in relation to SES.

Following this comment, we added: ‘”The healthcare system in Israel is public and comprises four healthcare funds. Each resident chooses a healthcare fund; the payments are equal. The characteristics of the populations in all the funds are similar, and thus the population in our study is likely a good representative of the general population in Israel”. P3, 66-69.

2. Methods - quite a bit more detail is needed to describe the methods.

   a. What statistical tests were used to derive the p-values in Table 1? What p-value was used as the level of significance? It does not appear that any p-value correction was used to account for testing multiple variables individually (e.g. Bonferroni), have the authors considered this?

   We added details regarding the statistical analysis - P 5, 123-130.

   Table 1 is now table 2.

   b. For each characteristic explored, describe it in terms of what type of variable it is (categorical, continuous, binary) and for non-continuous variables say what all the categories are. For example it is unclear whether the 'periphery' variable is binary (i.e. yes/no people live in the periphery) or otherwise specified. Also the religion-based variables are they individual (Arab: yes/no; Orthodox Jew: yes/no) or is there a single variable in which everyone belongs to one category (Arab, Orthodox Jew, Other)? A single variable with all the religious categories would be preferable because as individual variables you would be comparing Arabs to everyone else (which includes Orthodox Jews) and Orthodox Jews to everyone else (which includes Arabs) so there is the potential for some confusion here.

   In the revised manuscript, we described the type of each variable (p 5 105-110). Population sub-group was defined as a single variable (Arab/ Orthodox Jews, others), P 4, 99.

   c. I have understood the methods section to be saying that the "periphery" measure is your measure of SES but it is not fully clear how SES is measured and how robust a measure this is likely to be.

   Two distinct variables were considered, SES and periphery. To clarify, we added an explanation about the differences. P5, 105-110.

   d. It may be more informative to convert blood/urine measures to binary variables for "normal versus abnormal", for example in the discussion the results are compared with a study which looked at anemia as a binary variable rather than absolute levels of hemoglobin.
We converted haemoglobin level from a continuous to a binary variable, represented by anaemia (<10.5 g/dl, > 10.5 g/dl). We believe that for the remaining blood tests, continuous variables are more informative, P5, 102.

e. In the methods is states that data are available for fasting glucose and glucose tolerance tests (which are not reported in the results anywhere) but in the discussion it says that only chronic diabetes was measured - would it not be possible to use these test results to identify gestational diabetes?

In this study, we did not have access to fasting glucose levels or glucose tolerance test. Rather, diabetes mellitus was determined according to the appearance of this diagnosis on medical records. P5, 115-116.

f. Define all abbreviations on first use including blood tests e.g. TSH is not defined

The abbreviation of TSH is now added. P5, 119.

g. It is unclear whether the results being reported in Table2 are the results of a series of univariable logistic regression models or a single multivariable model. Also if it is a series of univariable models, then it appears that no adjustment for expected confounders has been done. Logically a number of the factors are related, for example socioeconomic status and smoking, therefore a single multivariable model would take some of this into account. As univariable models it is not possible to say whether the relationship between depression and hypertension was related to the relationship between depression and smoking (which is a risk factor for hypertension). Including all the variables in a single model would allow you to explore this.

Thank you. The data that was presented in Table 1 (which is now table 2) represent the univariate analyses that we performed. The data that was presented in table 2 (which is now Table 3) represent the results of the multivariate logistic regression analysis. See the Statistical analysis section, P5, 123-130. Text was added to the title of Table 2.

3. Results - Table 1

   a. In the row for mean age the SD is reported differently in the two columns (i.e. as □ in one column but not the other).

This is now corrected. We note that the original table 1 is now table 2.

   b. Only Arabs and Orthodox Jews are represented in the table but these are the minority group, report data for the other group as well.

The rest of the population is now added to what now appears as Table 2.

   c. Report the units for all blood/urine measurements
d. Indicate for each characteristic how many people provided data in each group (as has been done for the blood tests), for example rather than reporting a single number it could be reported as n/N (i.e. number with the characteristics/number providing data for that characteristic).

We tried to do this in the way you suggested (n/N). However, we think the presentation is clearer as shown originally (with N [number of women tested]) and in the right column, percentage from the overall number of women in the group.

4. Results - it is unclear how the last paragraph of the results section should be interpreted with the current level of detail about the methods, perhaps revisit this paragraph once the methods have been reviewed.

We added more detail to the results section and divided it to a descriptive analysis and a regression analysis. In the last paragraph, we highlighted all the major results.

5. Discussion - some of the variables which appear to be statistically significantly different by depression status are very small differences in real-world or clinical terms. For example when age is a categorical variable there is only a 1.5% difference between the proportion of people in the <25 group (10.3% versus 8.8%) and the difference in the proportion of people with cardiovascular disease is 0.6%. It is worth noting this so that readers can interpret your findings in context.

