Author’s response to reviews

Title: Nutritional status of children under 5 years of age in the Brazilian Western Amazon before and after the Interoceanic Highway paving: a population-based study.

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Author’s response to reviews: see over
Cover letter

We are resubmitting the manuscript “Nutritional status of children under 5 years of age in the Brazilian Western Amazon before and after the Interoceanic Highway paving: a population-based study.”

Reviewer’s recommendations were followed and the manuscript was reduced from 49 to 36 pages. Five tables were excluded, and all sections were summarized, as suggested. We adopted the STROBE recommendation for reporting observational studies, as before, and decided to maintain some statistical details on the manuscript, because we think this is important in evaluating manuscript results.

We hope the reviewers find this new version more concise and focused than before.
Referee 1

Reviewer's report
Title: Nutritional status of children under 5 years of age in the Brazilian Western Amazon before and after the Interoceanic Highway paving: a population-based study.
Version: 1 Date: 14 March 2013
Reviewer: Marcelo Bönecker
Reviewer's report:
GENERAL
This is an interesting study as it draws attention to the link between nutritional status and geographical location in preschool children in Brazil. There are about fifty pages of manuscript, so it turns the reading extremely heavy. The text needs to be rewritten and focused and in doing so it could be shortened substantially.

ABSTRACT
Results: it is necessary to mention the meaning of BMI (Body Mass Index?)

- The meaning of BMI was explained in the text.

INTRODUCTION
The entire introduction should be shortened. For example, paragraph 4 and 5 can be removed. It is necessary a paragraph describing the main purpose of the study at the end of the introduction.

- The Introduction section was rewritten, the 4th paragraph was removed and the 3rd, 5th and 6th paragraph were rephrased. The purpose of the study is described in the last sentence of the last paragraph.

METHODS
This section is generally confused. There is a lot of unnecessary information in the methods, information that is not related with the variables associated to the outcome. The authors can summarize the information concerning the “study area” and “comparison of city characteristics before and after the Interoceanic Road” sections.

- The Study area section and comparison of city characteristics, and the section describing the construction of the wealth index were reformulated. Some details on the statistical analysis were maintained in the text in order to provide readers with the certainty that statistical issues inherent to the design of the study were properly handled.

Concerning study design and population: Did the authors include in the study patients with systemic and neurologic diseases? It is possible to have bias in the study depending of these criteria (eg. Children with diabetes or anemia)

- The Census included children with anemia and intestinal parasitosis, as shown previously in Table 3, however no association between anemia and undernutrition was found in the final statistical model. No other
important systemic disease was referred by the child mother or guardian, therefore no children with diabetes or neurological diseases were included. A paragraph containing a discussion regarding the association between anemia, intestinal parasites and undernutrition was included in the Discussion section.

You could usefully include a section on who collected the data (outcome and variables). Who collected anthropometric measures? It was a trained examiner? This information is not in the manuscript.

- A description of who collected the anthropometric measures and other data was included in the last paragraph of Study design and population section.

The authors assessed the family socio-economic status based on a household wealth index, however data on family income is a better predictive of socio-economic status. It will be useful to include this data in the study.

- Data on Family income had many missing values, especially in 2003, and it was not possible to use it. The reasons for that were explained in ins 133-139 of the manuscript.

Please summarize statistical analysis.

- We summarized the statistical analysis, however we maintained the necessary details as required in the initiative STROBE (Strengthening the Reporting of Observational studies in Epidemiology, http://www.strobe-statement.org/). The statistical analysis was complex because we wanted to be sure that no superestimations of the magnitude of the reported associations were made. However, to make the manuscript more concise and focused we described some of the statistical procedures performed but only included in the results and tables the most important results.

RESULTS
There are too many tables and additional files for a manuscript. The authors need to focus on main results.

- See reply above. We excluded all additional tables, and reformulated Tables 1 and 4 to make them more focused.

DISCUSSION
The are many results (values) repeated in the discussion. There are many unnecessary paragraphs. It is better to focus to discuss main results. It is recommended to not use unpublished data.

