Author's response to reviews

**Title:** Equity in adherence to and effect of prenatal food and micronutrient supplementation on child mortality. Results from the MINIMat randomized trial, Bangladesh

**Authors:**

Rubina Shaheen (RubinaShaheen@kbh.uu.se)
Peter Kim Streatfield (kims@icddrb.org)
Ruchira Tabassum Naved (ruchira@icddrb.org)
Lars Lindholm (Lars.Lindholm@epiph.umu.se)
Lars-Åke Persson (Lars-Ake.Persson@kbh.uu.se)

**Version:** 2 **Date:** 7 July 2013

**Author's response to reviews:** see over
July 6, 2013

Dear Editors, BMC Public Health,

We thank the reviewers for their inputs and the insights that they have added in our manuscript. Please find below the point by point response to reviewers.

Also, please find attached the revised manuscript and figure 1 as separate files.

On behalf of all authors

Thanking you

Rubina Shaheen

Doctoral student
International Maternal and Child Health
Department of Women’s and Children’s Health
Uppsala University
Sweden

Response to reviewer 1 – Malavika Subramanyam

Reviewer’s report
Title: Equity in adherence to and effect of prenatal food and micronutrient supplementation on child mortality. Results from the MINIMat randomized trial, Bangladesh
Version: 1 Date: 31 March 2013
Reviewer: Malavika Subramanyam

Reviewer’s report:
Major compulsory revisions
I commend the authors for the selection of this important topic. The data come from a well-designed randomized trial which significantly strengthens this manuscript. However, the manuscript needs significant revisions to improve clarity and flow. I fear that I have missed many points while reading this manuscript just because of the poor readability and flow.
All of my comments listed below are what I would consider compulsory, whether major or not.
1. “Other efforts may show variation in equity effects in different settings due to design as well as the historical and political trajectories of the local health system.” – Need some explanation. What do you mean by “different settings”, “design”, “historical and political trajectories of the local health system”?

Response – It relates to the first sentence “One way out is to target interventions to those most in need [4]”.

Many propose to target the group most in need. This is the straightforward way. However, other efforts for example if we depend on that the existing health system and its personnel will take care that distributions are equal and that both poor and relatively rich will use that equally then there can actually be variations. This is because the design of the intervention and the history of development of the health system in that particular country and also the way the political trajectory has evolved may not allow equal distribution let alone equal effect. This has been addressed now in the manuscript.

2. “It is therefore relevant to examine large interventions targeted to populations in low-income countries.” Relevant to examine which aspects of the large interventions being referred to here? I can guess, but it might help to be explicit.

Response – We indicated about the effects. Now corrected in the manuscript.

3. The methods section needs to be re-organized to present information in a more linear manner. I had to keep scrolling up and down to find the information I wanted. More sub-headings would help, perhaps something such as: study sample, outcome variables (number of variables, how data collected, how data operationalized in analyses), predictor variables (number of variables, how data collected, how data operationalized in analyses), descriptive statistics, univariate analysis, multivariable analysis.

Response – we have now re-organized the methods section and clearly mentioned about study samples, the outcome and predictor variables, descriptive statistics, univariate and multivariate analysis but without adding any sub-heading.

4. Please mention the number of women who were recruited to this study either towards the end of the paragraph on design, or in the next paragraph, the one on study site participants.

Response- addressed.

5. Please spell out abbreviations at first instance of their use.

Response- addressed.

6. I understand that details of the MINIMat study have been previously reported. However, it will be helpful to readers of the current study to be able to learn some basic information regarding MINIMat in the current article itself, instead of having to look up the referenced article. For instance, a single sentence about the aim of the MINIMat study and the study population will be helpful.

Response- addressed.

7. “A birth notification system was established to ensure that study staff was
made aware of births as soon as they occurred.” – How did this system work? Have the details of this system been published previously? Please cite the reference if they have been previously published. Even if previously published, a sentence or two describing how this worked would be helpful.

Response- a detailed description has now been added. The reference is also added.

8. What was the reasoning behind dichotomizing maternal education and household asset score? Please include the rationale behind this decision in the manuscript.

Response- addressed. The reasons are now added in the manuscript.

9. “Information on infant and child mortality was collected at follow-up visits at 7-12 day postpartum, and at monthly visits during infancy. Community health research workers also collected information on child survival on a monthly basis as part of the routine surveillance system in Matlab. These workers visited households and collected information on vital events like births, deaths, and migration.” Who are the persons who collected the information referred to in the first sentence on infancy? Are they different from the community health research workers referred to in the second sentence? If so, how are they different?

