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:

First of all thank you to both reviewers for all these valuable comments. We believe that the reviewers comments have contributed to a better manuscript, and hope that reviewers and editors find our answers and changes satisfactory.

Reviewer #1:

1. This manuscript addresses the association of pre-pregnancy BMI with preeclampsia risk. It is well established in the literature that increasing BMI is associated with increasing preeclampsia risk. Although the authors acknowledge this, they state that study of this is novel in this population studied. I agree the manuscript can contribute to the literature. That being said, if the population is the novel contribution, I would like to see more in the discussion about this and how risk factors may be different in this population versus others. It would also be worthwhile to discuss if the rate of preeclampsia (3.3%) is consistent with or lower than anticipated.

Answer: We have rephrased the text about why it is important to study indigenous African women, see second and third paragraph of the Background. We also clarify this issue in the paragraph before Strengths and limitations. We have inserted some text under Strengths and limitations, second paragraph, about the rate of preeclampsia.

Abstract:
2. Sentence from lines 58-59: the wording of this sentence is awkward. Please revise. Additionally, in the methods portion of the manuscript, please include justification for why the analytic cohort was restricted to women with gravidity of 1 or 2 only.

Answer: We have revised the sentence in the Abstract. We have also included some text about selecting gravidity 1 and 2 for the study, see under Study design, setting, source of data and population:

3. Line 62: after underweight, please include the % of women who were of normal BMI.

Answer: OK.

Background:

4. Line 24: the sentence starting 'most large studies' . . is awkward. Please revise.

Answer: We suggest this should be line 94. We have revised this paragraph, cfr. first comment of this reviewer.

Methods:

5. Line 114: please provide additional details about the interview. Were these face to face interviews? Were they conducted in the hospital or at home? Etc. It would seem they are face to face in the hospital but please clarify. Were they tape recorded or notes taken? Did the questionnaires contain all easily quantified data (i.e. multiple choice, likert scales, discrete answers) or was there a qualitative component? If qualitative, how was the information captured and analyzed?

Answer: We have inserted some more text about the interview under Study design, setting, source of data and population, and included a reference (Bergsjø 2007).

6. What percent of the women in this community receive prenatal care and what percent have hospital deliveries? This has the potential to be a biased sample. Please include this in the discussion.

Answer: We have inserted text in the second paragraph of the Strengths and limitations.

7. Line 118: changes 'ae' to 'are'

Answer: OK.
8. Line 121: this sentence states that 'details of data collected during interview are shown in a questionnaire' - is it anticipated that the reviewers/readers can see this questionnaire? If yes, it should be included as a figure or appendix. Seeing it would also address some of the questions above.

Answer: No, it is not anticipated that the readers can see the questionnaire. We have now removed this sentence. As we have included details about the interview and also added a reference (Bergsjø 2007, see above), we hope the information about the interview situation is satisfactory.

9. Line 127 mentioned that the sample includes mothers 'whose reproductive history data were entered into the medical birth registry.' What dictates whether this happens or not? How does this bias or influence the sample.

Answer: We have removed the text “and whose reproductive history data were entered into the medical birth registry”, because practically all women who deliver at the hospital have the delivery entered in the medical birth registry, i.e. very few if any refuse to consent.

10. Line 130 describes that only women having their first or second singleton birth are included. Please provide justification for this. Please also provide additional details for how this was executed. For example, if a woman had an 18 week loss, followed by a twin delivery, and now delivered her first live singleton - is she included or not?

Answer: To address these two questions we have inserted the following text under Study design, setting, source of data and population: “We restricted the study population to women with no or one previous pregnancy. Definition of pregnancy order was based on information on previous pregnancies in the questionnaire including pregnancies lasting less than 28 weeks. Compared to a selection based on previous stillbirths and live births only, exclusion of such early losses reduced the study population by six percent. Exclusion of women with more than one previous pregnancy was done in order to focus on baseline BMI and not BMI as a result of high parity.” Specifically, this means that a woman with a 18 week loss followed by a twin delivery will not have her first live singleton included.

11. Line 131: please change 'multiple births' to multifetal pregnancies as it seems the authors are referring to twins, triplets, etc.

Answer: OK.

12. Line 141: the authors state that they use the WHO definition of preeclampsia include mild, moderate, and severe. Please provide a reference for this approach. The documents I reviewed only had mild and severe. Currently, through the task force on hypertensive disease of
pregnancy, we are referencing preeclampsia with and without severe features and have eliminated the term mild.

