Author’s response to reviews

Title: Adherence of Iron and folic acid supplementation and determinants among pregnant women in Ethiopia: A systematic review and Meta-analysis

Authors:

Melaku desta (melakd2015@gmail.com; melakd2018@gmail.com)
Bekalu Kassie (bekalukassiedmu@gmail.com)
Habtamu Chanie (habtclinton@gmail.com)
Henok Mulugeta (mulugetahrenok68@gmail.com)
Tadesse Yirga (tadesseyirga680@gmail.com)
Habtamu Temesgen (habtamutem@gmail.com)
Cheru Leshargie (chertesema@gmail.com)
Yoseph Merkeb (ymerkeb11@gmail.com)

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Author’s response to reviews:

Dear Editors of Reproductive Health

We would like to extend our deepest appreciation for devoting your time to review our manuscript entitled “adherence of iron and folic acid supplementation among pregnant women in Ethiopia: A systematic review and meta-analysis”. Iron and folic acid deficiency anemia is a global public problem that causes maternal morbidity, which can be prevented through improving the adherence of iron-folic acid supplementation among pregnant women. Even though, the adherence is inconsistent across the country. Therefore, this systematic review and meta-analysis estimates the pooled adherence of Iron and folic acid supplementation and determinants among pregnant women in Ethiopia.

Dear reviewer, there has been a major revision of this manuscript (Abstract, introduction, methods, results, discussion and conclusions). The language has been extensively examined to correct grammatical and spelling inconsistencies and the whole structure of the manuscript has been revised. We hope now the manuscript is clear and more acceptable than its previous version. We have tried to present the paper in proper manner according to your comment what to suppose to do so. More over, the point by point response was included in the supplementary material 2 in the previous manuscript submission. For this, here we have given our responses to each of the concerns you raised, highlighted by red color. Again, we would like to remind our
strongest gratitude for your effort for the improvement of this manuscript and all the points were addressed in the point by point response.

Regards

Section

Comment

Response

Abstract &; Introduction

1. Can the authors provide references to benefits of IFA in Ethiopia, even if the data are scarce, or explain why these studies are relevant to generating their hypotheses?

Valuable, but the importance of the supplement in other studies can be used to generate a hypotheses in Ethiopia due scare data even one ref was included.

2. Please could the authors provide a rationale for why this review was needed and limited to Ethiopia only and not other countries across the African continent? Are the reasons for non-adherence to IFA proposed to be very different in Ethiopia? Was this review designed to inform national policy? I am sure there are clear reasons, but these need to be stated so the reader has the appropriate context.

Highly valuable

This review was needed to get national level prevalence to inform the policy makers. Hence, studies regarding to the adherence, determinants and barriers are highly variable or inconsistent across Ethiopia. Moreover, knowledge regarding to any pills as IFAS are very limited in Ethiopia and more than 85% of populations are rural residents, which might be difficult to apply mobile interventions to improve maternal health care service, might reduce the adherence of IFAS.

3. Suggest including confidence intervals for "fear of side effects" and "forgetfulness"

4. You only mention I2 and Egger's test in the methods section, while in the manuscript you also mention Begg's, the Duval trim technique, funnel plots. However, please see my comment above.
5. I suggest using the same analysis throughout (perhaps replacing DALYs with morbidity/mortality in the introduction). I suggest you reference Daru J et al, 2018 Lancet Global Health for anemia-related mortality

Accepted and corrected

-The confidence interval was included.

- In regarding to the methods section of the abstract and the methods section and throughout the manuscript was revised. Hence, the eggers test is more specific and better we used eggers test for publication bias and revised through the document. The full explanation is on the methods section of the manuscript.

Methods 1.

What was the rationale to limit the search to 2000?

Valuable.

At the time different international organizations like the United Nations Children’s Fund, WHO. Iron deficiency anaemia prevention, and control mechanisms and Iron and folate supplementation was an integrated management of pregnancy and childbirth (IMPAC) by WHO Health Organization.

2. Please could the authors include a reference to the following statement: "Adherence of IFA supplementation was define by WHO"

Accepted and corrected

the reference was cited, with ref number 37

3. Please improve your description of your search strategy -perhaps include it as an appendix. Also include when the search was conducted

Accepted and corrected

The search string was included as appendix 1 and the period of search has addressed, from January 15 to March 25/2019.