- The whole discussion section was rewritten. Some data was excluded from the results and also from the Discussion section. The findings by
Martins et al. have already been submitted for publication elsewhere, and we maintained it in the text because their findings are relevant for this manuscript.

CONCLUSION
There are many results (values) also repeated in the discussion. The authors need to focus and write the conclusion succinctly and according to the objectives of the study.

- The whole conclusion section was rewritten.

POINTS:
1. Is the question posed by the authors well defined? No
   - The introduction section was rephrased.
2. Are the methods appropriate and well described? No
   - The statistical methods were summarized to some extent.
3. Are the data sound?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? No
   - We disagree from the reviewer. The manuscript adheres to STROBE, which is the most relevant standard for reporting observational study. The reviewer can specify which specific guideline was not observed so we can make amends on the text.
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes
6. Are limitations of the work clearly stated? Yes
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? No
   - We performed grammar revision to improve the quality of writing.
Referee 2
Reviewer's report
Title: Nutritional status of children under 5 years of age in the Brazilian Western Amazon before and after the Interoceanic Highway paving: a population-based study.
Version: 1 Date: 5 June 2013
Reviewer: Mourad Moursi
Reviewer's report:
Major compulsory revisions

1. Major compulsory revisions

1- While the title of the article and the introduction clearly make reference to the construction of the Interoceanic Highway, the research questions around it are not well defined. In the background section, the authors write that their objective is to "assess possible changes in nutritional status and factors associated with these disorders, caused or facilitated by the construction of this road". This is a vague objective and a very broad topic leading to confusing interpretation of the limited available data. The paper mixes the topics of population migration, nutrition transition, education, and access to health care. In the best case scenario, there is a very limited number of variables on each topic, and in the worst case there is no data at all. Please redefine the analysis objectives in light of the limitations of the dataset.

- The Introduction section was rewritten, the 4th paragraph was removed and the 3rd, 5th and 6th paragraph were rephrased. We opted for maintaining the title.

2- Consequent to that lack of well-defined research questions in the introduction, the discussion suffers from repeated educated guesses and extensive external referencing about what might have affected the increase in stunting and overweight found in this paper. The fact is that those extended explanations and discussions are actually not supported by the data. Therefore, the discussion ends up being a collection of well-known and studied factors to which this paper contributes nothing other than saying that those factors may have affected the results too but without knowing for sure. The discussion needs to be substantially shortened and refocused on the discussion of results that are supported by the data and the analysis.

- Discussion section was shortened and refocused.

3- Another major concern in this analysis is sample size and possible attrition bias. According to the populations sizes and percentages of 0-4 children reported, one would expect about 476 children in 2003 (3668 multiplied by 13%) and 782 (6017*13%) in 2010. The respective sample sizes reported are 200 and 388. Since this study was designed as an exhaustive survey of all children in Assis Brasil, where does the difference come from? Maybe it is because the study focuses on urban areas only? This is not clear from the current description. Why were only urban areas chosen if this is the case? This needs to be clarified and
its implications fully discussed since there is no sampling strategy here. What happens when a whole section of the population is purposively selected for the study and another whole section is left out? How can results be extrapolated from that?

The study focused on urban area only, because before 2003, there was no paved access to Assis Brasil, and what is called ‘urban area’ was in fact a conjunct of isolated dwellings mostly build of wood in unpaved streets. At that time access to urban area was difficult, what made it an isolated area, and therefore the possible changes that occurred during this decade after paving were of very much interest for us, and justified our interest in this particular setting.

At the same time, logistic conditions for conducting research work in rural and riverine areas in the Amazon requires a very complex structure, since there are no paved roads anywhere, both in 2003 and in 2010.

