Author’s response to reviews

Title: Vitamin D levels and deficiency with different occupations: a systematic review

Authors:

Daniel Sowah (sowahd@yahoo.com)
Xiangning Fan (x.fan@ualberta.ca)
Liz Dennett (liz.dennett@ualberta.ca)
Reidar Hagtvedt (hagtvedt@ualberta.ca)
Sebastian Straube (straube@ualberta.ca)

Version: 2 Date: 24 Mar 2017

Author’s response to reviews:

Dear Editor,

We would like to thank you and the peer-reviewers for the very helpful comments on our manuscript. We include a point-by-point response below.

For this revision, we submit the main manuscript file with changes tracked and we also submit a clean copy.

Occupational Vitamin D Reviewer’s comments

Please remove the 'Authors' Information' title from your manuscript.

Response: Addressed

>>> Please adhere to the PRISMA guidelines for reporting systematic reviews.
In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to PRISMA guidelines (http://www.prisma-statement.org/) for reporting systematic reviews. This is so your methodology can be fully evaluated and utilized. Can you please include a completed PRISMA checklist as an additional file when submitting your revised manuscript.

Response: Addressed

Reviewer reports:

Reviewer #1: Vitamin D levels and deficiency with different occupations: a systematic review.

An interesting angle on a global health problem assimilating a large number of studies via an extensive review.

I do however feel that the impact of the paper and its findings is reduced by the inclusion of some poorly defined occupational groups and unnecessary figures and that by clarifying aspects of the methodology and, where necessary, tightening the inclusion criteria a more impactful output could be produced.

Response: Thank you. We have thoroughly revised the manuscript and shortened the main text; details are described in response to the comments below.

Abstract:

Rates of vitamin D deficiency among healthcare professionals - could this data be presented in descending order of prevalence?
The abstract gives no indication of how the potential confounding by factors such as gender and body composition (which would be expected to differ significantly between occupational groups) may have been accounted for. Could this be added?

Response: We agree that this information would help inform the analysis. However, not all authors of the primary studies reported on this information, and this is a limitation of the systematic review.

Background:

A Japanese study demonstrated no significant differences in serum 25-(OH)D levels in shiftworkers working rotating shifts, including night shifts - can this sentence be expanded to clarify what the comparator to shift work was?

Response: Addressed

I am not convinced of the argument for using occupation status as a factor in risk screening over and above factors such as sunlight exposure which would be assumed to be directly related to vitamin D status. How would this improve the screening that is already possible, i.e if we ask people about sunscreen use and time spent outdoors is occupational status likely to be a better marker or likely to improve screening substantially given the likely variability in behaviours even within a specific job-family? The rationale for either asking about occupation in addition to or instead of current risk markers should be clarified.

Response: We are not suggesting occupational factors are the most important determinants of vitamin D status. However, with confounders adjusted for, occupational factors remain important in the determination of vitamin D status and therefore should be carefully considered as an important risk indicator, alongside other factors. Additionally, sunlight exposure is not the only
The use of Vitamin D-specific quality criteria is appropriate but I wonder whether a more general assessment of paper quality, suitable for cross sectional studies, could also be employed?

Response: Not all included studies in the systematic review were cross-sectional in nature; therefore a quality tool solely for cross sectional studies was not used.
The two paragraphs beginning on line 4 and line 22 of page 10 could be combined and tightened up to make the assessment of quality more succinct.

Response: We are not quite sure what this comment refers to. Neither on page 10 of the PDF (manuscript page 8) nor on page 10 of the manuscript (PDF page 12) does a paragraph begin on line 22. We presume the comment actually pertains to page 9, where quality is discussed: We have revised this part of the manuscript and shortened the text.

'Whenever there were three or more studies from an occupational group…' - how was he breadth of an occupational group defined and / or the number (3) deemed sufficient decided upon?

