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

Authors:

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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.

The paper was also edited by the Manuscript Presentation Service at the University of Aberdeen as the editor suggested.

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 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

None

Minor Essential Revisions

1. Reviewer: The issue of calcium as salt v. elemental calcium is not resolved. For example, in Table 2 the authors say that Hatton et al. (2003) provided 2 g elemental Ca daily as calcium carbonate. This seems implausible, as it implies a 5 g tablet. The authors need to look at each component study very carefully and tease out the real amount of elemental calcium (even if the individual study authors got it wrong!)

Women did receive 4 tables of 1.25 g each, for a total of 5 g of calcium carbonate.

One of the authors of this systematic review (Eduardo Bergel) was directly involved in the design and conduction of one of the randomized trials included in the review (Belizan et al, 1997). In this trial women were randomized to receive 2 g of elemental calcium daily in the form of 4 pills with 1.25 g of calcium carbonate each for a total of 5 g of calcium carbonate. Calcium carbonate is 40% elemental calcium and 5 g provide 2 g of elemental calcium. The amount of calcium supplementation used in the trial was based on previous studies on calcium metabolisms during pregnancy suggesting that such a large dose was required.

The trial by Hatton et al. (2003) clearly states in one of their papers (Levine et al. 1996) that the dose was 2 g of elemental calcium in the form 4 tables of 500 mg of elemental calcium each:

“Calcium tablets contained 500 mg elemental calcium in the form of calcium carbonate. A daily dose of 2000 mg elemental calcium was selected in order to equal the highest dose administered in previous trials.”
References:


Discretionary Revisions

None

Reviewer 2 - Ruth Morley

Major Compulsory Revisions

None

Minor Essential Revisions

None

Discretionary Revisions

None

Reviewer 3 - Malinee Laopaiboon

Major Compulsory Revisions

1. Reviewer: The main importance is heterogeneity between results of studies in children 12 months or more. The authors present that it was very small (I2 < 1 %). I am not sure whether the result is correct. If we consider the figure 1 of the 4 studies under sub-group of age 12 months or more, we can see that the I2 should not be < 1%). However, I could not check the results as I am not sure if the data of observational studies is enough to be used in the I2 analysis.

The value of I2 is 9.4%. There is a typo in the text, (I2 < 1%) should be (I2 < 10%). We thank the reviewer for spotting this mistake, which was corrected in the new version. However, the the results and discussion section was based on the correct value of I2 (I2 < 10%). A I2 value of 9.4% is indicative of a very low degree of heterogeneity. A value of I2
below 25% is considered as indicative of low heterogeneity, 25% to 50% as moderate heterogeneity, and > 50 as high heterogeneity (Higgins et al. 2003).

We have attached the computer output produced by the METAN command in the statistical package Stata (Stern et al. 2001) with the results of the meta-analysis, and the data needed to reproduce the analysis (effect size and confidence intervals). The same result can be obtained with Revman (The program used by the Cochrane Collaboration).

<table>
<thead>
<tr>
<th>Study</th>
<th>ES</th>
<th>[95% Conf. Interval]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGarvey 1990</td>
<td>-4.280</td>
<td>-8.945 -0.385</td>
<td>9.84</td>
</tr>
<tr>
<td>Morley 2004</td>
<td>-0.800</td>
<td>-4.171 2.571</td>
<td>18.84</td>
</tr>
<tr>
<td>Belizan 1997</td>
<td>-1.400</td>
<td>-3.282 0.482</td>
<td>60.49</td>
</tr>
<tr>
<td>Hatton 2003</td>
<td>-4.800</td>
<td>-9.249 -0.351</td>
<td>10.82</td>
</tr>
<tr>
<td>I-V pooled ES</td>
<td>-1.938</td>
<td>-3.402 -0.475</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Heterogeneity chi-squared = 3.31 (d.f. = 3) p = 0.346
I-squared (variation in ES attributable to heterogeneity) = 9.4%

Test of ES=0 : z = 2.60 p = 0.009

References:


2. Reviewer: If the comment of the heterogeneity results of studies in children 12 months or more as mentioned in 1 is correct, the final conclusion of this review have to be modified. Please check this point as the figure seems to be not relevant to the numerical result of < 1%.

As stated in point 1 the value of I2 (9.4%) is indicative of a very low degree of heterogeneity.