Therefore, the census was conducted in the urban area only in both years, and this is clearly stated in the manuscript (lines 111-115). There was no sampling bias as suggested by the reviewer since the main purpose of the study

4- Related to sample size, I am extremely concerned about the very small number of actual outcome cases in this dataset. The number of children suffering from the outcomes of interest ranges from 2 (!!!) to a maximum of 46. With these extremely small samples sizes, the choice of logistic regression and odds ratios becomes even more problematic (see Nemes S et al. Bias in odds ratios by logistic regression modeling and sample size. BMC Medical Research Methodology 2009, 9:56; just one example out of many that can be found on the topic).

The authors carried out additional modeling that should work better for small sample sizes. In the results section, paragraph 10, they report that no differences were found between the reference models and models controlling for small sample size citing additional file 4 in the process. I vehemently disagree and do not understand how the authors can ignore the differences. Authors chose to focus on ORs that did not change much and dismissed everything else altogether.

A close look at additional file 4 shows that compared to the reference model, the exact OR does not converge for wealth index. For open sewage, it moves from statistical significance (p=0.001) to being non significant at the 5% level (p=0.07). For maternal height, the OR moves from 3.72 to 4.74, a 27% increase, hardly stuff that can be dismissed. They wealth index and open sewage are key results on which this paper is built. These issues should at least been extensively debated in the discussion section. Unfortunately, in my opinion, the analysis conducted in this paper, i.e. logistic regression and reporting odds ratios, should not be carried out because of the extremely small sample size. Maybe it would be better to do a whole new analysis on continuous z-scores.
We agree with the reviewer that the number of events are small, and this poses limitations for the study. The reviewer is correct when noting that wealth index did not converge, and maternal height lost significance with exact modelling. However, this is a very statistical point of view that does not take into account epidemiological evidence, supported by several other studies cited in the text. We think, in fact, that although the exact model provides a more complex statistical analysis, it is not taking into account solid epidemiological and biological evidence provided by other studies, which the simpler modelling method confirmed. That is why we opted for maintaining the glm results.

Minor essential revisions

5- Malnutrition is a term that encompasses both under and overnutrition. Overweight and obesity are forms of malnutrition. Please do not oppose malnutrition and overweight as if they were on extreme opposites of the same spectrum.

- Malnutrition has changed to undernutrition.

6- Change weight-per-height for weight for height

- Changed as recommended.

7- For children older than 2 years of age, consider working with BMI-for-age instead of just high weight-for-height

8- When the cut-off of -2 z-score is applied please use the terms of stunting (instead of low height-for-age), underweight (instead of low weight-for-age), and wasting (instead of low weight-for-height).

- The report was limited to stunting e overweight, as suggested by other reviewers.

9- Please substantially shorten the methods section. Below are a few examples about what can be done but please do not limit the exercise those specific examples.

a- The comparison of city characteristics before and after the road is too long and contains too much useless details. For instance, methods section, paragraph 4 (about number of establishments, the court, the university) can be entirely deleted. The rest should be shortened.

- This was modified as suggested by this and other reviewers.
b- Paragraph 7, please do not list all the variables collected. Some of them are not presented in the results (and therefore have no use for this particular analysis), and the ones we do care about are listed in the results tables.

- This was modified as suggested by this and other reviewers.

c- Paragraph 8: please do not list all the goods used to come up with the wealth index. It suffices to say that it was based on 21 consumers goods and appliances.

- We think it is important to describe which goods were used in the construction of the wealth index. However, the description of the whole procedure was shortened.

d- Paragraph 9: on PCA and how it was conducted, please shorten the description.

- This was modified as suggested by this and other reviewers

10- Results: please avoid putting in the text all the numbers that are already presented in the tables.

- This was modified as suggested by this and other reviewers.

11- The authors currently have 3 tables (tables 1 to 3) reporting a very long list of background descriptive characteristics. Some of that information is not essential to the interpretation and discussion of results and is not even mentioned later on in the paper. Please delete all unnecessary variables and combine those 3 tables into one.

- As this population has not been described before, we feel it is important to maintain the three tables. However, a few variables were deleted.