The Reviewer is correct. In univariate analysis, for women aged < 25 years and women with cardiovascular disease, the differences between the groups with and without depression were of relatively small magnitude.

Following this comment, we added the following:

“Higher proportions of women with depression were aged > 40 years, than were aged 25-40 years, though the difference between the groups was of relatively small magnitude.” P6, 146-148

Regarding cardiovascular disease, due to the small numbers, we thought not to discuss the finding of the univariate analysis in the text; the table speaks for itself.

After reworking the data, as described in our responses to all the Reviewer comments, neither age nor cardiovascular disease was statistically significant in the multivariate analysis.
6. Discussion - the authors cite the accepted cut-off score for depression in Israel, but it may be worth noting the literature (from other countries) which recommends different cut-offs for pre- and post-natal depression and what implications this may have for your analysis.

As we elaborated in the background section, the cut-off points are the same for pre- and post-natal depression (which are actually considered as one entity; perinatal depression). One of the difficulties in comparing between studies is that cut-off points EPDS vary between countries, in the range of 9 – 14. For the current study, we set 10 as the cut-off, as determined by the Israel Ministry of Health. This cut-off was used in the majority of studies, and was recommended in the development of the EPDS.P7, 175-179

It is a potentially important limitation that you cannot identify for all participants when they completed the EPDS, however it may be an interesting addition to the paper to do some exploratory analysis on each of the two sub-groups who completed the measure pre- or post-natally.

Thank you. We have identified this as a potential limitation. Nonetheless, perinatal depression is considered to be one entity, as stated in the DSM-V (P3 46-48), without relevance to the exact timing (during pregnancy or after birth).

7. Discussion - in the methods section it states that the health ministry protocol suggests that all women complete the EPDS twice however it appears that you only have one data point for each of your participants and you also say that only around half of the women who visited a health centre completed it at all. It would be interesting to discuss this mismatch between the health policy and what is happening in reality, there may be biases in who is completing the EPDS which could have implications for these findings (some of which have been discussed already).

To clarify the apparent mismatch, we added “We used one EPDS score for every woman who filled the EPDS (if filled twice, the lower score was taken).” P4, 94-95.

We added a paragraph in the discussion section about the gap between the Israeli protocol and its implementation (~30% of women did not fill the EPDS at all). P8, 216-218.

8. Discussion - you suggest that Orthodox Jewish mothers may be less likely to report symptoms of depression due to social stigma, would this not also be the case for Arabic mothers?

Yes, this is true. Arabic women and orthodox Jewish are similar in several aspects (such as religious minority, high birth rate, and social stigmas), but different in other aspects. We elaborated on this point, P8, 204-209.

9. Discussion - this paper would be strengthened by adding something in the discussion about what this paper contributes to current knowledge, whether it is the first paper to address a
particular research question. Also some discussion of what the clinical/policy implications (e.g. better identification of women with depression) etc. are likely to be.

We added text regarding the contribution of this study to the literature (P9 222-224) and its implications (increasing the proportion of women who fill the EPDS (P9, 220-221) and better identification of women at increased risk for perinatal depression.

10. Discussion - you have not explored the relationship between parity and depression or described how many previous children the participants in your sample have - this has been shown to be associated with perinatal depression so if it is not possible to access these data then this is also a limitation of your study to note in the discussion.

We added this as a limitation of the study (P9, 228)

11. Conclusion - this section should recap the key findings from this study and the sentence about effects of depression on families is not appropriate here, and would be better placed in the discussion (see comment 9).

We revised the concluding paragraph accordingly P9, 231-236.

Sian Harrison (Reviewer 2): This study reports prevalence and factors associated with depression during pregnancy and the postpartum period in a large population-based sample of Israeli women. The study adds to the literature in this field and has a number of strengths, including the sample size and the use of a validated and universally recognised self-report measure for peripartum depression. The structure of the manuscript requires attention to ensure the rationale, methods and results are clear for the reader. Specifically, I have the following recommendations:

Background

The background provides an overview of the potential impact of peripartum depression on women and their families. It highlights some of the factors that have been associated with depression during pregnancy and the postpartum period. Consider presenting the background information on prevalence [page 3, lines 39-47] before the information on factors associated with depression.

Done. The background information on prevalence, P3 49-53, now precedes the discussion of the factors that have been associated with depression in P3.

The authors should present a stronger rationale for the study, i.e. what gaps there are in the literature and the need for this study.
Clarify the existing research which has focused specifically on Israeli women, or highlight that there is little research on this population.

We added this information to the end of the background section. P3-4, 70-74.