Response- the MINIMat project staff collected the information during infancy. They are different from the community health research workers; the latter staff is the fixed regular staff of ICDDR,B to collect only vital information such as birth, death, marriage and migration and deliver information.

10. Also, how was mortality data on children aged 1 to 5 years collected?

Response- addressed in the manuscript. The mortality data of 1 to 5 year old children were collected by CHRWs who are regular staff of ICDDR,B.

11. “Baseline characteristics between trial arms were evaluated by student’s t test, or Bonferroni adjusted post hoc ANOVA for continuous variables and chi square test for categorical variables.” The continuous and categorical variables referred to in this sentence, are they the outcome variables? If so, it might be better to say so. For instance, “Baseline characteristics between trial arms were evaluated by student’s t test, or Bonferroni adjusted post hoc ANOVA for continuous outcomes and chi square test for categorical outcomes” is clearer.

Response- No, they are intermediate variables that may influence the directions of our results, and therefore, we have compared them. We have clarified the sentence in the manuscript.

12. “The women having less schooling were in general from families having lower mean asset scores (-1.23 vs. 1.36, p<0.001), more frequent deficits in a scale for
income expenditure status (p<0.001), and more frequent presence of daily wager in the family (p<0.001).” This is the first mention of two new socioeconomic variables: income expenditure status and presence of daily wager in the family. Please introduce these variables in the methods section with details on how these data were collected and how they were operationalized in the analyses. It might be worth letting the readers know in the introduction itself that 4 and not 2 socioeconomic variables were used in this paper.

Response- addressed. The variables are now listed under a new section called variables.

13. Please mention that all analyses were Intent To Treat analyses in the methods section itself.

Response- addressed and now mentioned in the methods section.

14. Recommend changing “The baseline characteristics between trial arms were comparable indicating efficient randomization” to “The baseline characteristics between trial arms were comparable on X, Y and Z, suggesting efficient randomization.”

Response- addressed according to the comment made by the reviewer, Lieven Huybregts.

15. “Women having <6 years of schooling adhered more to food (83 vs. 68 packets, P<0.001) but less to micronutrient supplementation (105 vs. 119 capsules, P<0.001) than women having more schooling.” In this sentence it is not clear which randomization group the women having more schooling belonged to.

Response – we are not talking about the randomization groups but about women having different levels of schooling here since we have stratified the randomization groups based on this variable which is our key variable. Clarified in the manuscript.

16. Please structure the results such that the two groups being compared differ only on one aspect. For instance, when comparing consumption of food supplements in low educated women with that in higher educated women, it helps if the micronutrient intake etc is the same between the two groups. Perhaps some of the comparisons discussed are indeed in this form. But not all. Currently too many comparisons are presented without organizing them in a manner that makes it easy for the reader.

Response- Addressed, the comparisons are now organized. First compared between maternal schooling groups and then compared between a combination of maternal schooling and randomization groups in a separate paragraph.

17. Please re-organize the discussion such that points about each outcome variable are addressed in an orderly fashion. Perhaps this is has been attempted. But currently, it is not very clear, and puts the burden of reading and re-reading
and scrolling up and down on me. The manuscript suffers from lack of an easy flow to make it more reader-friendly. There are 6 different groups to be compared, and the addition of the socioeconomic variables makes it even more complex to follow.

Response- Addressed and the discussion is now organized incorporating also the comments from reviewer 2, Lieven Huybregts.

18. “A lower adherence to micronutrient supplements was observed among women with less schooling. This is consistent with the findings from a previous iron supplementation study in Bangladesh [19] and from a study among female garment employees in Cambodia [20]. A possible explanation may be that women having more schooling regarded capsules as indicative of modern care, while women with less schooling did not share that view and were also not aware of the added advantages of the tablets. A study in Vietnam reported concern for newborn health as a significant reason to comply with iron folic acid supplements [21]. Because of similar reasons probably women in our study adhered with micronutrient tablets but the differences between less and more educated women were not significant since concern for newborn health is a unique phenomenon as women perceive [22], and all women were equally worried for that.” It seems to me that the first sentence and the last sentence in this paragraph are not congruent.

