Author’s response to reviews

Title: The association between pre pregnancy body mass index and risk of preeclampsia: a registry based study from Tanzania

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Author’s response to reviews:

Thank you to reviewers and editor for spending their time to improve this paper. We hope that our answers and changes in manuscript are satisfactory.

Editor comments:

1. Please remove the cover letter at the beginning of the manuscript.

Answer: OK.

2. In the availability of data and materials section please state how the data were accessed including any permissions that were required.

Answer: We have added more text here (page 14), specifying that for this specific study we obtained research ethical certificate from Tumaini University Makumira (ethical certificate No. 641, Research proposal No. 633).

3. Please remove the figure title from the figure file.

Answer: OK.

4. When you have completed the requested revisions please also upload an entirely clean version of the manuscript alongside a tracked changes version.
Answer: We have uploaded both a clean version and a tracked changes version.

Reviewer 2:

1. In response to the question regarding repeated measures on individual women, the authors explain that some women will indeed be represented in the study more than once, but that they do not anticipate that adjustment for repeated measures will impact their results. While this may be correct, I nevertheless recommend that they acknowledge the presence of repeated measures in the study sample and provide information on how many women are included for two pregnancies.

Answer: We agree that this is a potential source of bias. We looked at the data and found that based on a hospital number that should be unique to each woman, we were able to identify 1499 women with two deliveries in the study population. We performed a multilevel analysis to account for the dependency between successive pregnancies and found that the main results were almost identical as those reported. This is now mentioned in methods page 7 lines 172-173 and in results page 9 lines 214-216.

2. The authors explain that they have specified confounders a priori and hence that choice of confounders to adjust for is not based on hypothesis testing. However, in Lines 195-198 they appear to additionally adjust for further variables (chronic hypertension, diabetes mellitus, and heart diseases before pregnancy). Are these variables also regarded as potential confounders and, if so, is this "second step" analysis to be regarded as a sensitivity analysis to assess the need for additional adjustment beyond the initially specified confounders? Please clarify.

Answer: We do not consider these variables as pure confounders because they may be a result of the main exposure overweight/obesity and hence be intermediate variables. Nevertheless, they are known to be associated with both overweight/obesity and preeclampsia, and therefore we wanted to assess their contribution to the association between BMI and preeclampsia. We have clarified this in Methods page 7 lines 159-162, and also added some text in Results page 9 lines 203-205.

3. The authors acknowledge that multiple comparisons are a concern in this study, but argue that this is mitigated by there being only one exposure of interest, BMI (and one outcome of interest, preeclampsia). In that case, the purpose of the many additional hypothesis tests carried out is not clear. The authors should acknowledge the multiple comparisons issue and that these additional hypothesis tests should be regarded as exploratory.

Answer: We acknowledge this limitation and has included this in the discussion, page 12 lines 283-286.
4. Lines 174-178: The text regarding cut-offs for height and weight is still not clear. Were, e.g., women whose records had a height <130 cm or >200 cm excluded from the study? The authors state this clearly for BMI: "we excluded records with BMI above 40 (0.4%) and BMI below 15 (0.5%)". It would be helpful if they made similar statements regarding height and weight if subjects were indeed excluded on the basis of these measurements also.

Answer: We have now included similar text for height and weight as for BMI (page 6 lines 137-141).

5. Lines 186-187: "P value for trend was computed for the ordinal variables" - it is still not clear here what trend is being assessed. For instance, in Table 1 the tests for trend are for the cross-classification of BMI categories with each of mother's age, mother's education and mother's height. None of these tests is associated with the primary aim (association between BMI and risk of preeclampsia) and the motivation for carrying out these tests in addition to Chi-squared tests for independence/homogeneity is not made clear.

Answer: We agree that the tests for trend are not justified in Table 1 and have removed them. We still include them in Table 3 because we want to test if there is a dose-response relationship between the ordinal risk factors and preeclampsia. We have tried to clarify the text in Methods page 7 lines 151-153 stating that “The ordinal variables (mother’s BMI, age, education and height) were also included as continuous covariates in the model to explore a possible dose-response relationship between these variables and preeclampsia”.

6. Lines 206-209: please make clear that the test was for interaction between, e.g., height and BMI in their impact on risk of preeclampsia.

Answer: We have changed the text, page 7 lines 168-171.

7. Lines 225-226: it is not clear what differences (comparisons) are being referred to.

Answer: We agree that the meaning of this sentence is unclear. We have changed to “Differences in mean BMI were modest, and only among mothers above 35 years of age was mean BMI above 25.” (Results page 8 lines 183-184).

8. Table 2: Gestational age is considered in categories of "Below 37" "More than 37". It is not clear which category includes gestational age =37.

Answer: We have changed to “Below 37 weeks” and “37 or more weeks”.

A number of typographical errors have been introduced in the revised manuscript. These include:
Line 155: "multiple":
Answer: Changed to “multifetal” (line 121)

Line 226: "mean BMI was above 25"?:
Answer: See answer to question 7 above.

Line 261: "showed"
Answer: Corrected. (line 223)

Line 320: "self-reported weight"
Answer: Corrected. (line 274)

Line 322: "socially acceptable"
Answer: Corrected. (line 276)