Author's response to reviews

Title: Dietary calcium intake and mortality risk from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies

Authors:

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Author's response to reviews: see over
July 13, 2014  
Joanna Denyer, PhD  
Senior Assistant Editor  
BMC Medicine

RE: MS 1271514873127659 R1  
Title: “Dietary calcium intake and risk of mortality from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies”  
Authors: Xia Wang, Hongxia Chen, Yingying Ouyang, Jun Liu, Gang Zhao, Wei Bao, and Maosheng Yan

Dear Dr. Denyer,

Please find the revised MARKED manuscript with changes highlighted and the revised CLEAN manuscript attached. Please also see below for a response to the Editor’s comments and a point-by-point response to the reviewers’ comments.

Thank you for carefully reading the manuscript and providing positive comments. To address the reviewers’ comments, we carefully revised the manuscript as the reviewers suggested.

We feel that the quality of the manuscript has been significantly improved as a result of the revisions. We hope that the revised manuscript is suitable for publication in BMC Medicine. However, if further changes are needed, please feel free to contact me.

Thank you for your kind consideration.

Kind regards,

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Response to the reviewers’ comments:

Reviewer: 1

Comments:
Major Compulsory Revisions
None

Minor Essential Revisions
Figure 3 should be redrawn with 800 mg/d as the 1.0 relative risk of CVD mortality. This will permit the reader to quickly see that both low and high calcium intake is associated with increased risk of CVD below about 300 mg/d and above 1250 mg/d.

Why was the figure changed from using 800 mg/d to 500 mg/d?
The abstract should be revised in accordance with this revision, stating optimal, lower and upper values which become statistically significant.

Response:
Thank you for your careful review of our manuscript.
Some studies(1, 2), showed that individuals in some populations have a low calcium intake, not higher than 500 mg/day. To compare the curves of both CVD mortality and all-cause mortality, both CVD mortality and all-cause mortality should ideally use the same reference. Originally, reviewer 2 did not think that Figure 3 was optimal. He or she required that curves used the same reference. Moreover, considering that the shape of both curves was optimal, we used 500 mg/d as the reference intake. We changed the figure from using 800 mg/d to 500 mg/d.

However, to state this issue the reviewer raised, Figure 3 was marked at 800 mg/d, which will permit the reader to quickly see that intakes around 800 mg/day conferred the lowest risk of cardiovascular mortality. We regret that Figure 3 was not be redrawn with 800 mg/d.

Comments:
The sentence in the abstract “The risk of all-cause mortality did not decrease further at intakes above 900 mg/day.” Is not clear. It would help if Figure 4 showed the results for calcium intake and all-cause mortality rate. My computer is not functioning well, so I was unable to look at it. It would be better if the readers could easily see it.

Response:
We agree with the comments. As the reviewer suggested, we have carefully revised the manuscript. We marked at 900 mg/d in the graph, which will permit the reader to clearly see intakes around 900 mg/day.

Comments:
p. 10, lines 11-12. Not clear what is meant by “vitamin D may influence the adverse effect of dietary calcium.” Do you mean reduce? Increase?

Response:
Thanks for the reviewer’s comments. We agree with the comments. Text revised as directed.
**Comments:**
- Discretionary Revisions

While the English grammar is better, there are still some errors:

p. 10, lines 19-20: “some studies suggests” should be “some studies suggest”

Therefore, please have a technical editor review the manuscript again.

In addition, as noted above, some passages are unclear regarding meaning.

**Response:**

To correct some errors and typos, we have asked a bilingual scientific editor with relevant training to proofread the revised version of the manuscript.

p. 10, lines 19-20: “some studies suggests” was revised to “some studies suggest”

In addition, as the reviewer suggested, we have carefully revised some passages to make it clear regarding meaning.

For details, please refer to the point-by-point response to the comments and suggestions of the reviewers (below).

**Comments:**

In Table 2, p = 0.076 should be p = 0.08

**Response:**

Text revised as directed.
Reviewer: 2

Comments:
My only point that was not addressed was this one:
“It would be helpful to see the levels of intake contributing to the curves indicated
on the graph, so the reader can see where the bulk of the data is, and how many
studies / observations are in the extremes.”
The authors have answered it with a detailed summary of their methods, which
as they state are now standard, and I have used them many times myself.
However, my point was that, additionally, the graph could indicate on the horizontal
axis where the data are on which it is based, e.g. using tick marks.
This is sometimes useful to know, because curvature can sometimes be induced
by a cohort effect rather than a real effect, e.g. where the curve is based on just
one cohort that has used a different dietary assessment tool, or with greater
measurement error, the different RR for the more extreme intakes do not reflect
true nonlinearity. So it’s nice to know that the curvature is based on several
studies, not just one. I apologise that I had not made this point clearer, but it is
just a minor point, and I’m happy for the authors to leave this off if it is problematic
for them.
There description of the test for nonlinearity is now much better, and describes
the test more in line with what I would have anticipated.

Response:
Thank you for your careful review of our manuscript.
In several studies (3, 4), the graph indicated positions of the included studies by using
tick marks on the horizontal axis. It would be a very nice thing to see such a graph.
We are trying to do, but now we still can not do good. We are very sorry about it.
Point-by-Point Response to Reviewers provided below:

Page 1, line 19: Change “between about 900 and 1100 mg/day” to “at intakes around 900 mg/day”
Page 3, line 10: Delete the first “mortality”
Page 8, line 2: “was” instead of “is”
Page 8, line 4: Insert the word “dietary” before “calcium”
Page 8, line 21: Change “between about 900 and 1100 mg/day” to “at intakes about 900 mg/day”
Page 10, line 2: Change “between about 900 and 1100 mg/day” to “at intakes about 900 mg/day”
Page 10, line 4-12: The part was revised to “Vitamin D, directly or indirectly, enhances renal conservation of the absorbed calcium and intestinal absorption of calcium. Some studies have noted that serum 25-hydroxyvitamin D levels, the major circulating metabolite of vitamin D, are inversely correlated with cardiovascular disease incidence rates. The coadministration of calcium with vitamin D may reduce the adverse effect of dietary calcium. Therefore, to explore a potential source of heterogeneity in our results, we also considered vitamin D status associated with dietary calcium intake. However, subgroup analyses showed that dietary calcium intakes were not significantly associated with all-cause mortality in studies that adjusted for vitamin D status.”
Page 10, line 18: “suggest” instead of “suggests”
Page 11, line 5: Insert the sentence “However, in the present study, sensitivity analyses showed similar results.” at the end of the passage.
Page 12, line 11: “related” instead of “relate”
Page 13, line 20: Change “are” to “were”

4 Greenwood DC, Threapleton DE, Evans CE, et al. Glycemic index, glycemic load,