Author's response to reviews

Title: Factors associated with prenatal folic acid and iron supplementation among 21,889 pregnant women in Northern Tanzania: a cross-sectional hospital-based study.

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Author's response to reviews: see over
Dear editor BMC Public Health

Thank you for the invitation to resubmit our manuscript entitled “Prevalence and correlates of prenatal folic acid and iron supplementation among 21,889 pregnant women in Northern Tanzania: a registry-based study”. We appreciate the thorough and helpful comments made by the reviewers. We have tried to follow all their advice, and believe that we now resubmit an improved manuscript. Our answers to the reviewers are attached below.

We hope the revised manuscript is acceptable and look forward to hearing from you.

Sincerely, Anne Kjerst Daltveit
NOTES FROM THE AUTHORS:

Editorial changes:
2. We have changed the title of the paper, based on reviewer 2’s suggestion. The new title: Factors associated with prenatal folic acid and iron supplementation among 21,889 pregnant women in Northern Tanzania: a cross sectional hospital based study.
3. We have removed the authors' qualifications (e.g. PhD / MD) or job titles from the submission system.
4. We have removed the visible vertical lines of the tables.

Reviewer 1:
Major compulsory revisions:
1. Background and conclusion sections need to be substantially reorganized.
   Answer: See below:

2. There are editing/grammatical problems throughout; needs careful proofreading.
   Answer: See revised manuscript for corrected errors. The manuscript has been carefully proofread.

3. Adjusted OR’s no discussion of what variables were “adjusted for” in table or text. This needs to be clarified.
   Answer: We now write in the Statistical analysis section: “All factors associated with iron or folic acid supplementation in bivariate analyses (defined as p value < 0.20) were included in a multivariate logistic regression model.” We also state this in the results section (first sentence of second paragraph). In footnote table 3 we also include the statement “all variables are in the adjusted model”.

4. Use robust standard errors to account for multiple observations on same person.
   Answer: We agree with the principle of robust standard errors. However, we did not consider analysis of repeated measures as linked data were not available in our data file. Accounting for dependency between siblings might increase the confidence intervals of our estimates. However, we do not believe such an adjustment would change the overall results and conclusion.

5. More needs to be made of the interesting finding that women with co-morbidities are least likely to supplement with FA and Fe—but not sure how this relates to PN visits—did they visit more or less?
   Answer: We have analysed the relationship between co-morbidity and PN visits. We found that the proportion with less than four PN visits was slightly higher in women with preeclampsia (29.3% vs. 25.0%), while the proportion with less than 4 PN visits was slightly decreased in women with malaria before pregnancy (23.4% vs. 27.6%), malaria during pregnancy (22.2% vs. 26.0%), and women with other diseases during pregnancy (21.6% vs. 25.4%). These numbers do not suggest a strong association between maternal morbidity and PN visits. Also, since the multivariate model includes PN visits, possible confounding by PN visits is already accounted for in the adjusted results. In the discussion section we now clarify
that the association is also evident after accounting for number of prenatal visits in the multivariate analysis.

Minor Essential Revisions:

Abstract:
1. Provide ORs for any results presented.
Answer: We have added ORs for malaria before pregnancy and malaria during pregnancy.

2. How do you define lower socioeconomic status mentioned in abstract but not in main text?
Answer: Because we are not dealing with a definition of lower socioeconomic status in the paper, we have changed the text to say “indicators of lower socioeconomic status”.

3. Make a stronger conclusion. The most interesting finding was that women with co-morbidities are least likely to supplement with FA and Fe--should be stressed more.
Answer: We have strengthened the conclusion to also include mention of morbidities.

Background:
1. Needs reorganization; currently is disjointed.
Answer: See changes below.

2. 1st para: First sentence is out of context, begs more explanation of methylation, etc. “At risk for pregnancy” is weird; should change to reflect that FA is recommended for women during child-bearing years, or preconceptionally. It is not only that women have problems upregulating iron, they have menses, therefore have regular blood loss, a straightforward explanation for why women have more anemia.
Answer: We have deleted the first sentence about methylation. We have altered the sentence so that it reads Whereas men generally have iron homeostasis even in settings where dietary iron is low, in women both before pregnancy due to blood loss resulting from menses, and during pregnancy, the body’s capacity to upregulate iron absorption is often insufficient accompanied by a reference.

