OPEN PEER REVIEW

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As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

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- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

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Peer Review Report for "Effects of Vitamin D Supplementation in Patients with Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis"

Author(s): Yali Wei, Shuli Wang, Yan Meng, Qingtao Yu, Qian Wang, Hongzhao Xu, Huacai Yuan, Xiaoxu Li, Liyong Chen

Review Timeline:

Submit Date: 18 Aug 2019
Revised Date: 31 May 2020
Accepted Date: 2 Jun 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Zahra Bahadoran: Reviewer | **Revision** (0) 26 Oct 2019

Dear AE,
The authors have carried out a systematic review and meta-analysis of current randomized clinical trials investigated the effects of vitamin D supplement on liver indicators in patients with non-alcoholic fatty liver disease (NAFLD). The manuscript is suffering from several limitations in study design and procedures as well as writing of the manuscript sections specially method and result sections. The major problem of this study makes it difficult to understand, is that the study hypothesis and the main outcome have not been clarified. Search strategy and selection of key words was not defined for a specific research question; so validity and reliability of literature search and the papers were retrieved by the search seem not to be acceptable. Another main issue is that interventions perfumed in the trials were not limited to vitamin D; in some studies, vitamin D plus other supplements e.g. calcium, vitamin E, docosahexaenoic acid (DHA) were used as an intervention.
There are some comments which should be addressed by the author:
1- The authors need to clarify which outcome in the trials was considered as the main; e.g. in the abstract the authors stated that “The Medline, EMBASE and Scopus databases were

researched to found randomized control trials (RCTs) that measured the changes between vitamin D supplement group and control group" while they did not provide any information about "changes" that the meta-analysis was conducted to estimate pooled effect size of them.

2- In the method section, the search strategy is not well-defined. There is no "keyword or key term" to explicit conducted search for outcome variables.

3- It is not clear which inclusion and exclusion criteria did the authors consider for studies.

4- In result section, a list of pooled effect size have been provided for several metabolic factors (i.e. alanine aminotransferase, serum aspartate aminotransferase, fasting blood glucose, homeostasis model assessment of insulin resistance, serum insulin concentration, and high-density lipoprotein levels) and it's not clear which outcome (s) was considered as the main.

5- In the abstract, the authors concluded that "The results obtained from the article provide evidence of the vitamin D supplement could not improve clinical symptoms in patients with NAFLD"; what the authors did actually mean when they stated "clinical symptoms'? Which clinical symptoms assessed in the obtained clinical trials?

Moreover, in this section, the authors also concluded that "However, a new insight of vitamin D and other supplements co-administration to treat NAFLD are provided". How such a conclusion can be raised by the data provided in this analysis?

6- In the same way, in all sections of the manuscript, specifically in the title and abstract, the authors should clarify which variable (s) was considered as main outcome.

7- The study flowchart provided for literature search needs to be revised according to PRISMA guideline. Some important details about inclusion and exclusion criteria have been ignored, both in the method section and flowchart.

8- Quality assessment of the studies, is suggested to be performed by Newcastle-Ottawa criteria, and be reported in the tables; the quality scores needs also to be considered in the analysis and sensitivity analysis by excluding low-scored trials needs to be conducted.

9- Estimated pooled effect sizes are provided as both weighted mean difference (WMD) and standard mean difference (SMD) and the authors stated that SMD was calculated when data units were different; there are several methods to unify the units of the variables and it's highly recommended that all estimated pooled effect sizes be provided as WMD.

10- The authors stated that "We didn't implement Egger test with Begg's funnel plots to assess potential publication bias due to less than ten reports were eligible". What did the authors actually mean by this statement?

11- The authors stated that the "age of the individuals enrolled in the study varied from 4 to 70 years", whereas mean age of the study populations provided in Table 1 ranges from 28 to 58.

12- There are some vague and meaningless statements in the manuscript; e.g. P13, line 102, "After title and abstract, 904 studies were excluded"; same page, line 106, "Itemized table was used to record relevant data from the trails".

Minor comment:

1- All WMD values and 95% CI are suggested to be reported by two significant digit, consistently throughout the manuscript.

2- In some cases P values have been stated as P=0 .000; all should be corrected as $P<0.001$.

Thanks.

