Author's response to reviews

Title: Short term micronutrient-antioxidant supplementation has no impact on a serological marker of gastric atrophy in Zambian adults: retrospective analysis of a randomised controlled trial

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Author's response to reviews: see over
The Journal Editorial Office,
BMC Gastroenterology.

Dear sir/Madam,

Thank you very much for the reviewer’s comments. We have taken note of all the comments and have made changes to the main document as follows;

Revised title of manuscript: Short term micronutrient-antioxidant supplementation has no impact on a serological marker of gastric atrophy in Zambian adults: retrospective analysis of a randomised controlled trial

Reviewer 1:

Major points

Reviewer- Abstract, methods and results: please be careful with using the PG-ratio as an equivalent of gastric atrophy since there is an inverse association between the ratio and the degree of atrophic changes. So if you state that gastric pH correlates with atrophy and you state an negative Spearman’s rho, this is just wrong. In these cases you should always just refer to the PG-ratio as surrogate since you don’t have data on the actual atrophy scores, and discuss this thoroughly. (The same accounts for table 4, where it looks like age over 40 years would be protective against atrophy as stated here.)

1. We have rephrased the title, abstract, methods, results and discussion, referring to the pepsinogen 1:2 ratio (PEP 1:2 ratio) as a surrogate to gastric atrophy. We have included a discussion on the non availability of histological confirmation of gastric atrophy in our participants.
2. We did state in the text that gastric atrophy inversely correlates with gastric pH as showed by a negative rho.
3. We have included data on the actual atrophy scores.
4. Table 4 shows that persons with low PEP 1:2 ratio were significantly higher among those above the age of 40years.

**Reviewer:** You should furthermore discuss very thoroughly the assumption that due to a "random allocation" the distribution of atrophy at baseline should be similar in both groups. It is very difficult to make assumptions on that fact without baseline values. I have several questions concerning that issue.

5. We do appreciate the concern over the assumption that the distribution of atrophy at baseline was the same in both groups as the allocation was random. This is the premise of a randomised controlled trial and we even provided a reference to the effect that unless there is reason to suggest otherwise, any differences seen after randomisation are only due to chance. (Ref 23).

**Reviewer:** First, you state that there have been baseline blood tests at inclusion and then "annually". Why are these not included in the study but just the "final outcome" values. To make hypothetical assumptions on the baseline values is very dangerous in my point of view.

6. This was a retrospective analysis of stored serum samples. We analysed samples that were available in the laboratory and only those that had clearly labelled dates and patient codes. We did not find sufficient baseline samples and therefore decided to only analyse the ones post intervention. Most importantly, this study had no external funding and we had limited resources to purchase more ELISA kits.

**Reviewer:** Second, you only refer to "presence of atrophy" but not to the degree (as you would in case of available histological data). As far as stated in the results there is no difference in overall presence, but you don't show the absolute data. Often there is no complete but partial regression of atrophy score, as shown e.g. after H. pylori eradication. Third, I miss information on prevalence of H. pylori infection in this population as a major confounder.

7. We have included the absolute data on the pepsinogen 1:2 ratios in the results section on gastric atrophy. We had no histological data on these patients (explained in detail below).
8. None of the participants received treatment for *H. pylori* infection during the follow up.

**Reviewer:** “gastric pH was measured in fasting participants by endoscopic aspiration...”. When was the endoscopy performed and isn't there any basic histology available?

9. Endoscopies were done on some of the study participants in the main trial to determine the fasting gastric pH but no biopsies were taken as that was not part of the trial protocol. For this analysis, we therefore did not have any histology data on either the presence or the degree of gastric atrophic changes.
Reviewer- Alcohol is not an accepted risk factor for gastric cancer. There is no convincing data as there is for tobacco smoking. Please rephrase the respecting sentences.

10. The statement that alcohol is a known risk factor of gastric cancer has been removed.

Reviewer- Discussion: The first paragraph is mainly a repetition of the introduction section and should be deleted from here. This is followed by information highly redundant top the results section. Please focus more on critical discussion of your data instead of repeating your results in different phrasing.

11. The beginning of the discussion has been rephrased.

Reviewer- Please discuss more meticulously the discrepancy between a 3-years study with respective follow-up and the discrepancy to the 18-19 months "follow-up" here.

12. We made reference to the main trial whose goals were different and there was a crossover of participant’s midway during that trial. The follow up for that trial was 3 years, but there was a crossover midway. For the purposes of this study, we could not use samples collected after the crossover as it would have been difficult to draw up any conclusions on the influence of the supplementation on the surrogate marker of gastric atrophy.

Minor points

Abstract

1. The sentence in the methods section has been split as advised.
2. We have adjusted the presentation of the confidence interval as advised.
3. We have changed advancing age to advanced age.

Background

1. The second sentence has been deleted.
2. Precancerous has been changed to premalignant.
3. We have rephrased the sentence that suggests that the cancer develops within metaplastic mucosa.
4. We have inserted the word of these as advised.

Results

1. Kelly 2008, have been written as a proper reference.
2. The word significant has been included.
3. A separate section on nutrition has been added.

Tables and figures

Table 1: All abbreviations have been introduced.
Table 2: Clarifications have been inserted on whether it was the mean or the median being considered for each entry. The ranges are also reflected were necessary.

The total numbers to be considered for each row are indicated at the beginning of the first and second columns. Different values of n are indicated for individual entries whose totals are different.

We cannot include decimal places on entries such as the one for Cannabis as these are the actual numbers on participants referred to.

Figure 1: The flow chart has been adjusted to make it clearer.

General comments:

Revisions of the language have been made as necessary. Introductions of all abbreviations have been included.

At least one decimal place has been added to outcome figures.

Reviewer 2:

We have amended the punctuation error and have included abbreviations.

Thank you.

Violet Kayamba.