12- For a given variable in tables 1, 2, or 3 do not report 2 percentages when one is enough to provide the information. For instance, in table 3, "diarrhea in the last 15 days", report only "present", no need for "lacking" one can deduce it. Same thing for anemia diagnosis, report only "yes", there is no need for "no".

- As this population has not been described before, we feel it is important to maintain the three tables. However, a few variables were deleted.

13- References: the number of papers cited here is 69. That is excessive for this kind of manuscript. Please delete unnecessary references and limit the references to only one paper where appropriate.

- The number of references was reduced to 50.
Discretionary revisions
None

Quality of written English: Needs some language corrections before being Published
- We performed grammar revision to improve the quality of writing.
Referee 3
Reviewer’s report
Title: Nutritional status of children under 5 years of age in the Brazilian Western Amazon before and after the Interoceanic Highway paving: a population-based study.
Version: 1 Date: 9 June 2013
Reviewer: Kaleab Baye

Reviewer’s report:
This is an interesting study with lots of data generated and the authors should be commended for this. The questions to be addressed are well posed, the title conveys the message, and the data are sound and the discussion and conclusion, except in some cases (see below), are balanced and supported by the data. Published as well as unpublished works on which the authors are building up are clearly acknowledged. However, there are certain limitations in the methods used and in the form of reporting that make interpretation difficult. Some of the limitations of the study are also not clearly stated. The writing could be improved both in the language and organization. Reviewing would have been much easier if the lines were numbered.

Major Compulsory Revisions
1. Two cross-sectional data were used to evaluate changes in nutritional status that might have occurred as a result of the construction of the interoceanic highway. Some of the parameters used to evaluate possible nutritional changes are short-term variables (WH, WA, etc.) and are likely to be affected by the situation prevailing during data collection. For instance, the number of children having diarrhea 15 days prior the survey in 2003 and 2010 is significantly different. Therefore, it cannot be excluded that the higher prevalence of low WA may be due to a possible epidemic during the survey in 2003, and hence the changes in WH and WA prevalence cannot be ascribed to the construction of the interoceanic highway. Preferably, the comparison should be made only on long-term variables (i.e. stunting). If data on short-term variable are to be included the limitations associated with it should be clearly stated.

- Short-term variables were excluded from the manuscript and both methods, results and discussion were rewritten.

2. The following sentences presume that there has been a dietary change as a result of the construction of the interoceanic highway; however data on dietary patterns have not been collected. These arguments are not backed by adequate data and thus if need for stating it, it should be clearly indicated that these are hypotheses to be tested.

§13: “It appears that the convenience and “novelty” factor may have influenced the mother or guardians…. which replaced everyday foods”…. “It is suggested that this unforeseen dietary change, made possible by the interoceanic highway maximized the nutrition transition phenomenon”
Similarly, §14: states that there is increase in sedentarily, this is not backed by data.

- All this comments were excluded from the manuscript, as suggested. The only comment that remained about sedentariness is when the process of nutritional transition as described by reference 24 is explained.

3. In the statistical analysis part, the authors stated that: “the distribution of the independent variables was identified using student’s t-test to compare means”. This statement is not clear. It is evident that the normality of the data (distribution) cannot be assessed using t-test, but the comparison of means can be. This sentence can preferably be separated into two. The first indicating the test used for normality (distribution) of the data and the second, the method used for comparison of means (presumably t-test2).

- The statistical analysis was corrected and the name(s) of the test was included in line 193, as suggested above.

4. Regarding the form of writing, the manuscript can be made more concise by removing some less important details. This will make the conveying of the essential message to the reader easier. Table and figure captions can be made clearer. Standard terms in describing nutritional parameters should be used. i.e. Low weight-for-age, low weight-for-height… and not low weight-per… BMI and not IBM… More standard abbreviations for Z-scores of height-for-age, weight-for-height and weight-for-age (HAZ, WHZ, and WAZ) should be used. In addition, some paragraphs that belong to the results section are found in the methods section and vice-versa.