3. Reviewer: From my previous comment 2 “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 authors’ response is not clear, “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.” The unclear point is that why the authors present calcium intake in 4 categories and what is the criteria of the classification.
Table 4 shows offspring systolic blood pressure by quartiles of maternal calcium intake. We have added the word “quartile” to the legend of the quartiles column in table 4 to make this point clear.

To explore the association between exposure and outcome by presenting outcome levels by exposure quartiles is common practice in epidemiology (Rothman and Greenland, 1998). With a few exceptions, the original articles included in the review presented the data this way. Please see below a table with calcium maternal intake presented by quartiles in one of the original articles included in the review as an example of the type of data sources used for table 4.

References

Table in McGarvey et al. 1991.

Table 4. Mean Infant Blood Pressure by Quartiles of Maternal Prenatal Intake of Nutrients

<table>
<thead>
<tr>
<th>Nutrient quartiles</th>
<th>Hospital</th>
<th>1 month</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>Potassium quartiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) &lt;3,610.8</td>
<td>71.2</td>
<td>42.2</td>
<td>82.4</td>
<td>42.5</td>
</tr>
<tr>
<td></td>
<td>(51)</td>
<td></td>
<td>(45)</td>
<td></td>
</tr>
<tr>
<td>2) ≥3,610.8−&lt;4,111.9</td>
<td>71.0</td>
<td>42.6</td>
<td>77.3</td>
<td>39.2</td>
</tr>
<tr>
<td></td>
<td>(51)</td>
<td></td>
<td>(41)</td>
<td></td>
</tr>
<tr>
<td>3) ≥4,111.9−&lt;4,687.4</td>
<td>69.8</td>
<td>42.2</td>
<td>79.0</td>
<td>42.3</td>
</tr>
<tr>
<td></td>
<td>(52)</td>
<td></td>
<td>(41)</td>
<td></td>
</tr>
<tr>
<td>4) ≥4,687.4</td>
<td>70.3</td>
<td>41.1</td>
<td>78.4</td>
<td>42.0</td>
</tr>
<tr>
<td></td>
<td>(52)</td>
<td></td>
<td>(46)</td>
<td></td>
</tr>
<tr>
<td>Calcium quartiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) &lt;1,380.5</td>
<td>71.5</td>
<td>42.1</td>
<td>82.4</td>
<td>41.0</td>
</tr>
<tr>
<td></td>
<td>(49)</td>
<td></td>
<td>(42)</td>
<td></td>
</tr>
<tr>
<td>2) ≥1,380.5−&lt;1,722.9</td>
<td>70.8</td>
<td>42.6</td>
<td>81.8</td>
<td>43.1</td>
</tr>
<tr>
<td></td>
<td>(52)</td>
<td></td>
<td>(45)</td>
<td></td>
</tr>
<tr>
<td>3) ≥1,722.9−&lt;2,048.2</td>
<td>70.2</td>
<td>41.8</td>
<td>77.9</td>
<td>41.2</td>
</tr>
<tr>
<td></td>
<td>(53)</td>
<td></td>
<td>(48)</td>
<td></td>
</tr>
<tr>
<td>4) ≥2,048.2</td>
<td>69.9</td>
<td>41.7</td>
<td>75.5*</td>
<td>40.9</td>
</tr>
<tr>
<td></td>
<td>(52)</td>
<td></td>
<td>(44)</td>
<td></td>
</tr>
</tbody>
</table>

Minor Essential Revisions

4.1 Reviewer: In Mcgarvey (1990), please check the offspring age at 3 months in the figure is not consistent to that in table 4 (6 months).

We have corrected the typo in figure 1 (3 month changed to 6 month).
4.2 Reviewer: On page 9, the authors present at the middle of the page that ‘In summary, the two randomized trial included[22,25]…………’. The reference of 25 should be 21, if the previous description of included studies is correct.

We have changed the reference.

5. Reviewer: For the response to the other reviewer about quality assessment for the observational studies. I am not sure whether the information related to MOOSE guideline is appropriate for the recommendation on the assessment. The MOOSE is a guideline for reporting systematic review of observational studies.

We agree, MOOSE is a guideline for reporting systematic reviews of observational studies. That being said, the guideline does include recommendation on the elements that should be taking into account to conduct the quality assessment of observational studies in the context of a systematic review, and we followed those recommendations.