Author's response to reviews

Title: Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis

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Author's response to reviews: see over
Dear Dr. Tom Rowles,

Executive Editor
BMC Anesthesiology

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Re: Manuscript ID 3080243741574285

Please find attached a revised version of our manuscript now titled, “Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis” which we would like to resubmit for publication in BMC Anesthesiology.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Please find attached revised version containing line numbers. In accordance with the reviewers’ suggestions, the entire manuscript has been revised for clarity, language, and formatting specific to your journal. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Anesthesiology.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of the editor

1. We recommend that you copyedit the paper to improve the style of written English.

*Response*: Thank you for your comment. We have copyedited for the style of written English and journal format.

2. Can you please include a completed PRISMA checklist as an additional file when submitting your revised manuscript. We would also ask that you include a completed copy of the PRISMA flowchart for your study as a figure in your manuscript.

*Response*: We have included PRISMA checklist as Additional File and included PRISMA flowchart as figure 1.

Responses to the comments of Reviewer #1

**Major Compulsory Revisions**

1. Line 175: Replace Ref. 24 with one of these papers and give an updated estimate of low 25OHD concentrations

*Response*: Thank you for your suggestions. We have updated a status of low 25OHD concentrations using Looker et al. article [line 201-205], which is reference 25 in the manuscript.

2. Lines 181-8. Consider these papers. They will result in a changed conclusion regarding 25OHD and mortality for those with sepsis.

*Response*: We looked into these articles and changed our conclusion of evidences of 25OHD and mortality in sepsis patients (line 210-212).

**Minor Essential Revisions**

3. Line 44: ultraviolet is radiation; light applies to the visible portion of the spectrum.

*Response*: We changed to radiation [line 44].

4. For Ref. 4, 5, consider instead or addition: Engelsen et al.

*Response*: We replaced this study as reference 5.

5. Figures 2-4: please state what is being compared. Is it 20 ng/mL?

*Response*: We added information in figure legend to state that vitamin D deficiency is compared with optimal vitamin D (25(OH)D $>$ 30 ng/mL)
Discretionary Revisions

6. Line 214: Perhaps the state of the art in treating those with sepsis can be discussed in a paragraph in the discussion section.

Response: We did not included current management of sepsis in general to the manuscript because the current guideline does not mention much about role of vitamin D supplementation. We did reviewed RCTs of vitamin D administration in critically-ill patients [line 217-225].


Response: We cited this article as recent RCT of vitamin D intervention in critical setting [ref. 38]

8. Title: The word "significant" might be added to the beginning of the title to indicate what was found in the meta-analysis.

Response: We added this word in the beginning of the title.

9. Line 86; 30 ng/mL is generally considered optimal rather than normal. My understanding of normal is that it is akin to mean or average. The global mean 25OHD concentration is about 54 nmol/L.

Response: We changed the definition to optimal [line 89-90].

Responses to the comments of Reviewer #2

1. A reasonable rationale is provided in the introduction. Sometimes the authors rely on the reader to draw conclusions based on statements made about results from papers. Overall points and ideas could just be stated more directly.

Response: We summarized results from studies that we referenced in the introduction.

2. This applies to the research question as well. The objective of this systematic review was to comprehensively determine the strength of association between vitamin D status and ....” Should also state secondary objectives and questions?

Response: We stated our research question, primary objective and secondary objective [line 62-66].

Major Compulsory Revisions [3-7]

3. The methods indicate that they would have included studies with 1,25(OH)2D . Did they find any? What did they show?

Response: We included finding of 1,25(OH)2D in result section [line 158] and table 1.

4. Please provide references for the 25(OH)D cut-offs? How did the authors operationalize this definition? Did they only includes studies that used this definition? How many different cut-offs
were used in the identified papers? Could results have differed based on cut-off?

**Response:** We provided reference for 25(OH)D cut-offs based on Holtick et al. article [line 88-91]. We included studies that defined vitamin D deficiency as <20 or vitamin D sufficiency or optimal as >30. We showed difference cut-offs between studies in table 1. Five studies used cut-off at <15 and four studies used cut-off at<20. Results should not be significant difference based on these different cut-offs.

5. The authors provide a definition for sepsis in the methods. How was the definition used or applied to the systematic review? Was it used to exclude articles?

**Response:** The definition was used as inclusion criteria.

6. Did the authors receive assistance from a librarian or health information specialist with expertise in systematic reviews. Did a second librarian validate the search?

**Response:** We performed database searches. We received help from librarian for validation of the search.

7. Why did they choose longest follow-up period instead of most complete data. Why not use both papers in case they presented different types of data that were relevant to the analysis.

