

Anita Jain
Editor The BMJ
29 June 2015

Dear Dr Jain,

Re: BMJ.2015.026209 "Systematic review and meta-analysis of calcium intake and bone mineral density"

Thank you very much for your provisional acceptance of the manuscript. We appreciate the Editors' and Reviewers' helpful comments and suggestions and have responded to them as below. We think the companion paper submitted on calcium intake and fracture (BMJ.2015.026208) is complementary to this work and so we have revised the paper in light of the possibility of co-publication. All the resulting changes to the manuscript have been highlighted using the track changes function, and clarified specifically below.

We believe our responses adequately address the reviewers' concerns and hope that the manuscript is now acceptable for publication. We look forward to hearing from you.

Yours sincerely

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Editors comments:

Detailed comments from the meeting: The committee felt this was an important and relevant topic. We had no specific criticism of the design or methods of the study. First and foremost, we would like you to revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. Please also respond to these additional comments by the committee:

***We would like you to tone down dismissal of significant results**

Response:

In the previous version, we deliberately made statements about the effectiveness of calcium based on both this paper and the accompanying manuscript (BMJ.2015.026208). We thought that when the results were taken together, they allowed definitive statements to be made. Based on this suggestion and that of Reviewer 1, we have removed the concluding statement in the Abstract conclusion and the penultimate paragraph in the Discussion, and reworked and rewritten the concluding paragraph of the Discussion so that the focus is on the bone density results alone. We have retained the text arguing that the effects on bone density are unlikely to translate into significant fracture reductions and the reasons for this view are clearly laid out in the Discussion. We do not think there is any dismissal of significant results in this revised version.

***Please share more details on publication bias as that may help with interpretation of the significant but small results**

Response:

We are not sure what further details would be useful. As indicated in the text, about half the Funnel plot/Eggers regression analyses with enough studies suggested that the data were skewed toward positive results with calcium. We have clarified in the text that the asymmetry was due to an imbalance of small and moderate studies with outlying large effect sizes in favour of calcium. One possible reason for this is publication bias, but other causes are also possible.

As explained under Reviewer 1, point 4, we do not think that publication bias is responsible for the small and consistent effects of calcium on bone density, but it may account for the asymmetry of funnel plots, and may lead to an overestimation of the effect of calcium on bone density.

***Please discuss implications of the observed heterogeneity where this was high**

Response:

We have added text to the limitation section of the Discussion addressing this.

“Another limitation is that in 60% of the meta-analyses, statistical heterogeneity between the studies was high ($I^2 > 50\%$). This indicates substantial variability in the results of trials included in these analyses, although this was often due to the presence of a small number of outlying results. Sub-group analyses generally did not substantially reduce or explain the heterogeneity. We used random-effects meta-analyses that take into account heterogeneity

and their results should be interpreted as reflecting the average result across the group of trials.”

Reviewer: 1

Comments:

BMJ.2015.026209 Tai V et al. Systematic review and meta-analysis of calcium intake and bone mineral density General Comments This ms. is very well prepared and represents a thorough analysis of available randomized controlled clinical trials, but a few substantive issues and a few minor aspects of English construction require additional consideration.

1. Several years ago, a meta-analysis by Shea B. et al. (Endocr Rev 23:552-559, 2002) arrived at a similar conclusion based on only a few RCTs as the current results reported by Tai et al., but no mention of the Shea ms. is included. On far fewer RCTs, Shea reported that a higher calcium intake was beneficial to bone measurements (BMD), though the quantitative skeletal improvement in treated vs. control subjects was small and not statistically significant.

Response:

We have added a sentence summarising the Shea meta-analysis in Paragraph 2 of the Discussion. This analysis was published in 2002 and only considered calcium supplements not dietary calcium. For each site, there were fewer than 10 studies and there was insufficient power to compare the time-course of effects.

