Reviewer’s report

Title: Exploring telomere length in mother-newborn pairs in relation to exposure to multiple toxic metals and potential modifying effects of nutritional factors

Version: 0 Date: 23 Oct 2018

Reviewer: Aleix Sala-Vila

Reviewer’s report:

This is a cross-sectional study in a mother-child cohort in Argentina aimed to investigate whether certain toxic metals and micronutrients in body tissues (blood, urine, placenta) relate to relative telomere length. The authors conclude that many tested exposures, either nutritional factors or toxic metals, influence relative telomere length in mother-newborn pairs in a tissue-specific manner. The underlying hypothesis of the paper and the analytical methodology is sound. However, there are some main pitfalls.

- Lack of pre-specified hypothesis. The authors need to specify what hypothesis are they testing, and construct statistical models accordingly. If thinking on a particular nutrient/toxic (hypothesis testing), please clearly state the rationale for doing so in the "introduction" and show unadjusted and adjusted models, including (if needed) other exposures as covariates. In contrast, if planning an "exploratory analysis" (i.e. does any micronutrient / toxic relate to telomere length? If so, which ones?), use stepwise (parsimonious) models adjusting for risk factors, allowing the entrance of pre-selected nutrients / toxics. Working with patterns or clusters seems more interesting that focusing on a particular exposure, unless (as said before) the authors are working with a pre-specified hypothesis. With the current approach the results might also be prone to positive results multiple hypothesis testing.

- In line with this, the paper would be much improved if the authors discussed the clinical relevance of one/two main findings rather than unduly expanding the amount of shown data. The Discussion, which is too long, would improve if built around a clear and concise message.

- Table 3a. Statistical analyses are oddly explained in the footnote. For instance, why the model with "cobalamin" as exposure is adjusted for "zinc, folate, homocysteine and COBALAMIN"? This reviewer presumes that the models were reciprocally adjusted (included all covariates except the dependent variable), but this should be better explained.

- Did the authors calculate the needed sample size? If not, this limitation should be acknowledged.

- The study is entirely descriptive / associative and provides neither a cause-effect relationship nor novel mechanistic insight. Hence, authors need to be sure that they do
not imply a cause-effect relationship. Only associations can be identified in cross-sectional data. So, please avoid using words (in relation to obtained data) such as "impact" (e.g. lines 85, 338...), "effect" (e.g. lines 339, 346...) or "influence" (e.g. lines 53, 54, 341).

Minor points:

- Line 40. Please define "ICP-MS".

- Table 2. Why superscript "a" appears for first time after "b"?

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Not applicable

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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