**Response:** We did not choose the longest follow-up period study. As shown in table 1, we included all papers that presented different type of data.

8. Please provide some basic information on the Newcastle Ottawa quality scale for the reader. Further explain how the authors (or the field) utilize the NCO score: range for poor, moderate, high quality. How was this information to be used? How did they operationalize the questions within the NCO. Controlling for first and second most “relevant” factors. From my experience, saying you are going to use this scale and figuring out how to use it is a very different thing.

**Response:** We described information on NOC score and ranged of quality. Two authors independent assessed quality of studies. Detail score were shown in Table 2. We excluded studies from meta-analysis if they had poor quality.

9. (**Major Compulsory Revisions) As prepared, table 2 is confusing and of limited value to the reader. Would recommend adding some detail to better describe the study to which they are referring and why the score is what it is.

**Response:** We changed table 2 format and described criteria for each scale.

10. It would help in the text to indicate what the score is out of: selection scale of 2 (maximum 4)

**Response:** We described maximum score of each scale [line 130-132].

11. The authors are relying too heavily on the table. Further, instead of stating “Reference 15” they should write out the authors name and date.

**Response:** We changed to authors name and year in the table.

12. (**Major Compulsory Revisions) The text in the results sections needs significant explanation and expansion describing how the results were presented and what the studies showed Some aspects
that readers might find interesting would include: i) how did the studies define vitamin D status? ii) what assays were used? iii) When were the measurements taken? iv) What assays were used to measure?

Response: We provided data in Table 1 on how each study define vitamin D status, what assays were used, and when measurements were taken. The reviewer’s iv) question is duplicate to the ii) question.

13. How many measured 1,25(OH)2D. What were the results

Response: We included finding of 1,25(OH)2D in result section [line 158] and table 1.

14. The 25(OH)D results presented in table 1 are confusing.

Response: We changed table 1 format to better understand 25(OH)D results. They were presented as overall mean (SD) except studies that described level in each group (sepsis vs control)

15. For the paragraph describing the meta-analysis work o Second sentence is too long. Break into two different points. For Figure 4... why does the 0 have a negative sign beside it?

Response: We broke to two sentences [line 170-175]. We deleted minus sign before 0 in figure 4 and in the text.

16. Is there value in doing fixed effects when the calculated heterogeneity was 0 and 5%.

Response: We used fixed effects model because of low heterogeneity. Random effects model was used in sensitivity analysis and results were not different.

17. Meta-regression... Fully acknowledge the point that there was little heterogeneity in the odds ratio results between studies. Did they authors perform any preliminary analysis here. Odds ratio by illness sepsis illness severity or NCO score?

Response: We did not perform meta-regression or subgroup analysis because of very low heterogeneity and because there is no much difference in NOC score.

18. (**Major Compulsory Revisions) Would request that the authors complete a PRISMA checklist. In doing so they will fill be encouraged to fill in the missing pieces.

Response: We included PRISMA checklist as Additional File 2

19. (**Major Compulsory Revisions) Overall the discussion is too short and does fully discuss and make relevant the systematic review findings. • What were the results and do they make sense biologically

Response: We summarized our findings [line 196-200], discussed how our findings related to previous literature and explained possible pathophysiology [line 202-215].

20. How are they relevant? o Prevention o Treatment – with reference to available RCTs including VITdAL-ICU

Response: We described role of vitamin D supplementation and normalization from previous RCTs including VITdAL-ICU [line 217-225].
21. What are the limitations?

**Response:** We added limitations including the accuracy of vitamin D due to effects of illness, time of measurement. We also included potential limitations on using the result by normalization of vitamin D to prevent or treat sepsis.

22. Recommendations? o More, better done, observational studies vs. clinical trials?

**Response:** We suggested large observational study investigating pre-illness vitamin D level and risk of sepsis. We also suggested RCT of vitamin D supplementation be performed [line 241-246].

23. Please remove the comment to low 1,25(OH)2D in the second paragraph

**Response:** We have removed that comment.

24. Why are the authors referencing the pilot RCT on calcitriol

**Response:** We have removed that reference.

25. (**) Major Compulsory Revisions) Really need to strengthen comments on how 25(OH)D levels may not represent pre-illness and how illness and interventions could impact 25(OH)D.

**Response:** We described that limitation [232-235]

26. (**) Major Compulsory Revisions). Unclear how this fits into a larger program... or how they propose others use the results

**Response:** Our results are consistent with other literature that there is significant association between vitamin D deficiency and risk of sepsis. This results may drive other investigators to perform RCT on the effect of vitamin D supplementation and sepsis control.