“The results are consistent with an earlier meta-analysis of 15 RCTs of calcium supplements, which reported an increase in BMD of 1.6-2.0% over 2-4 years.⁷²”

2. In the current report (Tai et al.) statistically significant improvements in BMD at practically all skeletal sites except the forearm (mid-shaft?) were found (Tables 1-5), even though the differences were small, so small that the authors considered that a reduction of fractures would be highly unlikely. In my opinion, the statements regarding “no benefit” made by the authors may be a little too strong. Therefore the Conclusion of the Abstract and the final (concluding) paragraph of the Discussion should be toned down a little (and rewritten), even though the probability of any fracture reduction is very low. Perhaps, a new concluding paragraph could be added that would be congruent with the Abstract conclusion.

Response:

As explained under the response to the Editors, we have removed the concluding statement in the Abstract conclusion and the penultimate paragraph in the Discussion, and reworked and rewritten the concluding paragraph of the Discussion so that the focus is on the bone density results alone. We did not use the term “no benefit” and are not certain which statements the Reviewer refers to. We think the issue is not that increasing calcium intake either from calcium supplements or dietary sources has no benefit on BMD (because our results clearly show it does), but that the benefits are so small that they are unlikely to translate into fracture prevention, as the Reviewer acknowledges. We hope the new concluding paragraph will address the Reviewer’s concerns about the tone.

“In summary, increasing calcium intake from dietary sources increases BMD by a similar amount to increases in BMD from calcium supplements. In each case, the increases are small (1-2%) and non-progressive, with little further effect on BMD after 1 year. Subgroup analyses do not suggest greater benefits of increasing calcium intake on BMD in any subpopulation based on clinically relevant baseline characteristics. The small effects on BMD are unlikely to translate into clinically meaningful reductions in fractures. Therefore, for most individuals concerned about their bone density, dietary calcium intake does not require close scrutiny.”

3. Statistically significant differences have been ignored under Primary Analyses on page 8, but the findings were so consistent that they deserve mention.

Response:

We are not certain which differences the Reviewer refers to. In this section, we report the significant increases in bone density for dietary calcium and that all the increases for calcium supplements were significant. We have carefully reviewed the text and cannot find any places where we have ignored significant differences.

4. It is not clear why publication bias was invoked to apply to these statistical findings across the board; could another explanation account for the highly consistent findings following 1 to 2 years or so of treatment with calcium from foods or supplements?

Response:

Publication bias was only invoked to explain the finding that about half the funnel plots/Egger’s regression analyses appeared skewed toward positive results for calcium- that is, the funnel plots were asymmetrical. We have clarified this point in the text. We agree with the Reviewer that the explanation for the consistent effects observed is that taking calcium supplements or increasing dietary calcium intake increases bone density by a small amount.

“Using Egger’s regression model and visual inspection of funnel plots, data appeared skewed toward positive results with increased calcium intake from dietary sources or supplements in about half of analyses that included 5 or more studies. The funnel plot asymmetry was due to more small-moderate sized studies reporting large effects of calcium on BMD than expected, raising the possibility of publication bias.”

Specific Comments

5. Forearm measurement: Which site was measured? Forearm mid-shaft or distal (wrist)?

Response:

Different papers used different sites in the forearm. We used all data reported for the forearm in the original paper regardless of the specific site, and where there was more than one site reported, we used the closest site to the 1/3 radius site. We have clarified this in the Methods.

“BMD can be measured at several sites in the forearm, although the 1/3 radius is most commonly used. For each study, we used the reported data for the forearm, regardless of site, and if more than one site was reported, we used the data for the site closest to the 1/3 radius.”

6. Page 4, line 13: Why were no references placed at the end of this sentence? Should this sentence be included?

Response:

This sentence “Recently, concerns have emerged about the risk-benefit profile of calcium supplements” introduces the idea that the adverse effects of calcium might outweigh its benefits. The following sentence states explicitly what the concerns are, and includes relevant references. Therefore, we think it is reasonable to include the sentence and that it does not require references.

7. Grammatical issues:

- 1. Overuse of we. Too repetitive!**
- 2. Overuse of There are, There were, There is, It is, and similar constructions. Too repetitive!**

Response:

These are style rather than grammar issues. We consciously attempted to write in the first person which necessitates the frequent use of “We” rather than using passive voice constructions. We think this approach is consistent with the BMJ house style.