4. Under outcome of interest you mention "index pregnancy period." I am unclear what is meant by this.

Corrected
We want to infer to during pregnancy, and if that is the case we corrected as index pregnancy period as “during pregnancy”

5. Suggest including the quality assessment according to the Newcastle-Ottawa as an appendix or embedded in Table 1.

Accepted and valuable.

The quality assessment scale was embedded in Table 1 and those included studies were have moderate and high quality.

6. Please include an explanation as to why you conducted sensitivity analyses. You include this in the results (paragraph 4) but this should be in the methods section. Relatedly, you need to explain also why you perform a Duval and trim technique.

Accepted and corrected

The possible reasons was included

Results

1. I notice that the flow diagram of included studies is an additional file. It would be more characteristic to have this as the first figure and there was some errors in the flowchart, and also explain why you exclude studies (e.g., irrelevance, language, location, not primary studies, etc., etc.) in all the boxes (e.g., box that says "records excluded (n=1219)

Accepted and corrected

The flow diagram was included in the main manuscript than additional file and the flow diagram was corrected based on what you supposed to do so.

In regard to 1219 excluded studies through title and abstract screening due to irrelevance and location out side from Ethiopia.

2. Can the authors provide a table of population characteristics of the women in the studies: where the women in the included studies similar or different (e.g. different profiles in obstetric risk factors, number of pregnancies, gestational ages etc). All of these factors are relevant to interpreting the results of the pooled analyses. Especially, as we know that gestational age will have a huge bearing on the definition of anaemia applied, and consequently the dose of IFA provided. Moreover an overview of the doses of IFA administered across all the included studies would also be helpful.

Valuable
The populations are all pregnant women who have ANC visit regardless of the variation of different factors across studies. The pooled adherence of IFA also reported in each study if the women are eligible to consume the supplement and included in the respective studies. Hence, WHO recommends all pregnant women should adhere to the supplement regardless of those factors. If a woman is diagnosed with anaemia in a clinical setting, she should be treated with daily iron (120 mg of elemental iron) and folic acid (400 µg or 0.4 mg) supplementation until her haemoglobin concentration rises to normal and she can then switch to the standard antenatal dose to prevent recurrence of anaemia.

3. I also notice there is just a description of the overall quality of the included studies and no mention of what were the design of these studies, or the quality per domain of the Newcastle Ottaway scale for all included studies. To my understanding, this is routinely reported in systematic reviews.

Accepted

The quality of included studies was reported or embedded with in Table.

4. There are multiple subgroup analyses presented, these are different to what was pre-specified in the PROSPERO registration. Please could the authors comment

Highly valuable

We completely agree with what you supposed to do so. Intially, we plan to do only the pooled adherence and its determinants of IFAS. But, while we search the barriers of adherence was reported and paramount to improve the adherence of the supplement. That why the subgroup analysis increased and also are much important for community interventions.

5. I am unclear as to why the authors are presenting p values for assessment of heterogeneity. This is not usual practice (to my knowledge), so please can the authors explain why this was necessary.

Valuable and responded

I accept your suggestion. But, p-value was used to declare presence of significance heterogeneity and I-statistic is used to know the level of heterogeneity, i.e low, moderate or high. Hence, presence of heterogeneity doesn’t support the presence of statistical significance.

6. The application of assessments of publication bias, (again to my knowledge) are done overall and not for each specific end point. Please could the authors explain why they thought this was necessary?

Accepted and corrected

Thank you for your scholarly comments, I included as some statisticians recommends that it will be better to assesss the publication bias in regard to the factors explored in the meta analysis.
7. There are many pooled analyses presented as separate figures, can these be rationalized in any way?

Accepted and corrected

I deleted many separate figures and come up with as one file.

