Author's response to reviews

Title: Fracture prevention with vitamin D supplementation: explaining the inconsistent results

Authors:

Gerbrand J Izaks (g.j.izaks@int.umcg.nl)

Version: 2 Date: 27 December 2006

Author's response to reviews: see over
Dear Editor,

Please find attached the revised manuscript "Fracture prevention with vitamin D: explaining the inconsistent results" by Gerbrand J. Izaks that I would like to submit to BMC Musculoskeletal Disorders.

I thank the reviewers for their valuable comments and I hope that the revised manuscript meets all their points of criticism. A detailed response is listed below.

Thank you for the opportunity to submit the revised paper to your journal.

Kind regards,

Gerbrand Izaks.
General response to the reviewers' comments

The reviewers' comments showed considerable overlap and I feel that most of their criticism was appropriate and useful. Therefore, I reconsidered my point of view and thoroughly revised the manuscript. Accordingly, I changed the format from "Debate" to "Research" as I think that this is the best way to address all concerns.

Other main changes are:
- more data on the role of adherence and achieved vitamin D level.
- discussion of other explanations for the discrepancy between the meta-analysis and subsequent RCTs.
- more cautious conclusions.

Reviewer 1: Dr Togerson

1. Another explanation: I agree with Dr Togerson and the manuscript was changed on this point.

2. Interpretation of funnel plots: Here also, I agree with the reviewer although I think that lack of sensitivity is not a big problem in my paper since asymmetry of the funnel plot can be clearly detected. Nevertheless, I acknowledge the problem that only a small number of studies was included and therefore, the conclusions are more cautious in the revised manuscript.

3. Y-axis funnel plot: "sample size" was replaced by "standard error of log risk ratio" [Systematic reviews in health care. Egger M, Smith GD, Altman DG, eds].

4. Wessex study Smith et al: As far as I know, this study is only available as an abstract. Therefore, I prefer to exclude it from this analysis.

Reviewer 2: Dr Hart

1. Cochrane review: I agree with Dr Hart that the Cochrane systematic review appears to be very fair and has more cautious conclusions than the meta-analysis. Unfortunately, however, the meta-analysis has attracted far more attention than the Cochrane review and is cited more often - in clinical practice as well as in the scientific literature. I think that this is not justified and therefore, the aim of my paper is to draw attention to the shortcomings of the meta-analysis.
2. Cochrane review 2: What my paper adds is, in my opinion, an explanation for the discrepancy between the meta-analysis and the subsequent trials and the Cochrane review. This point is marginally discussed in the Cochrane review.

3. Other reasons for discrepancy: I agree with the reviewer on this comment and I think that the revised manuscript meets this point of criticism.

4. Premise of argument unsubstantiated: this phrase was removed from the manuscript.

Reviewer 3: Dr Jones

1. Manuscript too long: as the manuscript was thoroughly revised, this comment may no longer apply.

2. Dose and level of vitamin D: these points were added to the revised manuscript.

3. Conclusion too strong: according to Dr Jones' suggestion, the conclusions were diluted.

4. Lack of publication bias: I am not sure if I understand the reviewers' comment correctly but I meant to say that there is no publication bias for hip fracture. I think that this comment is met in the revised manuscript.

Reviewer 4: Dr Adachi

1. Adherence to therapy: this point is addressed more extensively in the revised manuscript.

2. WHI and estrogen: Dr Adachi is right that the majority of the participants in the WHI trial was concomitantly enrolled in a hormone trial and I agree with him that this may be an important confounder. In the WHI analysis, however, there was no clear interaction between vitamin D with calcium supplementation and hormone therapy [NEJM 354 p. 678].

3. Limited benefit if adequate intake: I agree with the reviewer and this point is addressed in the revised manuscript.

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