Response: The breadth of an occupational group was defined by the number of studies on the given group that were included in our review. We chose to only perform quantitative meta-analysis on occupational groups where three or more studies were published as we did not think meta-analysis on fewer than three studies would add additional information beyond that provided in the individual studies.

Given that one occupational group, such as healthcare, could be much broader than another, e.g. miners, I am not sure of the validity of applying a quantitative cut off. Please can you clarify if your occupational groups were defined a priori?

Response: The occupational groups were not defined a priori but were formed in the light of the search results. Details of the rationale are provided in the above response.

Is Cochrane handbook webpage needed in the main text since you also provide a citation?
'Some of the studies reported averages as geometric means without indication of a measure of spread and these were not included in the computation of the overall mean' - this could be combined with the sentence describing the same process for medians without IQR (line 20)

Response: Done

Not clear whether, when authors had already calculated % deficient/insufficient you utilised that data (if means were also provided) or calculated your own percentages. If author calculated % were used assume these were only allowable if they reported using the IOM cut offs? Please clarify.

Response: When authors had already calculated % deficient/insufficient, these data were used in our computation provided the appropriate cut-offs had been used. In order to calculate the overall percent deficient in an occupational group, we weighted the reported percentage in each study by the size of the study population. As mentioned below, the cut-offs mentioned in the manuscript were actually those of the Endocrine Society.

Results:

'Of the excluded articles, two were in Persian and one each was in Korean and Turkish.' As this only accounts for 4 of the 21 papers excluded perhaps indicate what the other main causes for exclusion were OR do not report in this and just give total number excluded.

Response: The statement has been deleted.
'Where reported, the proportion of participants who were women ranged from 0% to 100%. - give this wide range would the median gender split be more informative?'

Response: We have removed the statement and now give the overall % women.

'Based on the latitudes of study locations, the included studies spanned a range of latitudes' (Fig. 6A). - again not very informative. Could the exact latitudes be given (at the extremes of the range) or this sentence omitted?'

Response: Exact values for extremes of latitudes are now given in the text.

Did the shift work category exclude health care workers or was there overlap between these categories?

Response: The shift work category excluded healthcare workers based on primary study authors’ descriptions.

If authors of the original articles did not report that their samples of health care worked excluded shift workers, or that their sample of shift workers excluded healthcare workers were these studies excluded?

Response: If authors did not report that their samples of healthcare workers excluded shift work, that article would have been categorized under the corresponding healthcare worker category. If the authors reported that their sample of shift workers excluded healthcare, the studies would have been classified under shiftworkers and not excluded. However, in our systematic review, we did not encounter either scenario.
What was the benefit of including the studies where subjects were classified as 'other' or miscellaneous?

How would the vitamin D levels of this group help to address your question when their occupation could not be defined? Could you omit these from the paper and as such provide a more clearly defined sample?

Response: The other/miscellaneous category has been omitted as suggested.

The section relation to quality assessments is very long and repetitive. This information may be better presented in table format indicating the quality assessments for each paper and occupational group. The text could then focus on just the overall summary of the data, i.e., the overall % of studies that were high/medium/low (not divided by occupational group) and the overall frequency of different assay types.

Response: Addressed as suggested.

From results presented it seems that you did not calculate your own percentage deficiency/insufficiency although this was suggested in the methods? Was this done for any studies or were all % values provided by the original authors?

Response: Percentage values for deficiency and insufficiency were taken from the original papers or calculated from numbers of participants who were deficient/insufficient when these were provided in the original papers. It was not possible to back calculate % deficiency or insufficiency from other data.

How confident are you that your 'other' healthcare group did not include members of the specific professions already mentioned, e.g. nurses? (Especially since their results were not significantly
different from nurses and nurses are presumably the largest sub-division or healthcare worked). If this cannot be assured should these be excluded since there may be considerable overlap between the two groups and therefore this 'other' group does not add substantially to your findings. If there 'other' status can be assured please describe.