Firoozeh Hosseini-Esfahani: Reviewer | **Revision** (0) 3 Dec 2019

Dear AE,
There are some comments which should be addressed by the author:
- 25-hydroxy vitamin D should be corrected in all of the manuscript.
- In title of the manuscript “liver indicators” should be mentioned.
- Objectives in abstract and introduction were different.
- What is the origin of your search?
- The liver indicators of NAFLD should be included in your keywords.
- The second aim of the study was not considered in inclusion or exclusion criteria.
- What are the reasons of studies which were excluded?
- What is the definition of NAFLD?
- Why did the most studies conducted in Iran?
- The dependent and independent variables should be specified exactly.
- The vitamin D deficient or non-deficient of subjects in 9 studies should be specified and discussed.
Thanks.

REFEREE: Reviewer | **Revision** (0) 5 Dec 2019

Dear AE,
The current systematic review and meta-analysis found that vitamin D supplementation could not improve clinical symptoms in patients with NAFLD. However, some concerns exist in particular in the methods section which should be addressed by the authors:
Major comments:
1. No background has been given on published systematic reviews on vitamin D and NAFLD. An important Cochrane Database Systematic Review (PMID: 29099543) or three recently published systematic reviews (PMID: 29035092; 28751149; 28274829) or others should be precisely explained in the introduction and added value of the current systematic review should be clearly stated.
2. The systematic review has not been registered in PROSPERO or other relevant registries of systematic reviews. All the aims of the study should have been prior defined. No exploratory analysis is acceptable. For example, the type of vitamin D for supplementation is different. It was better to categorize them and bring in the sub-group analysis.
3. The search strategy is not informative. The three mentioned databanks are different. Each has its own strategy. The search strategy of each databank should be reported in a supplementary file. Were keywords used in the title/abstract or in all fields of the papers? “vitamin D” and “vitamin d” are not different. Databanks are not sensitive to upper-or lower-case letters. Did the author use the MeSH terms for the exposure and outcomes?
4. Inclusion and exclusion criteria: according to the aim of study-combining VD supplementation with other supplementations or therapies- only vitamin D was stated as inclusion intervention criteria. What about other co-supplementations? It is not clear. Furthermore, the inclusion of participants in a wide range (4 to 70 years) for comorbidity such as NAFLD, which its incidence is increasing by age is not logical. At least, sub-group analysis by age may help for better interpretation of results.
5. The flow chart of the study should be according to PRISMA. The number of included papers using a hand search was not reported. How many duplicates were among the

studies? All details are mandatory to report.
6. The quality assessment score for each study should be reported.
7. Was the placebo different among studies?
8. No meta-analysis was conducted for hepatic steatosis? If not, please state.
Minor comments:
1. The title of this manuscript is not clear. There is an effect between exposure and outcome but the author only mentioned exposure. The topic of a systematic review is generally as specific as possible; the outcome of interest was not specified in the title.
2. What did the author mean by “liver indicator”?
3. The search strategy has been written in the background part of the abstract. It is incorrect and brings it to the method part.
4. The terms were used in this manuscript for the outcome are inconsistent “liver indicator”, “NAFLD outcomes”
5. Page 10 line 27: “NAFLD is the most common chronic disease 28 globally” seems to need a revision. CVD is the most common chronic disease.
6. Page 10 line 34: “Moreover, the important clinical features of NAFLD closely associated with obesity and diabetes mellitus (DM), include overweight and insulin resistance” did not make sense.
7. Page 10 lines 42 to 44: what did authors mean by “Many recent RCTs have focused on the effects of VD supplementation on patients with NAFLD, However, the effects of VD on NAFLD remains unclear.”?
8. Page 11 line 46: needs a reference.
9. Page 14 lines 112 to 114: The category of overweight and obesity in the manuscript needs revision.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 6 Jan 2020

Dear EIC,
Based on the reviewers’ comments, the manuscript needs a major revision. The most concerns are:
- Previous systematic reviews have not been cited; inclusion and inclusion criteria have not been characterized very well; the search strategy has not been clearly specified; quality assessment has not been addressed.
- All the reviewer's comments need to be addressed.
Thanks.

REFEREE: EIC | **Revision** (0) 6 Jan 2020

Dear Author,
Based on the reviewers' comments the manuscript needs major revision.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewer 1

1:*25-hydroxy vitamin D should be corrected in all of the manuscript.*

Response: All *25-hydroxy vitamin D* expressions have been corrected in this paper.

2: In title of the manuscript "liver indicators" should be mentioned.

