Author's response to reviews

Title: Effect of maternal calcium intake during pregnancy on children blood pressure. A systematic review of the literature.

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Author's response to reviews: see over
Dear Dr da-Silva,

Re: Manuscript Ref 6709610391058574 “Effect of maternal calcium intake during pregnancy on children blood pressure. A systematic review of the literature.”

We have now modified the above paper taking into account the referee comments.

Please see detailed below for our response to the reviewers.

We hope that you will now consider this manuscript suitable for publication.

Many thanks for your time.

Yours sincerely,

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Response to Reviewers Comments

Manuscript Ref 6709610391058574 “Effect of maternal calcium intake during pregnancy on children blood pressure. A systematic review of the literature.”

We would like to thank the three reviewers for their useful and constructive comments.

We have rewritten the manuscript in line with these comments and believe the article has benefited from these changes.

Reviewer 1 - Matthew W Gillman

Major Compulsory Revisions

1. Reviewer: Some details of search strategy and study selection are missing or unclear. What do the authors mean by "insufficient?" (page 4, Methods line 2).

   By “insufficient” we intended to say that if the evidence from randomized trials was limited (i.e. small trials, trials of bad quality, etc) to assess the effect of the intervention, then data from observational studies would be included. We have expanded the text to make this point clear.

Reviewer: Under types of outcome measures (page 5), what do they mean by hypertension, adjusted by age? It would seem that continuous BP should be adjusted for age as well.

   We have also added more details on the definition of hypertension (see point 5, Minor Essential Revisions). The strategy for reporting crude and adjusted outcome measures is now described in the “Details of analysis methods” section of the paper.

Reviewer: Under selection of studies (page 5), the authors should summarize the "pre-specified criteria."

   The "pre-specified criteria" refers to the study inclusion criteria stated in the methods section (i.e. Types of studies, Types of participants, Types of intervention or exposure, Types of outcome measures). The text was changed to clarify this issue.

Reviewer: How did the authors find unpublished studies? (page 6, top). Was the strategy to find unpublished studies standardized?

   We didn’t have a strategy to find unpublished studies. We added a paragraph to the text acknowledging this issue.
Reviewer: Under Details of study, it seems as though the authors extracted data on covariates (chiefly for observational studies), but they do not so state.

This was stated in the second paragraph of the Details of Analysis Section. “When adjusted analysis was performed, type of analysis and factors adjusted for were recorded.” We have added a paragraph in the data extraction section to clarify this issue.

2. In text and tables, when the authors specify a calcium dose, it is unclear whether the dose is elemental Ca or the Ca salt. The authors should specify the salt and the amount of elemental Ca for each study, eg, 1000 g calcium carbonate, which is equivalent to 400 g elemental Ca.

Calcium was expresses as elemental calcium. This issue is now stated in the text.

3. Reviewer: The authors should address publication bias, either quantitatively or at least qualitatively.

We produced a funnel plot to assess publication bias. The figure is not very informative given the small number of studies. We have included the conclusion of these analyses in the text and added a new reference.

Minor Essential Revisions

1. Under Quality assessment (page 7), what does "processed" mean?

The paragraph was rephrased.

2. Reviewer: The authors should remove the word "significant" from the ms. They use the term in many different ways, causing confusion.

The word significant is now used only to express “statistical significance”. All other instances of the word were removed from the text.

3. Reviewer: In particular, the authors should not refer to statistical significance, but rather to effect sizes and confidence intervals.

The text was rephrased to comply with this recommendation. Only a few instances of the word significant are left in the text.

4. Reviewer: The authors refer to examining effects of foods and supplements separately as "controversial." They should specify what the controversy is, given that this approach is fairly standard in nutritional epidemiology.

It is not clear if the sub-group analysis by food and supplements was pre-specified. The text was rephrasing to clarify this point, and a new reference on the strengths of the evidence from subgroup analysis was added.

5. Reviewer: Text and tables. What were the definitions of high SBP or hypertension?
A paragraph with definition of high blood pressure used in the article was added.

6. **Reviewer: Figure. The authors should say what the size of the box and length of the line represent**

These legends were added to the figure.

7. **Reviewer: Language. Some edits are needed, e.g.,**

- logistical v. logistic
- conduct v. conduction
- misplaced "only"
- mispelling of McGarvey
- "This" without a noun
- subject-verb agreement
- mixing present and past tense

The English in the paper was revised.

**Discretionary Revisions**

1. **Reviewer: It is curious that the authors define a 2 mmHg difference in either DBP or SBP as "clinically significant" (page 6) It seems as though this point could be in the Discussion, but does not have to pre-specified since it does not change the analyses.**

Two reviewers criticized this statement, and we acknowledge that it is out of context in the methods section. We have removed the paragraph from the methods section of the paper.

2. **Reviewer: The authors question whether BP measurements in observational studies were blind to levels of exposure (page 10). It would be very unusual cohort study in which blinding did not obtain.**

We stated that blinding was not reported in the papers. This is one of the items in the Moose guidelines for reporting systematic reviews of observational studies.

3. **Reviewer: "All five studies seem to be well conducted" (page 10). By what criteria?**

By the criteria in the Moose guidelines, as was stated in the methods section.