Response: Thank you. We acknowledge the reviewer’s comment. However, as we performed a systematic review of published studies, we are limited by how the primary study authors chose to define their occupational groups. We feel that this additional category still does include information of value, as it may indirectly capture the vitamin D status of other occupational groups linked to health care (e.g. hospital employees who are not healthcare professionals that are described in separate occupational categories).

The paper is very long. I feel it could be improved by removal of all potential ambiguous groupings and data so that the focus is firmly on those studies and participants from clearly defined occupational groups, e.g. excluding studies of unknown/ miscellaneous occupation and of 'other' healthcare. The data from these groups do not add to your conclusions. Similar there are a large number of figures presenting very similar data, e.g. % deficiency by latitude. These should be rationalised to focus on the key messages/ outcomes of interest.

Response: The major figures of the manuscript are original Figs. 1, 5A, 5B and 9 (now re-numbered as Figs. 1-4). Original figures 2, 3, 4 were included to clarify the comparison we intend to establish between certain occupational groups. Accordingly, we have now moved these figures as well as original Figs. 6-8 to the supplement.

Clinical implications

Given the high prevalence if deficiency you have reported is screening, for example in shift workers, really a justifiable approach?

Response: Screening is a justifiable approach because, even in a vitamin D deficient population, knowledge of the magnitude of the deficiency is required to inform clinical care. Further, not every individual from a group that on average is deficient will indeed be deficient herself/himself.
Given the logistical and financial implications of routine Vit D screening would attention be better focused at addressing assumed deficiency/ insufficiency rather than further attempts to check this is occurring?

Response: Addressed in response to the comment above.

Limitations:

'In the present study, we used the IOM's definition of vitamin D deficiency and insufficiency' - as mentioned previously please clarify whether by this you mean that values were recalculated or that only studies already reporting deficiency rates according to IOM cut offs were used.

Some of the potential confounders, such as gender and diet, are touched on but this does not acknowledge the limitations inherent in the occupational categories used which would seem to have a great potential for overlap and as such under or overestimating effects related to these artificial groupings. If the suggestions for removing ambiguous groupings are acted on this may be resolved but any remaining ambiguity should be addressed here.

Response: Actually, we intended to use the Endocrine Society’s cut-offs for vitamin D status and this has been corrected in the main text. Some of the ambiguous groupings have been removed, as described above. The calculation of % deficient or insufficient has been described above also.

References

Is it appropriate to present only a web link for an online reference, e.g. reference 2? I would expect to see additional information regarding author, site or document name and date accessed.

Response: Addressed
Tables:

Please ensure these are formatted according to standard publication guidelines/ journal specific guidance.

Could the date of the publication be included in the table? I appreciate numerical referencing is used but there is space under the authors to add a date and this would make the table much easier to interpret without needing to cross reference to reference list to see date.

Response: Addressed, added to Table 1.

Figures:

See previous comments about the number of figures currently presented.

Response: Addressed

Reviewer 2:

This manuscript presents a systematic review exploring the impact of occupation on vitamin D status. Although not specifically stated, it presents a meta-analysis of pooled data in an attempt to identify occupations at risk of low vitamin D status. While the aim of the review has merit, there are some methodological issues that undermine the findings.

GENERAL COMMENTS

1. Although the authors state that "...vitamin D and 25-(OH)D were used interchangeably", this is best avoided so as not to cause confusion. "Levels" should be used in relation to 25-(OH)D only whereas "status", "deficiency" and "insufficiency" should be used in the context of vitamin D.

Response: Addressed accordingly.
2. Further to point (1), there is some discrepancy regarding the authors definitions of deficiency/insufficiency (this relates also to the methods on Page 11). It is true that there is no international consensus on the 25-(OH)D levels defining deficiency/insufficiency etc. However, the authors' interpretation of the IOM report (for the US and Canada) is incorrect. The IOM recommends a population target of 50 nmol/L 25-(OH)D for vitamin D sufficiency. It's remit was not to define a level for deficiency but they suggest <30 nmol/L represents risk of deficiency and between 30 and 50 nmol/L represents risk of insufficiency. In light of this, use of vitamin D status terms needs reviewing throughout the manuscript.