Response: The title of this article was changed to"The effects of Vitamin D supplementation on patients with non-alcoholic fatty liver disease: a meta-analysis".

3：Objectives in abstract and introduction were different.

Response: The last paragraph of the "INTRODUCTION "has been revised to make it the same as the research purpose of this article. (Line52- Line55)

4: What is the origin of your search?

Response: According to the PRISMA guide, we revised the flow chart of literature retrieval, in which the literature source is described in detail. (Figure 1)

5: The liver indicators of NAFLD should be included in your keywords.

Response: We appreciate your Suggestions. However, since there are many indexes in this paper, including liver enzymes, blood glucose, blood lipid, inflammation and other indexes, there are a large number of retrieved articles, and many of them are irrelevant. Our search strategy was modified to include a comprehensive search of articles on NAFLD and vitamin D, and a review to find articles that might have been missed. (Line60- Line66)

6: The second aim of the study was not considered in inclusion or exclusion criteria.

Response: Inclusion exclusion criteria were modified for the purpose of the articles.

(Line72- Line79)

7: What are the reasons of studies which were excluded?

Response: Articles that do not meet our inclusion exclusion criteria will be excluded. For example, some articles are not RCT, and some articles cannot provide enough data.

8: What is the definition of NAFLD?

Response: The first sentence of the preface adds the definition of NAFLD. (Line30- Line31)

9: Why did the most studies conducted in Iran?

Response: Three databases were fully searched, and all articles that met the inclusion exclusion criteria were included. There was no deliberate screening of articles from Iran, only in the end they were mostly from Iran, and fewer from other countries.

10: *The dependent and independent variables should be specified exactly*
Response: The result part has been modified. The dependent and independent variables Are specified exactly. (Line126- Line154)

11: The vitamin D deficient or non-deficient of subjects in 9 studies should be specified and discussed.
Response: The included literature was subgroup analyzes based on whether or not vitamin D was deficient. （Table3）

Reviewer 2:
1- The authors need to clarify which outcome in the trials was considered as the main; e.g. in the abstract the authors stated that "The Medline, EMBASE and Scopus databases were researched to found randomized control trials (RCTs) that measured the changes between vitamin D supplement group and control group" while they did not provide any information about "changes" that the meta-analysis was conducted to estimate pooled effect size of them.
Response: The changes of liver enzyme spectrum were considered as the main indexes. For example, AST and ALT. The figure2、figure3、 appendix1、appendix1 and table 2 contains detailed results of forest plot and subgroup analysis of the two indicators. The result part also makes the profound analysis to two indexes. (figure2、figure3、 appendix1、appendix1 and table 2)

2- In the method section, the search strategy is not well-defined. There is no "keyword or key term" to explicit conducted search for outcome variables.
Response: We appreciate your Suggestions. However, since there are many indexes in this paper, including liver enzymes, blood glucose, blood lipid, inflammation and other indexes, there are a large number of retrieved articles, and many of them are irrelevant. Our search strategy was modified to include a comprehensive search of articles on NAFLD and vitamin D, and a review to find articles that might have been missed. (Line60- Line66)

3- It is not clear which inclusion and exclusion criteria did the authors consider for studies.
Response: Inclusion exclusion criteria were modified for the purpose of the articles.

(Line72 Line79)

4- In result section, a list of pooled effect size have been provided for several metabolic factors (i.e. alanine aminotransferase, serum aspartate aminotransferase, fasting blood glucose, homeostasis model assessment of insulin resistance, serum insulin concentration, and high-density lipoprotein levels) and it's not clear which outcome (s) was considered as the main.

Response: The changes of liver enzyme spectrum were considered as the main indexes. Other indicators are secondary. We have conducted subgroup analysis, Regression analysis, sensitivity analysis and bias analysis for the main indicators.

(figure2、figure3、 appendix1、appendix1 and table 2)

5-① In the abstract, the authors concluded that "The results obtained from the article provide evidence of the vitamin D supplement could not improve clinical symptoms in patients with NAFLD"; what the authors did actually mean when they stated "clinical symptoms'? Which clinical symptoms assessed in the obtained clinical trials?

②Moreover, in this section, the authors also concluded that "However, a new insight of vitamin D and other supplements co-administration to treat NAFLD are provided". How such a conclusion can be raised by the data provided in this analysis?

1 Response: The language of the author is unclear here, and has been changed to "improving relevant indicators for NAFLD patients". (Line24-Line25)

②The sentence should appear in the discussion section and has been deleted.

