Reviewer’s report

Title: Thymic size is increased by infancy, but not pregnancy, nutritional supplementation in rural Gambian children: A randomized clinical trial

Version: 0 Date: 16 Nov 2018

Reviewer: Kathryn Dewey

Reviewer's report:

This is a well-written paper on an important trial investigating a novel outcome. I have several comments regarding the current version of the manuscript, listed here in line number order (not in order of importance):

L80-82: Should mention the energy content (746 kcal) of the daily dose of PE supplement, which is otherwise available only by downloading the supplemental material.

L116-117: What was done if an infant was wasted, at any of the anthropometry time points? Was there any referral for treatment? If so, did this differ across groups and potentially influence outcomes?

L132-133: Why were all types of morbidity pooled together?

L150-152: Some of these variables in Models 1 and 2 are outcomes that could have been influenced by the intervention and hence may be on the causal pathway, including infant length, infant feeding and morbidity. A clearer explanation is needed for why these variables were included and how they were handled during analysis and interpretation of results.

L166-167: The results for compliance with the LNS supplements (81-82%) are hard to interpret because lines 62-63 in the OSM state that “for LNS products a 'score' based on the amount of supplement left remaining in the jar was made (empty, half-empty, full)” but lines 130-131 in the OSM state that compliance was based on the number of jars of LNS the mother consumed divided by the number she was offered. Which is it?

L168-175: Hemoglobin is influenced by many factors (such as inflammation), not just nutrient intakes, so this is not a good proxy for assessing supplement compliance. Plasma folate is a much better proxy because it is related to recent intake of folate. Showing hemoglobin by maternal intervention group in Figure 2 goes beyond the scope of this paper, and I recommend
that it be deleted herein - it is an important outcome by itself and as such deserves much more consideration in a separate paper.

L196-197: Lines 147-148 state that "analyses were also conducted using data on supplement compliance", but I do not see any such "per protocol" analysis results. This is quite important (regarding the impact of maternal supplementation), given the difference in compliance among the maternal intervention arms.

L197: I did not see any mention of pre-specified effect modification (interaction) analyses in the methods section. Was maternal BMI the only characteristic considered as a potential effect modifier? What p-value was used to identify p-interaction?

L238: Regarding the statement that "supplemented children had a non-significantly lower incidence of morbidity" - this wasn't stated in the Results section, and the only place where I could find this was in the OSM, and only for the pooled cases of all types of morbidity. I think that more could be done with the child morbidity data in this paper, e.g. presentation of fever, respiratory infections and diarrhea separately. This could complement the data on thymic index. It would also be useful to report whether thymic index was correlated with morbidity outcomes in this cohort, which is directly relevant to the text on lines 214-224.

L240-255: It is important to mention here that this trial used a very large quantity of LNS, 746 kcal/d. It is highly likely that this dose was too large for women to eat all of it during pregnancy, when nausea and vomiting are common and limit food intake. This is likely to be the main reason for low compliance. Regarding L250, several other trials using small-quantity LNS have reported compliance, and medium-quantity LNS was used in a prenatal trial in Burkina Faso (Huybregts et al. 2009) for which data on compliance were reported. There are also several published papers on acceptability and uptake of maternal small-quantity LNS (see Klevor et al. 2015; Harding et al. 2016). Regarding L253-255, do the authors think that "high dose" LNS supplements during pregnancy are really appropriate for future trials or interventions, given issues of compliance and cost? If not, this sentence seems unnecessary.

Table 3: This table is a bit hard to interpret. Also, there is a p-value of 0.05 in the top row of results - was this not considered significant? I would suggest including a figure with the primary outcome, to aid in understanding these results. This would be far more useful than Figure 2.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
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Yes

Are the conclusions drawn adequately supported by the data shown?
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