Answer: You are right, this should be only mild and severe preeclampsia. We have corrected the text and now refer to the registry manual where this is specified.

13. Line 142-143: BMI was based on 'self-report' maternal prepregnancy weight and height - please include in discussion any potential imitations of this approach.

Answer: We have included a reference (Fattah) on self-reported prepregnancy weight, and included some text in the last paragraph of Strengths and limitations.

14. Line 144 - please clarify that it was gestational age 'at delivery' used as a proxy for 'preeclampsia severity' rather than' a proxy for severity of preeclampsia'

Answer: OK.

15. Line 155 - see prior comment about line 130.

Answer: To avoid to repeat information we have deleted this sentence.

16. Line 175-176 - please provide justification for weight cut-off between 164 and 165 cm - how was this informed?

Answer: Unfortunately this analysis was wrongly reported. The cutpoint used in the interaction analysis was <160 cm vs. ≥ 160 cm. This cutpoint was selected because it represents a natural cutpoint and also divides the population into two groups of comparable size (45% and 55%).

Results

17. Line 184: please include % for normal BMI mothers

Answer: OK.

18. Line 185: although these are the 'highest mean BMI' it is worth noting that they are overwhelming within the normal range and there were small differences between categories within the same variable.
Answer: We agree that there were small differences, and inserted the following sentence in this paragraph: “Differences between the groups were, however, modest, and only for mothers above 35 years of age mean BMI was above 25.”

19. Line 185: highest proportion of obesity in marriage group was actually those with missing data, not marked women. Please clarify if 'married' is the same as 'with partner'.

Answer: We have corrected this error and also changed the wording to “with partner” and “without partner. We have also changed the sequence to correspond with the sequence of the variables in Table 1.

20 Line 187: remove the extra period

Answer: OK.

21. Line 188-191: make the sentences consistent with what is presented in the table - for example, highest proportion of underweight was found in moms missing information on education, not those without education; and the highest proportion of underweight was found in moms with height >=165 cm, not <155 cm.

Answer: OK.

22. Line 195: a preeclampsia rate of 3.3% strikes me as low for this population. Please address this in discussion - is it consistent with relevant literature, might there be something about this population that it has such a low rate.

Answer: We have rewritten the paragraph on selection bias under Strengths and limitations and have included text about the preeclampsia rate

23. Line 202: designate the OR in parenthesis as an adjusted OR, if that is what it is.

Answer: OK.

Discussion:

24. Please discuss rate of preeclampsia (3.3%) and if expected or not - and if not, possible explanations.

Answer: We have rewritten the text under Strengths and limitations, also see answer above.
25. Lines 263-270: self-report prepreg wt is acknowledged as a limitation. However, please bring in relevant literature to speak to how this may or may not have influenced your results. Is there anything to support whether women from this population are likely to over or underreport their weight?

Answer: We have added some text under Strengths and limitations and also included a reference about self-reported prepregnancy weight among pregnant women (Fattah).

Conclusions:

26. Line 273: please change sentences to say 'There appears to be an association between increased pre pregnancy body mass index category and increased preeclampsia risk, in this resource limited population.'

Answer: Thank for this suggestion, we have changed the sentence.

Table 1:

27. Take out the 's' and capitalize 'Characteristics' in column 1

Answer: OK.

Table 3:

28. This table is confusing as to which p-values go with which tests/columns. Additionally, there are some entries in cells that shouldn't be there (e.g.; 'ref' in 5th row, 5th column) - look at this table carefully and try to make easier to read and interpret.

Answer: We have corrected the errors. Also, we have tried to format the table and we hope that it is now more easy to read.

Reviewer 2: This registry-based study draws on 13 years of birth records to assess the association between pre-pregnancy BMI and the risk of preeclampsia. The paper is well written and methods and results are mostly clearly presented. While the association of pre-pregnancy BMI with risk of preeclampsia is known, I would think there is value in confirming the association in a large African cohort, particularly with the increase in overweight and obesity in transitional African societies.