- We rewrote the manuscript as suggested. Abbreviations were changed to HAZ and WHZ, and BMI as asked. Introduction sections was rewritten, Results was rewritten and made more concised. Discussion was rewritten in order to avoid repetitive information and excluding unnecessary data. Methods section were abbreviated in the Study area section and comparison of the city was switched to the Results section. We opted to maintain a somewhat detailed statistical description to make sure readers will understand how we came up with the results and how some important statistical issues were handled (e.g. having more than one child per household, having small number of events for some of the variables and how we dealt with children that were not born in the urban area of the city), but such results were not shown and all additional files were deleted to make the manuscript more concise.

- Some new information was added in the Methods section, according to other reviewer’s request.

5. The absence of information on the number of years of maternal residency in
2003 is a limitation and should be stated. The cross-sectional nature of the study limits the comparison between 2003 and 2004, in particular for short-term nutritional parameters. Thus caution on interpreting short-term variables should be noted.

- Short-term outcomes were excluded from the manuscript. A comment on the limitation of the study due to the lack of the information on years of maternal residency was included in lines 476-482.

**Minor and discretionary revisions per section**

**A- Abstract**

*Minor Essential Revisions*

**Background:**

5. “...to analyse the prevalence of extreme nutritional conditions and associated factors...” Would read better if stated as: ‘...’ to analyse the prevalence of undernutrition and overweight...The term extreme nutritional condition is somewhat odd.

- Background has changed as suggested above.

6. “Polulation-based cross-sectional study in children under 5 years of age ... Assis Brazil.” This should be moved to the methods section of the abstract.

- This sentence moved to method section of the abstract.

**Methods**

7. The prevalence of underweight (instead of nutritional deficits) was obtained....

- It was changed as suggested by reviewer.

8. Z-scores were calculated relative to WHO 2006 reference data.... Instead of “all indicators were obtained from the WHO 2006 reference data” as currently stated.

- It was changed as suggested by reviewer.

9. More standard abbreviations for Z-scores of height-for-age, weight-for-height and weight-for-age (HAZ, WHZ, and WAZ) should be used. This comment applies to the rest of the paper as well.

- It was changed as suggested by reviewer in the whole paper.

**Conclusion**

*Minor essential revisions:*
10. “… the arrival of people in search instead of searching…”

- It was changed as suggested by reviewer.

Discretionary Revisions
11. “The growth of overweight within this malnutrition scenario reveals the nutritional transition in the country.” This study can only tell us that nutrition transition is occurring in the municipality of Assis and thus the current findings should not be generalized for the country.

- The sentence has been changed to limit the interpretation of the findings for the municipality only.

B- Background
Minor Essential Revisions
12. 2nd paragraph: “The Brazilian Northern region, where the state of Acre is located…” preferable to rewrite it as: The Northern region of Brazil…

- It was changed as suggested by reviewer.

13. On the same sentence: … showed twice the prevalence of low height and weight values…
Low height and weight value does not mean anything unless put in relation to age or height; this part of the sentence should be removed or corrected.

- Rephased as “prevalence of low height-for-age (HAZ) and high weight-for-height (WHZ) were 14.8% and 6.2%, respectively”

C- Methods
Minor Essential Revisions
Study area
14. In 2000 had a total … authors should specify, i.e. In 2000, Assis had… Comparisons of city characteristics before and after the interoceaninc road.

- It was changed as suggested by reviewer.

15. This section is misplaces and may be well placed in the results section. Study design and population

- This section has changed to results.

16. “Principal component analysis (PCA), carried out using the XLSTAT software… this statement is misplace and should be moved to statistical analysis.

- This text moved to statistical analysis.
17. Results of the principal component analysis should be moved to the results section and should not be part of the methods section.

- Most of the description of PCA methods refers in fact how the index was constructed and are not results per se. The results refer to the range of the sum of scores, which was in fact excluded from the text. We summarized the section describing the construction of the wealth index score but maintained in in the Methods section.