- 3. Improper conjunction, such as on page 9, line 55. Start a new sentence with Thus,**
- 4. Subject-verb agreement, such as page 10, line 26. Effects ... suggest [plural].**

Response:

We have corrected these two points.

Reviewer: 2

Comments:

These researchers have again performed a detailed meta-analysis of RCTs, and this time they have examined the effect of calcium from supplements or foods on bone mineral density. The topic is of great importance since calcium supplements are used by many and an increase in the intake of calcium from foods has for long been promoted. The methodology is sound and the manuscript is very well presented. Some few remarks are found below:

- 1. Since the osteoid content (immature non-calcified bone) and bone turnover is lower at cortical bone sites than in cancellous bone, the authors might wish to further elaborate in the discussion about the more modest short-term effect of calcium (<1 year) on BMD at the total body compared with the effect on the total hip and spine (the latter sites have a higher proportion of cancellous bone compared with the total body). Is there a possibility to test for the homogeneity or heterogeneity of the estimates between these different sites, also by time of follow-up? Or do the authors find the differences in BMD response at the diverse sites small/non-significant, and not worthy to be commented?**

Admittedly, there could also be other explanations for the differences related to technical aspects of the DXA measurements.

Response:

We agree that the effects on the total body site from calcium supplements or dietary calcium are smaller than other sites. We are not sure whether this has clinical relevance or not. Most agents in current use for osteoporosis show the same pattern, in that changes in bone density at the spine are greater than those at the hip, which in turn are greater than those at the total body site. It is interesting that the effects at the forearm for calcium supplements were similar to other sites, and the forearm site is considered to be enriched for cortical bone. This suggests that the issue is not simply a cortical/cancellous difference. We think the point the Reviewer raises is interesting but we felt that addressing the specific point and related issues in the Discussion would be over-speculative and might distract from the major finding that the increases at all sites were very small, did not increase over time, and are unlikely to be of clinical importance.

2. Can the authors translate the effect on BMD by calcium supplementation to a theoretical impact on overall and hip fracture relative risk reduction, i.e., to the reader provide the actual estimates? The reader can then compare these theoretical estimates with those obtained in the accompanying manuscript dealing with fracture outcomes.

Response

We have added the following text to the Discussion to address this helpful suggestion. This new text now leads immediately on to the section discussing the effects that both weak and potent antiresorptive agents have on BMD and fracture.

“Epidemiological studies suggest that a decrease in BMD of one standard deviation is associated with an increase in the relative risk of fracture of approximately 1.5-2.0.⁷⁵ A one standard deviation change in BMD is approximately equivalent to a 10% change in BMD. Based on these calculations, a 10% increase in BMD would be associated with a 33-50% reduction in fracture risk. Therefore, the 1-2% increase in BMD observed with increased calcium intake would be predicted to produce a 5-10% reduction in fracture risk. These estimates are consistent with findings from RCTs of other agents. The modest increases in BMD with increased calcium intake are...

3. Stratified analyses were performed by baseline dietary calcium intake or baseline 25-hydroxyvitamin D. Cut-offs of 800 mg calcium and 50 nM 25-OH-D were used and the conclusion made by the authors is that there existed no interaction between supplementation and these baseline variables. There ought, however, to be an average lower threshold in calcium intake and in vitamin D status, leading to true deficiency/osteomalacia, not captured by the meta-analytical approach. Pooled individual data might reveal such thresholds - and also an interaction between calcium intake and S-25-OH-D - and the authors might wish to acknowledge this limitation in the Discussion. E.g., rickets or osteomalacia can be developed at relatively high S-25-OH-D concentrations with a concomitant very low calcium intake whereas rickets is not developed when the individual has a high calcium intake even though S-25-OH-D is very low.

Response:

We agree with the Reviewer that such analyses would be valuable and have added text to the Discussion section on future research on this point.

“In subgroup analyses, we stratified trials by thresholds of baseline dietary calcium intake (800 mg/d) and 25-hydroxyvitamin D (50 nmol/L). However, the clinical consequences of low calcium intake or vitamin D status such as osteomalacia probably only occur at much lower thresholds, and there might also be interactions between calcium intake and vitamin D status. Analyses of individual patient data would be valuable in exploring these issues further.