Response- addressed now and clarified.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests

Reviewer’s report
Title: Equity in adherence to and effect of prenatal food and micronutrient supplementation on child mortality. Results from the MINIMat randomized trial, Bangladesh
Version: 1 Date: 20 April 2013
Reviewer: Lieven Huybregts
Reviewer’s report: This paper investigated the role of social differentials on adherence and on the effect of prenatal food and micronutrient supplementation on child mortality. The research question is a relevant and interesting one. The paper could benefit from some important restructuring and providing more details on methodology and analysis. The robustness of the conclusions needs to be checked with other characteristics that might confound the reported associations. I’m looking forward to some additional data (analysis) and revised version of the manuscript.
Major Compulsory Revisions

1. Analysis strategy is a bit unclear. At the end of the introduction, it is announced that subgroup analyses will be conducted according to maternal education and socio-economic status (HH assets), however throughout the article the main focus is on maternal education, while HH assets stratification is only used as a sort of secondary analysis. In the discussion some arguments are given for this choice. I recommend the rationale for this choice is already given and more thoroughly argumented in the introduction as why maternal education is more important than an asset based estimate of HH socio-economic status. As a consequence, the objective should also be slightly modified as maternal education is not the same as ‘equity’. I think caution should be exercised not to oversell the results based on maternal education as a straightforward equity analysis. Such analysis entails many more dimensions (decision power, ownership, rights,…), so a bit more careful wording in the discussion (last part) is recommended.

Response - education reflects individual SES and is more related to the decision and freedom to use an intervention. And since the effect of an intervention largely depends on the extent of its utilization, it is more relevant to use education as a SES variable when we talk about achieving equity from an intervention. We corrected the text now and clarified why we have used maternal education as the main SES variable for testing whether equity has been achieved or not.

2. You have reported far more analyses than described in your methods section. I notice the testing of interactions below your tables, but nothings was mentioned on testing interactions in models.

Response - Addressed. Now in analysis under methods section the tests and the rationale for the tests are mentioned and clarified.

3. Why did you use the asset score as a binary variable and not in tertiles (or regrouped quintiles) as one might have expected? Moreover, in table 1 you report is in tertiles. I suggest you present the results for tertiles.

Response – There is not sufficient power to split analysis by using asset score tertile values. Therefore, we used dichotomized values of asset score both in mortality analysis and also revised table 1 accordingly.

4. I recommend you report the association between your asset based score and the maternal education level. This is an important result to understand the data structure.

Response – Addressed in the manuscript.

5. I noticed a very important detail below table 2. Adherence was only assessed until week 30’s examination. Either this is a mistake or if true: why is this the
case? I assume adherence could have further been monitored after 30 weeks when replacing the monthly doses of food and also capsules? This aspect should be added to the methods and discussion. It limits the external validity of the results somehow.

Response – this has been addressed now. Adherence after 30 weeks examination, for food supplement upto 34 weeks in order to avoid influence on adherence data by preterm delivery. This aspect is now added to the methods.

6. Table 2 is not easy to read. The results from the tests are not really shown in the table. Maybe adding the subtotals makes it easier to add the statistical test to the difference. I think it’s better than to write ‘14’ packages and ‘14’ capsules nelow the table. I would also put the anova results not related to schooling in the text of the results section and remove them from below table2. In the results/abstract section you write (83 vs 68) food packages, but here you mention a difference of 14 packages.

Response – addressed. The table is now clarified, and some notes under the table are now moved to the text.

14 packages difference is in between the schooling groups, <6 years vs. ≥6 years, P<0.01; 14 capsules difference is in between the schooling groups, <6 years vs. >6 years, P<0.01, student’s t test; those presented in the abstract are between the combination of schooling groups and randomization groups, such as <6 years schooling UFe60F vs. <6 years schooling EMMS, 65 vs. 101 packages, P=0.0001, presented under Table 2; the similar comparison for micronutrients are, 99 vs. 109, P=NS, ANOVA post hoc multiple comparisons. The discrepancy between table 2 and the abstract occurs due to rounding, now corrected in both.

7. Discussion pg 13: you consider it unlikely that there would be differential reporting according to schooling, however you cannot really demonstrate this aspect. Therefore, I would add this to the limitations of the study.

Response – We agree with the reviewer but only partially since at the early part of pregnancy the women consumed at the CNCs, but yes this can be a limitation since we cannot demonstrate this by our data. Addressed and added in the discussion under the subheading limitation.

8. It is suggested that most of the food was consumed in community centers. I find this difficult to believe since weekly portions were distributed (for 6 days a week). Does this mean women came to the community centers every day and group sessions were organised?

Response- In general, till the end of 2nd trimester women visited feeding centres and consumed food supplement at CNCs. The food supplement sessions were organized by BRAC the implementing organization, in both the ICDDR,B and government service area
at Matlab and also in many sub-districts which were then under the supplementation program. Only during the 3rd trimester and occasionally during the last part of the 2nd trimester the food was delivered at home by the project staff. Addressed in the manuscript under the subheading intervention in methods.