3. 2nd para: WHO guidelines sentence is out of place. Add “enough” after (HbM8.5 g/dl), missing parentheses in citation 15.
Answer: We have corrected the parenthesis and moved the sentence to the first paragraph.

Methods:
1. Folic Acid/Fe+: Make it clear this is binary outcome.
Answer: We have included a sentence under the paragraph “Folic acid and iron supplementation” clarifying that the outcomes are binary.

2. Sociodemographic correlates: Occupations in secondary level not described. There are missing parentheses.
Answer: We have corrected the text so that the definition of secondary level should now be clear (see paragraph “Socio-demographic correlates of supplementation”).

3. Health indicators: move last sentence defining infections to third sentence...(malaria, anemia, infections). This section was confusing and might
be better described in a figure. Check typos in this paragraph.

Answer: We have moved the last sentence about infections, this is now second sentence in the paragraph. We have corrected some minor typing errors.

Statistical analyses: First sentence: Insert “ever” between “who” and “used”. Make it more clear that this is a dichotomous outcome. Sentence starting with contingency tables needs to be re-written to clearly state that each was analyzed separately (yes/no).

Answer: We have inserted “ever”, we have inserted (yes/no) for the three outcomes, and we have rephrased the sentence about the contingency tables to: “Contingency tables were employed to estimate crude odds ratios (ORs) with 95% confidence intervals for the association between each of the three dichotomous outcome variables, and socio-demographic, health services utilization and pre-pregnancy and pregnancy related morbidity.”

Results:
1. 2nd paragraph: adjusted OR’s, write at AOR: need to state what variables were “adjusted for” in table or text. Some sentences don’t provide AORs in text, need to add.

Answer: We now write in the second paragraph that “In the multivariate analysis with all presented variables included in the model”...We have also added AOR for maternal conditions before or during pregnancy.

Discussion:
1. Needs reorganization.

Answer: See below.

2. Important finding is that those with co-morbidities aren’t supplementing. Should be discussed earlier than 5th paragraph. Is that after controlling for frequent visits? Need to state what was “adjusted for” in AORs.

Answer: This paragraph is now second paragraph. In paragraph 3, we also state that the finding of decreased supplementation among women with morbidity was evident in the multivariate model where adjustment is made for number of antenatal visits.

3. 1st para: Add “at” before 43%. Instead of using small studies, can’t you look at country-wide DHS data for African/lower-income countries?

Answer: We have added “at”.

4. 2nd para: add “e”-- “choloroquin” spelled wrong. This med. is used for malaria, so not sure about this study, were they looking at anemia and malaria together?

Answer: We have corrected the typing error. We also specify that the chloroquine dose was standard for all participants in the study, see revised text: “…standard weekly dose of prophylactic chloroquine for malaria prophylaxis, dramatically reduced the prevalence of anaemia during pregnancy in a prospective intervention study of 1045 women in two antenatal clinics in Dar Es Salaam.”

5. 3rd para: check typos, missing words in “Dar Es Salaam” sentence.

Answer: We have corrected typing errors.

6. 4th para, 1st sentence: insert were after co-morbidities. What is the difference
between prenatal and antenatal? Isn’t this the same thing? This paragraph needs to be moved earlier and discuss number of visits in relation to co-morbidities.

Answer: This is now second paragraph of discussion, and specify that the results are adjusted for number of prenatal visits. We have removed the word “prenatal”.

7. 5th para: rewrite first sentence: “Notably, primiparous women with….were also found to…supplements during their first pregnancy….”
Answer: Done.

8. “Major strength” para, last sentence: “Some of the information…” Need to give percent, this is too vague.
Answer: We have deleted the word “Some”, because the text relates to the information in general.