6- In the same way, in all sections of the manuscript, specifically in the title and abstract, the authors should clarify which variable (s) was considered as main outcome.

Response: Thank you for your suggestion. The title and abstract of the article have been modified for this problem. AST and ALT are the main indicators.

(Line13、Line17、Line53-Line55)

7- The study flowchart provided for literature search needs to be revised according to PRISMA guideline. Some important details about inclusion and exclusion criteria have been ignored, both in the method section and flowchart.

Response: According to the PRISMA guide, we revised the flow chart of literature retrieval, in which the literature source is described in detail (Figure 1)

8- Quality assessment of the studies, is suggested to be performed by Newcastle-Ottawa criteria, and be reported in the tables; the quality scores needs also to be considered in the analysis and sensitivity analysis by excluding low-scored trials needs to be conducted.

Response: We used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials to evaluate the quality of each study. (Table2)

9- Estimated pooled effect sizes are provided as both weighted mean difference (WMD) and standard mean difference (SMD) and the authors stated that SMD was calculated when data units were different; there are several methods to unify the units of the

variables and it's highly recommended that all estimated pooled e ffect sizes be provided as WMD.
Response: Thanks for your advice, all estimated pooled effect sizes have been provided as WMD.

10- The authors stated that "We didn't implement Egger test with Begg's funnel plots to assess potential publication bias due to less than ten reports were eligible". What did the authors actually mean by this statement?
Response: Egger test with Begg's funnel plots were prepared to assess potential publication bias. （Appendix）

11- The authors stated that the "age of the individuals enrolled in the study varied from 4 to 70 years", whereas mean age of the study populations provided in Table 1 ranges from 28 to 58.
Response: Because one of the articles studied children, it lowered the average age of the study population. The effect of vitamin D on NAFLD varies with age. A study of vitamin D in children with NAFLD was excluded in this study of adults over the age of 18.

12- There are some vague and meaningless statements in the manuscript; e.g. P13, line 102, "After title and abstract, 904 studies were excluded"; same page, line 106, "Itemized table was used to record relevant data from the trails".
Response: The full text was thoroughly examined. The article has modified or deleted meaningless *statements*.

Minor comment:
1- All WMD values and 95% CI are suggested to be reported by two significant digits, consistently throughout the manuscript.
2- In some cases P values have been stated as P=0 .000; all should be corrected as P<0.001.
Response: Thanks for your suggestion, we have revised it to two digits and P values have been corrected as P<0.001.

Reviewer 3
Major comments:
1. No background has been given on published systematic reviews on vitamin D and NAFLD. An important Cochrane Database Systematic Review (PMID: 29099543) or three recently published systematic reviews (PMID: 29035092; 28751149; 28274829) or others should be precisely explained in the introduction and added value of the current systematic review should be clearly stated.
Response: We appreciate your suggestion, two of them were quoted in the preface, and another article has been quoted in the discussion（References 5，6，35）

2. The systematic review has not been registered in PROSPERO or other relevant registries of systematic reviews. All the aims of the study should have been priori defined. No exploratory analysis is acceptable. For example, the type of vitamin D for supplementation is different. It was better to categorize them and bring in the sub-group analysis.

Response: Thanks for your suggestion, we will register in the systematic system. As for the types of vitamin D supplementation we made a subgroup analysis for the main indicators ALT and AST.（Table3）

3. The search strategy is not informative. The three mentioned databanks are different. Each has its own strategy. The search strategy of each databank should be reported in a supplementary file. Were keywords used in the title/abstract or in all fields of the papers? "vitamin D" and "vitamin d" are not different. Databanks are not sensitive to upper-or lower-case letters. Did the author use the Mesh terms for the exposure and outcomes?

Response: MESH terms and all free words are used for retrieval. In the three databases, we all used the keyword described in the article to copy and search in the search box. The specific search results are shown in figure 1.（Figure1）

4. Inclusion and exclusion criteria: according to the aim of study-combining VD supplementation with other supplementations or therapies- only vitamin D was stated as inclusion intervention criteria. What about other co-supplementations? It is not clear. Furthermore, the inclusion of participants in a wide range (4 to 70 years) for comorbidity such as NAFLD, which its incidence is increasing by age is not logical. At least, sub-group analysis by age may help for better interpretation of results.