**Reviewer 2 - Ruth Morley**

**Major Compulsory Revisions**

1. **Reviewer: In the last sentence of the abstract: “and may be a way to prevent hypertension and its sequels in the next generation” is too strong and should be replaced by “and may be a way to reduce the risk of hypertension and its sequels in the next generation”**.
We have changed the abstract according to this suggestion.

2. Reviewer: On a population basis, it has been estimated that a reduction in diastolic blood pressure of 2 mm Hg would result in a 15% reduction in risk of stroke and transient ischemic attacks and a 6% reduction in risk of coronary heart disease[15]. Thus, a difference of 2 mm Hg in systolic or diastolic blood pressure was considered clinically significant.
What this says to me is that there are no data on the clinical relevance of a small change in systolic pressure. If this is true it would be better to say so. Otherwise please define and justify a clinically relevant change.

Two reviewers criticized this statement. We have removed the paragraph from the methods section of the paper.

3. Reviewer: Page 8. For the Belizan study please provide N randomised in the private hospital and total N randomised.

Number randomized in the private hospital added.

4. Reviewer: Table 3. Baseline N needs to reflect number randomized in the RCTs, not number selected for follow up. There could be a footnote indicating N selected for follow up.

The two randomized trials included in the review are multi-center trials, and the randomization was stratified by center. The authors choose to follow-up subjects from only one center. It can be assumed that because the randomization was stratified by center selecting only one center would not result in a bias effect estimate. Subjects randomized at other centers cannot be considered loss-to-follow-up. However an impact on external validity can be expected. This is now commented in the results and discussion section of the paper. The total number of patients randomized, selected for follow-up, and lost-to-follow-up are in table 1.

5. Reviewer: Discussion. In the first paragraph of the discussion: it is not true that the largest RCT (need reference) was the only study with a small loss to follow up. It had over 50% loss because only subjects from the private hospital were followed up. The authors need to discuss the possible implications, in terms of bias, of selective follow up for both RCT.

See point 4.

6. Reviewer: The conclusions need to state explicitly the need for large and well-conducted randomised trials, and I think it would be fair to indicate that future studies should also investigate the effect of maternal calcium supplementation on other cardiovascular risk factors.

We have included the reviewer’s suggestion in the new version.

**Minor Essential Revisions**
1. Reviewer: More recently experimental and observational studies in humans and animals have reported an association between maternal calcium intake during pregnancy and blood pressure in the offspring [5,6], with some studies showing contradictory results[1,7]. would be better as More recently some experimental and observational studies in humans and animals have reported an association between maternal calcium intake during pregnancy and blood pressure in the offspring [5,6], but others have not [1,7]. We have included the reviewer’s suggestion in the new version.

2. Reviewer: There are a number of minor typographical errors, to be expected from authors whose first language is not English. I anticipate that these will be dealt with during the editorial process.

The English in the text was revised.

3. Reviewer: Please replace calcium maternal intake with maternal calcium intake.

We have included the reviewer’s suggestion in the new version.

4. Reviewer: sudden death syndrome (bottom of page 6) should be sudden infant death syndrome.

We have included the reviewer’s suggestion in the new version.

5. Reviewer: Page 10, last para of methods: For two studies, a small sample size was also a significant problem. Please provide references to these studies.

References added.

6. Reviewer: Please provide a reference to I2

There are now four references to I2 in the manuscript (references 16-19).

Discretionary Revisions

1. Reviewer: In the conclusions, calcium deficit might be better as low calcium intake.

We have included the reviewer’s suggestion in the new version.

Reviewer 3 - Malinee Laopaiboon

Major Compulsory Revisions

1. Reviewer: The authors did not define the cut of point of hypertension, which is very important as it is the main outcome.
Because this is a systematic review we have to use the cut-off point used by the authors of the original papers, as we do not have access to the raw data. In the revised version of the review we are now reporting the cut-off point values used in the included papers.

2. Reviewer: Table 4 shows data of offspring blood pressures in four levels of calcium intake of the women. It was unclear which groups provide the data of the crude and adjusted effect size.

The effect size in table 4 is the regression coefficient between maternal calcium intake and offspring blood pressure. It does not refer to a single level of calcium intake. We have added a footnote to table 4 to clarify this issue.

3. Reviewer: The results of pooled effect size for studies in children at 1 year or more may be not appropriate as the studies were different in various methodological aspects, especially the various period of outcome measure.

We believe that although there are differences between the studies, a pooled estimated is informative for the reader given the relatively small heterogeneity between studies for children over one year of age. We have stated in the discussion the limitation of the evidence from the pooled estimate.

4. Reviewer: Conclusion of the paper seems to be based on the statistical significant result of binary outcome of the Belizan’s trial (1997). However, the result of difference of means systolic blood pressure of the trial at the same time (7 years of age) was not significant -1.4 (-3.2 to 0.5). The difference of the results direction between two scaling measurements of the same outcome must be discussed. But this is not found in the paper. The results of this paper is not convincing for the evidence in supporting the association of calcium maternal intake during pregnancy and offspring blood pressure.

We have added a paragraph to the discussion comparing the results of the binary and continuous outcome for this trial.