9. Last para: Last sentence is a fragment.
Answer: We have deleted part of this sentence.

**Conclusion:**
1. Last para: change “risk women” to “women at risk”
Answer: Done.

Table 2:
2. Spell out Dis.
Answer: Done.

3. Remove “” from Number of ANC visits and spell out “ANC”
Answer: Done.

Table 3:
1. In table 1 you use “mothers” and “fathers”. In table 3 you use “woman’s” and “husband’s” be consistent.
Answer: We have changed to “woman’s” and “husband’s” in all tables.

2. You lump together occupation to Professional, skilled and “other”. What does other include, that seems to be a big lump of farmers and business people..?
Answer: “Other” includes all other observations, this is now added in the footnote of table 3. We also write in the last sentence in the “Socio-demographic correlates of supplementation” paragraph: To avoid many and small categories in the multivariate analysis, we grouped some categories for maternal age, parental education and parental occupation.”

3. Remove “” from Number of ANC visits and spell out “ANC”
Answer: Done.

4. In footnote to table, list all of the adjustments made to these OR’s
Answer: Done.
Reviewer 2:

Title and abstract
Indicate the study’s design with a commonly used term in the title or the abstract
Title is a little unwieldy.
How about: Factors associated with prenatal folic acid and iron supplementation in Northern Tanzania: a cross sectional hospital-based study
Answer: We like that suggestion and have changed the title accordingly. We have inserted “cohort” in the first sentence of Methods/Abstract.

Introduction
Objectives 3
Please clarify objectives and any prespecified hypotheses
Answer: We have rephrased the objectives in the last sentence of Background.

Methods
Study design 4
Present key elements of study design early in the paper
This needs to be done – suggest using the terms observational, cross-sectional and hospital based to describe the study
Answer: We state the study design in the first sentence of Methods: “In this hospital based cross-sectional observational study we utilize data from....”

Variables 7
Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Please clearly clarify the outcomes. Also clarify if the variables listed are considered exposures of interest, or confounders etc.
Answer: We have clarified the binary outcome variables, see answers above under reviewer 1.

Bias 9 Describe any efforts to address potential sources of bias
Were any steps taken to reduce bias?
Answers: As for selection bias, women who were referred to give birth at the hospital for medical reasons (n=3582) were excluded from the analysis, see Methods/Study population.

Statistical methods 12
(c) Explain how missing data were addressed
Please clarify – the paper reads as if data were complete for all covariates, which is hard to believe for routinely collected hospital data.
Answer: We have included a footnote in table 1 stating that “The numbers do not add to the total due to missing information”. We have also included a similar sentence in the Statistical analysis section.
Results

Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.

This is unclear and requires clarification. 21,889 pregnancies in the analyses sample after exclusions, but in table 3 it is unclear how many pregnancies feature in each of the models.

Compulsory
(b) Give reasons for non-participation at each stage

Answer: From tables 1 and 2 one can see from the numbers that there are missing values for some of the variables. This is now stated in the footnotes of the tables.

Participants 13*
(c) Consider use of a flow diagram

Please consider

Discretionary

As above

Answer: Since we now have clarified the questions regarding missing values, we think that a flow diagram is not necessary and would take up too much valuable journal space.

Descriptive data 14*

Indicate number of participants with missing data for each variable of interest

As above – requires clarification

Answer: We have added a sentence about missing data in the footnotes of tables 1 and 2. We have added a footnote in table 3 stating that: Number included in the model is 21,027 (862 observations had one or more missing values).

Discussion

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

A major concern is how generalisable are these results to the population. This is a hospital-based sample taking referrals from a zonal area. How representative is this of the general population. This is touched upon in the discussion but needs to be expanded.

Compulsory

Answer: The hospital is a regional referral and teaching hospital with a catchment area of ~10 million people. It is estimated that only 20% of women do not use this facility for delivery. Hence, at the very least, the findings are likely generalizable to Northern Tanzania as whole. Given the sociodemographic characteristics generated by the international Demographic Health Surveys, findings may be generalizable to other countries. We have expanded the section discussion the generalizability of our study.

Generalisability 21 Discuss the generalisability (external validity) of the study results

Answer: See above.