Response: We thank the peer-reviewer for this crucial, insightful comment. The cut-off points in the manuscript were those of the Endocrine Society and thus, the text has been modified to reflect this.

3. The language is a little clumsy in places with some statements not making sense (e.g. background points 2 & 3 below). Please carefully proof-read for accuracy and clarity.

Response: We have now proof-read the manuscript multiple times, making changes to make it more clear.

SPECIFIC COMMENTS

Background

1. Page 4: The first sentence refers to the US population only but reference 2 relates to Canada. It should also be noted that the data in reference 1 is >10 years old but is presented as if current.

Response: We have re-worded this sentence.
2. P4, para 1: Vitamin D is not "implicated" in Ca homeostasis and bone health, its role is firmly established.

Response: Addressed

3. P4, para 2: It is not proven that endogenous vitamin D synthesis accounts for 90% of total acquisition, this is an estimate/assumption.

Response: Addressed

4. P4, para 2: It is important to note that 1,25-(OH)2D can be synthesised extra-renally, including in skin.

Response: Addressed – reworded to say that synthesis is primarily (not exclusively) in the kidney.

Methods and Results

The literature search criteria, and thus data included, are too broad to provide meaningful outcomes. Some studies are 30-40 years old. Changes in lifestyle, working habits/patterns and sun exposure behaviour have changed significantly, not to mention improvement in 25-(OH)D assay methods. Furthermore, and perhaps more importantly, skin colour and ethnicity is not taken into account in the analyses. This has a major impact on vitamin D status in terms of ability to synthesise vitamin D and sun exposure/protection behaviour which will undoubtedly confound the results. Lack of robust seasonal data is also an issue. Such confounders are mentioned in the discussion but are not addressed in the analyses. Overall, this systematic review would benefit from narrower search criteria in terms of publication year and target population in order to provide meaningful results and enable directed advice/recommendations.
Response: We acknowledge some of the limitations in the analysis. In performing the systematic review, our goal was to assess the overall impact of occupation on vitamin D status. Given that vitamin D deficiency was seen as a theme among multiple occupational groups, in multiple geographic locations, and in studies published over a number of years, we believe that the variables the peer reviewer has identified do not substantially change the overall conclusions. Additionally, individual studies did not consistently report on these variables, and they could not therefore be accounted for in the meta-analysis.

Statistical Analyses: The use of multiple t-tests, even with correction, is not an advisable approach and does not allow for meaningful interpretation. The aim of a meta-analysis such as this should be to determine whether occupation (essentially as a proxy for sunlight exposure) impacts on vitamin D status through relative risk analysis. This will show which occupations are of greater/lesser risk relative to the entire cohort. It would be advisable to re-analyse the data using more robust methods and re-write the discussion around the findings. At present, the discussion is very unfocussed and seems to comment on individual studies/groups of studies rather than the findings of the review.

Response: We appreciate the idea of reporting relative risk, and will do so for each occupational group, stating both high and low confidence interval limits, based on the proportions. Since we are amalgamating a number of studies that reported proportions, we combine these estimates based on established methodology. The multiple hypothesis correction allows us to conduct formal hypothesis tests to tease apart differences, but we recognize that interpretation is challenging, and we trust the relative risk calculation then aids interpretation.

References: Please proof read for consistency of presentation (e.g. journal abbreviations).

Response: Addressed

Figures: There are too many graphs. Latitude plots are unnecessary and too crowded to easily see the data. Re-analysis of data will guide the figures required. Refer to other meta-analyses for examples.
Response: Addressed – we have reduced the number of figures. Thank you.

We hope this answers the peer-reviewers’ comments to your satisfaction.

With best wishes,

The authors