There is information about the EPDS in the background which would be more appropriately placed in the methods section (page 3, lines 32-39).

We moved this information to the methods section. P 4 89-95.

Methods

The methods could be presented with more clarity. Consider structuring the methods with additional subheadings: for example, this could include: design, population/sample, measures, variables (identify outcome variable and predictor variables), analysis, etc.

We added subheadings to the Methods section.

The EPDS assesses mood/symptoms of depression. Consider rephrasing the following sentence: The EPDS comprises 10 questions that access information about the respondent's state of being [page 4, line 18].

We changed “state of being” to “mood and depressive symptoms”. P4, 92-93.

A reference should be provided for using a score of >0 on item 10 of the EPDS to classify women as depressed, in addition to using an overall score of 10 or above, which indicates ‘possible depression'.

Following this comment, we changed the criteria for depression for the purpose of this study. Specifically, in the Israeli protocol for the EPDS, a score of “yes” to question 10 (regarding thoughts of suicide) automatically determines depression. However, since this criterion does not appear in the literature, we decided to remove it from the criteria of depression used in the current study. This change makes our findings more easily comparable to those of other studies. Following the described change, the prevalence of depression decreased somewhat and age was no longer statistically significant in the multivariate analysis.

'Blood test results' is one of the variable groups. Consider moving this paragraph below the paragraph describing the other variable groups [page 4, lines 46-57]. Done

Are 'blood test results' medical factors? For example, could medical factors be further categorised as: 1) medical conditions 2) medication 3) blood markers? Done. P5, 102-103.

Define 'living in the peripheral region of the country' for readers who are not familiar with the geography, and perhaps comment of differences between populations living in the periphery or otherwise. P5, 105-107.
The subsection titled 'The study protocol' describes the sample and would be better labelled as such.

We changed the title accordingly.

Provide a clear overview of the descriptive, univariate and multivariate analyses which were conducted in the statistical analysis section. We revised this section and hope it is clearer now. P5, 123-130.

What level of significance was required at univariate level for variables to be included in the multivariate analysis? We now stated this. P6, 126-127.

What method was used to enter the variables into the multivariate analysis? What statistical programme was used to complete the analysis? We now described this. P5, 130.

Results

The results would also be clearer if subheadings were used. Consider presenting: 1) descriptive analyses (including description of sample, prevalence and characteristics of depressed/non-depressed women) 2) regression analyses organised by variable categories: sociodemographic, medical, etc.

We added subheadings to this section.

If available, data should be included to show the differences between women who did and did not complete the EPDS, women who did and did not attend the MHS clinics, and women who were and were not members of MHS. This would enable assessment of the representativeness of the women included in the study. If data are unavailable for any of these groups, some description should be included regarding any potential differences.

We added table 1, which compares characteristics of the women who answered the EDPS and all women who gave birth in 2015-6. We do not have access to information of women who were not members of MHS. However, we added the following sentence to the Discussion:

"The healthcare system in Israel is public and comprises four healthcare funds. Each resident chooses a healthcare fund; the payments are equal. The characteristics of the populations in all the funds are similar, and thus the population in our study is likely a good representative of the general population in Israel". P3, 66-69

Report the proportion of women who scored 10 or more on the EPDS and the proportion of women who scored above 0 on item 10 of the EPDS. Were there differences between the women classified as depressed according to these different scoring protocols?

See our response above regarding the criteria of depression in the revised version of the manuscript.
Provide details of the univariate analyses: it would be helpful to see both crude odds ratios and adjusted odds ratios for each of the variables.

We added crude and adjusted ORs to table 3, and described these in the Results sections of the Abstract and of the manuscript.

Discussion

The authors state that they found lower rates of depression compared to other findings and then report the results of a review indicating a range, which includes the rate found in this study.

As detailed above, in our revised analysis, a response of “yes” on item 10 of the EPDS was not considered a sole criterion for perinatal depression. Accordingly, our revised rate of perinatal depression, 4.9%, is in fact lower than that reported for other studies conducted in Israel.

Tables

Structure the characteristics in Table 1 and the variables in Table 2 according to group: sociodemographic, medical, lifestyle, etc.

We revised the tables as recommended (the original table 1 is now table 2, and the original table 2 is now table 3).

Indent the subcategories, as you have with age.

Done.

Consider breaking down 25-40 years age group as this covers a wide range of ages, including both relatively young and relatively old mothers.

Thank you. In our updated analysis, age was not found to be associated with depression. Therefore, we decided not to rerun the analysis on more categories of age.

The SD for age is presented in the percentage column for 'without peripartum depression'.

This is corrected.

Declarations

- Ethics approval and consent to participate

- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

P9, 241-251.