Author’s response to reviews

Title: The Effect of Vitamin D Supplementation on Hemoglobin Concentration: A Systematic review and Meta-analysis

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Point to point response to the editor's comments:

Reviewer #2 comments:

Reviewer #2: Overall, the current study addresses non-conclusive but very serious issue concerning major public health problem. The study based on convenient available retrospective. This study is well written but not well designed.

1. The authors should provide key points and the contribution of current study to literature and what messages are provided with the present study?

According to previous studies, the relationship between vitamin D effects and hemoglobin levels are still controversial and no conclusive review on this topic has been conducted on different health conditions. Therefore, we decided to assess related RCT results in a comprehensive meta-analysis in seven groups with different health conditions. We categorized subjects in RCTs to seven groups as such: healthy adults, anemic patients, chronic kidney disease patients, heart failure patients, hypertensive patients, critically ill patients and athletes. The levels of hemoglobin and ferritin in participants from these groups were assessed and compared when supplemented with vitamin D. Please refer to subgroup analysis section, line 150-154.
2. Limitations: The authors not reported the key limitations of this study, I think the major concern of this submission is it lacks sufficient novelty, as many of such similar reports were seen published in previous literature.

Although many studies have been conducted in this area, no single study examined all of the following groups in a comprehensive way: healthy adults, anemic patients, chronic kidney disease patients, heart failure patients, hypertensive patients, critically ill patients and athletes. Examining all of said seven groups in one study represents the novelty of the current meta-analysis. Also, as a second matter of novelty, this study includes both primary and secondary outcomes, where all of the fourteen RCT studies reported, discussed hemoglobin levels as their primary outcomes, while, iron markers such as levels of ferritin, serum iron, and transferrin saturation were measured as their secondary outcomes. Notably, previous studies have assessed these factors only in healthy subjects.

Regarding limitations of this study, dosage, type and duration of vitamin D treatments were different in these studies which led to heterogeneity in this meta-analysis. RCTs were not long term and the pooled analysis lacked one of the RCTs due to the absence of placebo group. Moreover, there is limited evidence regarding the mechanism of action between vitamin D and iron levels. Please refer to line 284-292.

Reviewer #3 comments:

Reviewer #3: Thank you for addressing the previous reviewer's comments. My recommendation is that this manuscript be accepted with minor changes. Please see below.

There is one reviewer comment that asked the authors to remove data on serum iron and transferrin saturation as they are unreliable markers of iron status due to their diurnal pattern. The authors have requested the data be allowed to stay but as secondary outcomes.

I am happy for authors to leave these data as secondary outcomes but because of this, I would ask authors to remove the statement about these markers in their conclusion. Currently the conclusion states "supplementation with vitamin D had no significant effect on hemoglobin and ferritin levels while positive effects on transferrin saturation and iron status were observed". I recommend to remove the latter part of the sentence "while positive effects on transferrin saturation and iron status were observed".

Amendments are done according to your request, please refer to conclusion part.