Statistical analysis
18. The authors stated that: “the distribution of the independent variables was identified using student’s t-test to compare means”. This statement is not clear. It is evident that the normality of the data (distribution) cannot be assessed using t-test, but the comparison of means can be. This sentence can preferably be separated into two. The first indicating the test used for normality (distribution) of the data and the second, the method used for comparison of means (presumably t-test).

- The statistical analysis was corrected and the name(s) of the test was included in line 193, as suggested above.

19. “The factors associated with DHA…” abbreviation not defined

- DHA was replaced by “undernutrition”.

20. “No statistically significant interaction terms were identified. No important influential points were identified for any of the…” Not clear, these two sentences should be re-rewritten.

- The sentence were rewritten as: “The existence of significant interaction terms was evaluated and none was found …. Diagnostic test were applied to identify outliers”

Discretionary Revisions
21. In my opinion, the study area section has too much detail unlikely to add any essential information to the interpretation of the results of this study. This section can be shorted for the sake of brevity.

- The Study area section and comparison of city characteristics was reformulated.

D- Results
Minor Essential Revisions
22. The first paragraph of this section belongs to the methods section.
Parental and child socio-economic characteristics in 2003 and 2010

- Transferred to methods section.

23. “… the average age was 2.43 years in 2003 and 2010…” should specify the
average age in 2010.

- Average age is the same for 2003 and 2010. The sentence was rewritten to clarify it.

24. §4: “Table 3 shows the characteristics of children under 5…” what characteristics? please specify. This comments also applies to the table caption (table 1).

- Caption for Table 3 was rewritten as “Individual socio-demographic, birth and breastfeeding characteristics, and morbidities. The word “family” was added to captions on Table 1.

Prevalence of anthropometric extremes
25. “Table 4 shows the prevalence of anthropometric indicators of malnutrition and overweight…”

Overweight is also a form of malnutrition. The word malnutrition should be changed to undernutrition.

- Changed to undernutrition.

Low height-for-age
26. Last §: “Also, no important differences…” should be replaced by “ No significant differences….

- Changed as recommended.

27. Low weight-per-height should read as low weight-for-height

- These nutritional indices were excluded from the manuscript.

E- Discussion

Minor Essential Revisions
29. 1st §: “However, the population growth in the period from 2003 to 2010 was better than usual”

Odd sentence formulation; the population growth cannot be better but higher…. 

- Changed as recommended.

30. “The municipality did not ….resulting in increased areas of invasion”. The word invasion is of negative connotation, can use illegal settlements if relevant.

- Changed as recommended.

31. “Longitudinal studies could better elucidate whether there is any recovery process in relation to linear growth after the three first years”. It is already
established that reversing stunting past the age of two is difficult if not impossible.

- This sentence was excluded from the manuscript.

32. The second and third paragraph should be merged into one and the same Paragraph
- Changed as recommended.

33. §9:="...” although the reduction in the prevalence….Brazilian Northern region…” Clarify, rewrite.
- Discussion was reformulated and this sentence was excluded from the manuscript.

34. §10= “Obesity occurs more often in the first year of life , between 5 and 6 years of age, and adolescence” May be rewritten as:”obesity occurs more often in the first stages of the life cycle or in the first stages of the life cycle…
- Changed as “in the first years of the life cycle”.

35. §13: 1st sentence requires reference
- Reference 23, 24 and 25 were added to this sentence and the sentence per se was reformulated.

36. §17: Souza et al – referencing should be consistent. This reference is missing.
- Reference 17 was already in the text. The year of the study was added to the text.

37. §18: “In the study, for the year 2003, each new pregnancy increased the chance of a low height-for-age in children under 5 years by 35%” Is it the pregnancy that increases the chance of a low height-for-age? Can be restated as: Gravida was associated with a 35% increase in low height-for-age in children under 5 years of age.
- Rewritten as: …… In this study, for the year 2003, each new pregnancy increased by 35% the chance of an already existing child under 5 years of age to develop low height- for-age.