8. Suggest summarizing the data from table 1 you wish to present in the text - focus on the most important data.

Highly valuable and revised

9. Under "adherence of IFA supplementation" you state you performed an I2 test of heterogeneity resulting in high heterogeneity with a p-value <0.05. Under "knowledge of related factors and history of anemia" you performed the same test, state that there was "statistical evidence of heterogeneity" with a p-value=0.108. Please consider revising. Moreover, at times when presenting results of heterogeneity you present a percentage, at other times a percentage and p-value, at others just a p-value. Please be consistent.

Accepted and corrected

I completely agree with what you supposed to so. Hence, it was editing errors it has extensively edited.

10. Under "frequency of ANC visit" you present adjusted odds ratios and in the methods section you do not mention you would be adjusting for any factors. Could you please clarify or revise?

Accepted and revised

again we have revised it, AOR was replaced by OR.

11. Under "barriers of adherence of iron folic acid supplementation" you present numbers and it's unclear if these are percentages or ORs.

Valuable

We try to present it is the percentage or the prevalence those not adhere to the IFA. Thus, we have replaced prevalence by percentage

12. Suggest only referring to one of two tests for publication bias and stating whether it was significant or not. No need for p-values.

Accepted and revised through out the manuscript.
Eggers test was used and P-value in the publication bias was removed and again additional file 2 was removed.

Discussion

1 There are many limitations to the data collected within this review, as demonstrated by the high heterogeneity across most outcomes as well as the quality of studies. This needs to be addressed in the discussion section of the manuscript. This will have an impact on the validity of the results and a comment to this effect is necessary.

Accepted and corrected

the high heterogeneity across most studies in the discussions section have to addressed.

2. The discussion section requires a little more refining. At times, interpretation of results points towards reverse causality - I think this can probably be amended by revising grammar. At others, while there is mention of other studies looking at similar topics, there lacked a real interaction with said literature, i.e., stating how your findings support prior evidence or contrast prior findings and how. There are also some statements made with no references (e.g., fourth paragraph where you state that women with higher levels of education might have better knowledge on IFA supplementation).

Valuable

We try to rephrase or refine our discussion again. In addition, We are going to explain the possible justification of the variation with other findings which have already cited no need of citation again. If the possible explanation is different from those cited one it will be better to cite. But in this case only explanation is made instead of others claim.

References

There are a lot of references (91!) and while it's good that you are interacting with the literature, this seems excessive. Please revise to see if all these are necessary - i.e., if there is updated data or guidance, then just reference the newest. I would also suggest not adding the studies included in the review but rather include them in a table which can be an appendix. Please also check some of the references for accuracy and completeness (and appropriateness/correct citation style).

Accepted and corrected

This sentence has cited based on your comments and the citation have reduced to some extent.
Reference 1 is used to support burden of anemia when this is a reference to a guidance on iron supplementation. Please correct.

I suggest using the most updated reference for iron supplementation during pregnancy (to replace references 1 and 8), with the following https://extranet.who.int/rhl/topics/preconception-pregnancy-childbirth-and-postpartum-care/antenatal-care/who-recommendation-daily-oral-iron-and-folic-acid-supplementation

Accepted and corrected.

References 12, 13, 14 I assume are from the same author but spelling is differently – also are these all necessary

Yes

Accepted and corrected

Suggest including as an appendix although I am unsure of whether this was a good analysis given the very small number of studies in each - unless the unit in number of women, in which case this needs to be included in the table headings (e.g., include sample size for each subgroup).

Valuable

It is possible to report the number of sample in overall included studies than in the subgroup analysis.

Why did you include a national level study under "others"? I'm not convinced the national level study should be included in a sensitivity analysis by region.

Accepted and corrected

I have see what you supposed to do. But, the confidence interval of the two was under the pooled prevalence in others part and the two are some what similar in population characteristics and the afar region is part of the national level. It is possible to do a subgroup analysis if there is similar characteristics in our case, hence, the national level as included Afar region again.

suggest removing Table 3 and 4, and Figure 2 and 3.

Accepted

but table 4 is simportant and remained, and rename as Table 3.

Additional files
Additional file 1: see my comments above about including this in main text but making the necessary corrections

Accepted and corrected

Additional file 2: unsure this is necessary, but if so, you should add all the results from the test used (suggest using only one test) for all the different variables. It is unclear why you only included some in this file

Accepted and not much necessary and remove from the file.