Response: I'm sorry that you misunderstood the main purpose of this paper due to unclear expression. In this paper, VD supplements are the only intervention means. The combined use of other supplements is the discussion part, which has been revised in the full text. There was only one study in children, and the intervention was a combination of vitamin D and DHA, so we couldn't do a subgroup analysis. A study of a combination of vitamin D and DHA in children with NAFLD was excluded, in this study of adults over the age of 18.

5. The flow chart of the study should be according to PRISMA. The number of included papers using a hand search was not reported. How many duplicates were among the studies? All details are mandatory to report.

Response: According to the PRISMA guide, we revised the flow chart of literature retrieval, in which the literature source is described in detail (Figure 1)

6. The quality assessment score for each study should be reported.

Response: We used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials to evaluate the quality of each study. (Table2)

7. Was the placebo different among studies?

Response: Some of the articles don't talk about what a placebo is, but what is certain is that the placebo doesn't affect the end result.

8. No meta-analysis was conducted for hepatic steatosis? If not, please state.
Response: Due to the small number of articles, most of them are written descriptions without data, we did not conduct a meta-analysis of steatosis, as explained in the article. (Line117-Line119)

Minor comments:
1. The title of this manuscript is not clear. There is an effect between exposure and outcome but the author only mentioned exposure. The topic of a systematic review is generally as specific as possible; the outcome of interest was not specified in the title.
Response: The title of this article was changed to"The effects of Vitamin D supplementation on patients with non-alcoholic fatty liver disease: a meta-analysis".

2. What did the author mean by "liver indicator"?
Response: In this article, "liver indicators" refer to AST and ALT, and the article has been revised to emphasize these two indicators.

3. The search strategy has been written in the background part of the abstract. It is incorrect and brings it to the method part.
Response: Our search strategy was modified to include a comprehensive search of articles on NAFLD and vitamin D. (Line72-Line79)

4. The terms were used in this manuscript for the outcome are inconsistent "liver indicator", "NAFLD outcomes".
Response: The outcome of NAFLD in this paper is the quantitative index of AST and ALT and the qualitative index of hepatic steatosis. (Line117-Line140)

5. Page 10 line 27: "NAFLD is the most common chronic disease 28 globally" seems to need a revision. CVD is the most common chronic disease
Response: We appreciate your suggestion. The sentence has been deleted.

6. Page 10 line 34: "Moreover, the important clinical features of NAFLD closely associated with obesity and diabetes mellitus (DM), include overweight and insulin resistance" did not make sense.
Response: Thanks for your suggestion. The sentence has been deleted.

7. Page 10 lines 42 to 44: what did authors mean by "Many recent RCTs have focused on the effects of VD supplementation on patients with NAFLD, However, the effects of VD on NAFLD remains unclear."?
Response: I am sorry that it's not well expressed here. This sentence is revised as follows: "However, there is no consensus on whether vitamin D is effective in improving indicators in patients with NAFLD". （Line52—Line55）

8. Page11 line 46: needs a reference.

Response: References have been inserted here.（Line50—Line51）

9. Page 14 lines 112 to 114: The category of overweight and obesity in the manuscript needs revision.

Response: According to the comments of other reviewers, this paragraph has been significantly modified, and this sentence has been deleted. Thank you for your guidance.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 10 May 2020

Dear EIC,
Since most of the reviewers' concerns have been addressed, the manuscript merits publication in the IJEM.
Thanks.

REFEREE: EIC | **Revision** (1) 11 May 2020

Dear Author,
The revised manuscript is preliminary accepted; however, the manuscript needs a critical English grammar editing to be accepted for publication in the IJEM.
Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear editor and reviewers,

We are truly grateful to your critical comments and thoughtful suggestions. Based on these comments and suggestions, we have made careful modifications on the original manuscript. We hope the revised manuscript will meet the journal's standard. Below you will find our point-by-point responses to the reviewers' comments/ suggestions:

Reviewers' Comments:

Associate Editor's Comments:

Associate Editor 1:

Since most of the reviewers' concerns have been addressed, the manuscript merits publication in the IJEM.

EIC Decision:

The revised manuscript is preliminary accepted; however, the manuscript needs a critical English grammar editing to be accepted for publication in the IJEM.

Response: We have carefully revised the grammar and language of the article, which has been emphasized in the article. Sentence changes were marked as whole sentences and individual word changes was marked separately. No changes have been made to the content of the article.

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision** (2) 2 Jun 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.