1. Women of gravida 1 or 2 with singleton pregnancies were included in the study, but I wasn't clear whether it was possible for women to be included in the study for more than one pregnancy. If so, how were repeated measures addressed in the analyses?
Answer: Yes, it is true that some women may have been included more for two pregnancies in this study. In previous analyses based on these data, the authors were able to confirm that among 19,811 women who had a first singleton delivery at KCMC during 2000-2008, 3,909 had a second delivery by 2010 (Mahande et al. PLoS One. 2013 Nov 1;8(11)). This suggests that most women in our cohort were only included once. It would have been possible for us to construct data files to account for repeated deliveries in the analyses. We did not perform such analyses, and believe that they would have had minor effects on the results.

2. Was gravidity (1 vs 2) considered as a potential confounder?

Answer: Thank you for this suggestion. We think that gravidity should be considered a confounder and have now included gravidity in the analyses in Table 3. There were, however, only minor changes in the effects.

Points 3-6 below relate to the role of variables other than pre-pregnancy BMI ("main exposure") and preeclampsia (outcome):

3. The stated aim of the study is assessing the association between the risk of preeclampsia and pre-pregnancy BMI, in which case the role of other variables is presumably only of concern if they are potentially confounders. In the adjusted analyses, it seems a variable selection approach was used for inclusion of predictors of preeclampsia other than BMI (lines 170-171). Ideally, confounders would specified a priori rather than being decided on by hypothesis testing. However, for an assessment of confounder selection strategies, see, e.g., Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993;138:923-936.

Answer: Thank you for this suggestion. We agree that confounders should be specified a priori. Indeed, what we did was to a priori select a set of potential confounders represented by classical socio-economic and demographic factors, plus maternal height. All of the selected variables turned out to be associated with the outcome at a significance level < 0.10. We have now rephrased this, see last paragraph under Data analysis.

4. In Tables 1 and 2 the association of other variables with BMI is assessed and Table 3 considers crude and adjusted association of other variables, in addition to BMI, with preeclampsia. Are these associations of interest in their own right (i.e. is assessment of these associations part of the study aims?). I would note that they receive little attention in the Discussion.

Answer: These associations were not part of the study aims, but we agree that it could be interesting to put some more focus on these variables, as a reference for the BMI variable. We have included a sentence in the first paragraph of the discussion: “Among the maternal characteristics included in our analysis, only maternal age above 35 years of age shoved a higher odds ratio.”
5. In addition to there being multiple comparisons in Tables 1-3, the large sample size means that differences of statistical, but not clinical, significance may be identified. I also wasn't clear what null hypothesis and test statistic were associated with the tests for trend in Table 1.

Answer: We agree that there may be a problem with multiple comparisons in the study. But as stated above we only had one exposure of particular interest (BMI). We also agree that associations may be statistically significant although not clinically significant. Although we report p-values, effect estimates and corresponding confidence intervals should be considered when interpreting the results. As for test for trend in Table 1 we have now inserted in the table that this was a Chi square test, where the null hypothesis is that the two variables are independent.

6. Line 256: I was not sure why the authors would be including mediating variables unless assessment of mediation effects is also a study aim.

Answer: We did not mention this in the study aim, but to be consistent we have added the following in the aim: As a secondary aim we explored to which extent this association was explained by maternal disease before pregnancy.

7. The authors carry out separate analyses stratified by preterm vs term delivery. Did they consider a single analysis, with an interaction for term status, which would have allowed formal assessment of effect modification (as they did with height)?

Answer: Yes, we also performed a test for interaction between gestational age at delivery and BMI, parallel to the test for maternal height and BMI, but this was not clearly presented in methods or results. This should now be more clear, see last paragraph under Data analysis: “We tested for interaction between maternal height (<160 cm vs ≥ 160 cm) and BMI, and between gestational age (<37 weeks, ≥ 37 weeks) and BMI, by adding an interaction term in the model.” See also reported results in last paragraph of the Results.

8. Lines 148-149: the role of the height and weight cutoff points was not clear. Were they used for exclusion of subjects as with the BMI cutoffs?

Answer: We have tried to make this more clear and have inserted a sentence in the last paragraph before Data analysis: “Cut-off points for height, weight and BMI were used to reduce potential effects of typing errors.

9. In addition to the mean BMI provided in Tables 1 and 2, it might have been useful to include the SD or the range, to provide a sense of variability within each category. It would also be good to provide units for BMI (presumably kg/m2).
Answer: We have included SD in Tables 1 and 2 and have provided unit for BMI in the tables.