tdelamothe@bmj.com

Subject: BMJ - Decision on Manuscript ID BMJ.2015.026209

Body: 01-Jun-2015

Dear Dr. Bolland

Manuscript ID BMJ.2015.026209 entitled "Systematic review and meta-analysis of calcium intake and bone mineral density"

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

https://mc.manuscriptcentral.com/bmj?URL_MASK=5170446e14d84c34bbf0fc8c25af75c6

Yours sincerely

Anita Jain
Editor The BMJ
ajain@bmj.com,

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are athttp://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option.
If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

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As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: Elizabeth Loder (chair), Angela Wade (statistician), Wim Weber, Georg Roeggla, Jose Merino, Anita Jain, Rubin Minhas

Decision: provisional acceptance

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
*Please share more details on publication bias as that may help with interpretation of the significant but small results
*Please discuss implications of the observed heterogeneity where this was high

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at
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d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis"

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a systematic review and/or meta-analysis:
point estimates and confidence intervals for the main results

one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
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Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

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a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional

data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
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Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREE COMMENTS

Reviewer: 1

Recommendation:

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

Specific Comments
Forearm measurement: Which site was measured? Forearm mid-shaft or distal (wrist)?
Page 4, line 13: Why were no references placed at the end of this sentence? Should this sentence be included?
Grammatical issues:
1. Overuse of we. Too repetitive!

2. Overuse of There are, There were, There is, It is, and similar constructions. Too repetitive!
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].

Additional Questions:
Please enter your name: John Anderson

Job Title: z

Institution: University of North Carolina

Reimbursement for attending a symposium?:

A fee for speaking?:

A fee for organising education?:

Funds for research?:

Funds for a member of staff?:

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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

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:
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.
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.
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.

Additional Questions:
Please enter your name: Karl Michaëlsson

Job Title: Professor and senior consultant

Institution: Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Date Sent: 01-Jun-2015