9. Discussion pg 14 last §: This is my main point of comment. I would really compare the two groups of women with different level of schooling more than it is now the case. The statement that materal education explains different effects on child mortality and adherence deserves a more solid analysis. Did the two groups for instance differ in BMI which might explain the higher compliance for food for lower schooled women? If the main objective is to assess the effect modification by schooling , I think a descriptive table with the characteristics of these women (age, parity, BMI at inclusion, father’s schooling, hemoglobin at inclusion) really necessary. I would replace table 1 by such a table (current table 1 is already published).

Response – addressed, that table is now added.

10. Finally, why wasn’t father’s schooling used for stratified analysis?

Response- We considered maternal education would indicate her own SES, would relate to her own adherence to the intervention, we used mother’s schooling as the main stratifying variable. Further, although father’s schooling has the same median value as mothers schooling, 6year, and some differences in mean, and the maximum value, paternal schooling did not discriminate the effects of the intervention by showing reduction in child mortality as mother’s schooling did.

Father’s schooling <6 years UFe60F vs. Father’s schooling <6 years EMMS, HR=0.42, (95% CI: 0.18 to 0.96).

Minor Essential Revisions
1. Please check your data again. It seems there are 3625 liveborn and not 3659. This number refers to the number of women analysed. I base myself on the JAMA paper and also the data mentioned in this paper (later on on page 11 ‘mortality paragraph’). Also the JAMA paper mentions that usual supplementation started at 20 weeks. In this paper 17 weeks is mentioned (pg5, abstract)

Response – Total 4436 women were recruited in the study who had 3659 live births. All of these women and their children were included in analysis if the women had information on schooling resulting in 3591 women, 3591 live births, 36 twin births and 3627 children included in analysis. This is now addressed in methods under study subjects and participants. The usual invitation started in 17 weeks of pregnancy.

2. Abstract: add the stratification variables in the methods section
Response- Addressed in the manuscript.

3. Abstract: second line of results add “a little less to micronutrient”. If expressed in % the difference in food supplements is much larger compared to the difference in capsules.

Response- Addressed in the manuscript.

4. ‘Statistical analyses’ section: you mention that you have tested the differences in baseline characteristics, however, this doesn’t make that much sense. Your power is too low to test such small difference and it is no a study hypothesis.

Response- This is now corrected and baseline characteristics are tested between higher and lower schooling groups. We agree that our study does not have enough power to test such small differences.

5. ‘Statistical analyses’ section. Not so much is mentioned on the stratified analysis by HH asset score. Also explain how interactions were tested.

Response- Now addressed in the manuscript.

6. ‘Statistical analyses’ section. You mention that you conducted analysis on the effect of food supplementation and MMN on mortality, replace this by that the analysis was previously done (+add reference to JAMA paper).

Response- Addressed in the manuscript.

7. Results section. Last line first paragraph: you reports expenditure status and daily wager. However, nothing is mentioned in the methods. Please enlist all items you have been asking about (also the ones not statistically significant) in methods section.

Response- Now addressed under the methods under a new subheading variables.

8. “Adherence to food and MMN supplements’ section. The first 3 lines are a bit redundant. I think it’s logic that less supplements will have been taken by women starting at 20 weeks. I would drop these lines, results are in table anyhow.

Response- Addressed in the manuscript.

Discretionary Revisions
1. pg 5 bottom. ‘if pregnancy was confirmed by ultrasound and gestational age was <14 weeks she was randomized” This seems not very logic if the early food supplementation starts at 9 weeks already. Does this mean that early food was before 14 weeks rather than at 9.5 weeks on average?
Response – Almost always women went for ultrasound at around 9 weeks of pregnancy. The 14 wk criterion was kept as the maximum time limit when she was still considered to be randomized to early, or usual invitation to prenatal food supplement.

2. pg 6 Interventions – section: ‘ongoing’ instead of ‘on-going’

Response – Addressed.

3. pg 7: is the company’s name Apex or Aprex? For the eDEM device.

Response – Aprex is the correct company name.

4. post hoc is written in italics

Response – corrected.

5. The P for P-value, is always a capital letter, and in most journals it is italic.

Response – corrected.

6. student t-test (italic)

Response – corrected.

7. Results section (pg10), line 4,5 and 6: replace ‘and’ by ‘vs.’ For the comparisons between brackets.

Response – addressed.

8. pg 11: 4th last line: “households” instead of “household”.

Response – now corrected.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests