

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol
<b>AUTHORS</b>	Asghari, Golaleh; Farhadnejad, Hossein; Hosseinpanah, Farhad; Moslehi, Nazanin; Mirmiran, Parvin; Azizi, Fereidoun

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Dr Aoife Carroll Department of Paediatrics, University Hospital Waterford, Dunmore Rd, Waterford, Ireland
<b>REVIEW RETURNED</b>	15-Feb-2018

<b>GENERAL COMMENTS</b>	This systematic review /meta-analysis will provide useful information to help guide in recommendations for appropriate vitamin D supplementation in children and adolescents. The exact dates of the study are not clear apart from a reference to September 2017 - is this the date up to which all publications will be eligible for inclusion in the review?
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<b>REVIEWER</b>	Jennifer Hilger-Kolb Mannheim Institute of Public Health, Germany
<b>REVIEW RETURNED</b>	28-Mar-2018

<b>GENERAL COMMENTS</b>	<p><b>Reviewer comments on the manuscript “Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol</b></p> <p>Although the protocol of this systematic review covers an interesting topic, several issues prevent me from accepting this manuscript in its current form. Please find my detailed comments listed below.</p> <p>Abstract and Keywords:</p> <p>Comment 1: If possible the authors should add the keywords “supplementation” and “systematic review”. I the maximum number of keywords has already been reached, I would prefer the keyword</p>
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“systematic review” instead of “meta-analysis”. Because at the protocol stage it is often unclear, if the data allow conducting a meta-analysis.

Comment 2: The authors should consider deleting “as a hormone” in the first sentence of the abstract.

Comment 3: I would suggest making a dot after vitamin D supplementation (page 2 line 25) And giving a detailed clarification of the different control groups included in a separate sentence such as: “We considered articles with the following control groups as eligible: placebo control, control group without any supplementation, or a comparative arm investigation. A detailed definition of these different groups should be provided in the method section of the full-text article.

Comment 4: The statement on page 2 line 28 “One reviewer will assess articles for eligibility” seems to contradict the statement in the second bullet point on page 4 line 17 (The study screening, data extraction and quality assessment...” and also the statement on page 10 line 8 “Two review authors...” Could the authors please clarify this issue.

Comment 5: A typo appeared in the third bullet point on strengths and limitations “25-hydroxy” and “vitamin D” should not be separated (see page 4 line 22). In addition, the authors might consider changing the sentence to something like “Based on previous reviews (Reference) dealing with vitamin D we expect considerable heterogeneity of our data that might be due to variables such as...”.

Comment 6: In the statement made in the fourth bullet point (page 4 line 30) authors should add “Studies included” to clarify what is exactly meant by “studies”. In addition, a statement on the consequences that not all outcomes are present could be added here (or if it is not possible due to the word limit, it should appear in the discussion section).

Introduction:

Comment 7: In line with the abstract the authors should consider deleting “as a hormone” in the first sentence. They should also

	<p>provide a reference for this statement.</p> <p>Comment 8: For the sentence starting in line 13 page “Since...” the authors should also provide a reference.</p> <p>Comment 9: The authors should consider if they use the term “various/different doses” instead of the term “variable doses” (page 5 line 29). If they change the term they should use the same term throughout the whole manuscript.</p> <p>Comment 10: Typo in line 45; page 5 should be corrected to “achieving”</p> <p>Comment 11: The sentence on page 5 line 50 ff should be corrected “...adolescents at risk of vitamin D deficiency such as obesity” is grammatically incorrect.</p> <p>Comment 12: Authors should provide a reference for the statement starting on page 6 line 6-10 “Exposure...”</p> <p>Comment 13: The authors should revise the sentence starting with “Supplementation...” (page 6 line 10). The should mention dietary intake as the second source for vitamin D and supplementation as the third one. In addition, some example e.g., fatty fish should be named as dietary sources of vitamin D. Again, a reference for this statement is missing.</p> <p>Comment 14: Authors should consider introducing an abbreviation for 25-hydroxyvitamin D using 25(OH)D.</p> <p>Comment 15: As obesity is only one possible factor that is discussed to influence vitamin D levels, and this is not the main topic of the manuscript, I would prefer shortening this section and only mention in a single sentence that previous studies have shown that obesity might also influence 25(OH)D levels (followed by a respective reference).</p> <p>Comment 16: In the sentence “Recently...”(page 6 lin36) the</p>
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authors should delete the word “optimal” here.

Comment 17: As a general comment authors should also consider revising the current structure of their introduction. I would prefer that the paragraph on prevalence rates of vitamin D deficiency should be followed by the paragraph on 25-hydroxyvitamin D (Currently starting on page 6 line 3). As the paragraph ends with supplementation the paragraph starting currently on page 5 line 24 “Although many trials...” would fit next. Afterwards the paragraph starting with the sentence on page 6 line 31 “A systematic review...” could follow.

Methods:

Comment 18: Is it by default that the objectives have to be stated in the methods? Otherwise I would replace the last paragraph of the introduction by these objectives to avoid repeating them.

Comment 19: As already indicated in the abstract the authors should clarify the different study types included in more detail.

Comment 20: Could the authors give one or two examples of mild diseases? (see line 6, page 8).

Comment 21: As the role of obesity was very prominent in the introduction section, a statement on including or excluding children/adolescents with obesity should be provided.

Comment 22: Authors should provide the meaning of NYHA (see page 8 line 24)

Comment 23: What is meant by “active” vitamin D supplementation? Could the authors please clarify.

Comment 24: In the sentence “We will perform...” (page 9, line 15) the word “intervention” should be replaced by “supplementation”

Comment 25: The authors should delete the sentence on page 9 line 31 “Inclusion criteria will be  $\leq 18$ ...” as this was already mentioned in the inclusion criteria and also in the first sentence of the paragraph (line 15)

Comment 26: Could the authors please clarify what is meant by “excess relevant keywords”.

Comment 27: I would recommend revising the sentence on other resources accordingly (see line 48, page 9): We use snowballing techniques to complement the database searches by screening the reference lists of included articles for relevant studies” or something like this.

Comment 28: Authors should delete “review” and just write “two authors” (see page 10 line 6, line 25, and line 42).

Comment 29: I would switch the order of the terms “title” and “abstract” (page 10, line 9)

Comment 30: Authors should clarify what is meant by “...extract data based on inclusion and exclusion criteria” (page 10, 26ff) do they mean “select”. But although if they mean select I do not understand the meaning of the whole paragraph. Especially the sentence “In first the review authors will select articles by keywords...” gets not clear to me. I recommend revising the whole paragraph.

Comment 31: On page 11 line 21 the term “population studies” appears for the first time. But in the previous sections authors talk about including only “clinical trials”. If this is not the case, this has to be made clear in all previous sections of the manuscript. Or do the authors mean “study population”? Please clarify

Comment 32: Authors should not report in the protocol that they will conduct a meta-analysis. Especially, as they are expecting high heterogeneity, it is not clear, if conducting a meta-analysis is appropriate.

	<p>Comment 33: As the first two sentences in the discussion section repeat content of the introduction, I would delete these sentences and start with “The findings...” Perhaps it is also possible to delete the caption “discussion” or replace it by “Summary statement”.</p> <p>Comment 34: In general, I do not know if there are any author guidelines on writing a discussion section of a study protocol. But if yes, would expect also dealing in the discussion on potential limitation. As I do not know the guidelines the discussion section had no influence on my decision of accepting the study or not.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer number # 1

C1: The exact dates of the study are not clear apart from a reference to September 2017 - is this the date up to which all publications will be eligible for inclusion in the review ?

R: Yes. We performed a systematic search of published randomized trials on vitamin D supplementation in subjects aged  $\leq 18$  years old in various databases up to 27-Sep-2017.

Reviewer number # 2

Abstract and Keywords:

C1: If possible the authors should add the keywords “supplementation” and “systematic review”. I the maximum number of keywords has already been reached, I would prefer the keyword “systematic review” instead of “meta-analysis”. Because at the protocol stage it is often unclear, if the data allow conducting a meta-analysis.

R: Agreed. Keywords have been modified as following:

Page 3, lines 25-26 (in marked copy file): Keywords: Vitamin D; 25-hydroxyvitamin D; Children; Adolescents; Supplementation; Systematic review

C2: The authors should consider deleting “as a hormone” in the first sentence of the abstract.

R: Agreed and deleted.

Page 2, lines 2-3 (in marked copy file): The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been documented.

C3: I would suggest making a dot after vitamin D supplementation (page 2 line 25) And giving a detailed clarification of the different control groups included in a separate sentence such as: “We considered articles with the following control groups as eligible: placebo control, control group without any supplementation, or a comparative arm investigation. A detailed definition of these different groups should be provided in the method section of the full-text article.

R: Agreed and modified in the abstract and in the method section of the full-text article as following:

Abstract: Page 2, lines 8-12 (in marked copy file): PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to the 27-Sep-2017 will systematically be searched for randomized controlled trials of vitamin D supplementation. We considered articles with the following control groups as eligible: placebo control, control group without any supplementation, or a comparative arm investigation.

Methods: Page 7, lines 87-91 (in marked copy file): We will include randomized controlled trials of vitamin D supplementation with placebo, no intervention control, or comparative arm studies.

Comparative arm is an arm type in which a group of participants receives another dose of vitamin D,

or fortified foods with vitamin D, or other micronutrients such as vitamin E during the clinical trial. Also, all of included studies must have reported 25-hydroxyvitamin D level at baseline and at the end of the study.

C4: The statement on page 2 line 28 “One reviewer will assess articles for eligibility” seems to contradict the statement in the second bullet point on page 4 line 17 (The studyscreening, data extraction and quality assessment...)” and also the statement on page 10 line 8 “Two review authors...” Could the authors please clarify this issue.

R: Agreed and corrected in the abstract as following:

Page 2, lines 12-13 (in marked copy file): Two reviewers will assess articles for eligibility according to pre-specified selection criteria.

C5: A typo appeared in the third bullet point on strengths and limitations “25- hydroxy” and “vitamin D” should not be separated (see page 4 line 22). In addition, the authors might consider changing the sentence to something like “Based on previous reviews (Reference) dealing with vitamin D we expect considerable heterogeneity of our data that might be due to variables such as...”.

R: Agreed and modified as following:

Page 4, lines 33-35 (in marked copy file): Based on previous reviews dealing with vitamin D we expect considerable heterogeneity of our data that might be due to variables, including sex, 25-hydroxyvitamin D baseline level, length of intervention, frequency of intervention, doses of vitamin D supplementation (references).

It is worth mentioning that, based on author guidelines of BMJ Open journal, we must provide Strengths and limitations in separate section before of introduction section. On the other hand, this journal has ordered that reference citations must begin in the introduction in the main text of our main document. Therefore, we cannot consider reference for this section in the main document. However, we provide appropriate references as follows:

References:

1. Renzaho AM, Halliday JA, Nowson C. Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: a systematic review. *Nutrition (Burbank, Los Angeles County, Calif)*. 2011;27:868-79.
2. Akbari M, Ostadmohammadi V, Lankarani KB, Tabrizi R, Kolahehdooz F, Heydari ST, et al. The Effects of Vitamin D Supplementation on Biomarkers of Inflammation and Oxidative Stress Among Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2018;50:271-9.
3. Golzarand M, Hollis BW, Mirmiran P, Wagner CL, Shab-Bidar S. Vitamin D supplementation and body fat mass: a systematic review and meta-analysis. *European journal of clinical nutrition*. 2018.
4. Li X, Liu Y, Zheng Y, Wang P, Zhang Y. The Effect of Vitamin D Supplementation on Glycemic Control in Type 2 Diabetes Patients: A Systematic Review and Meta-Analysis. *Nutrients*. 2018;10.

C6: In the statement made in the fourth bullet point (page 4 line 30) authors should add “Studies included” to clarify what is exactly meant by “studies”. In addition, a statement on the consequences that not all outcomes are present could be added here (or if it is not possible due to the word limit, it should appear in the discussion section).

R: As for the current review study, we will include studies based on only one distinctive outcome (serum 25-hydroxyvitamin D concentration); therefore the following clause is not applicable for our study and we have deleted it.

Page 4 (in marked copy file): “• Studies may not systematically report all outcomes.”

Introduction:

C7: In line with the abstract the authors should consider deleting “as a hormone” in the first sentence. They should also provide a reference for this statement.

R: Agreed and deleted as follows:

Page 5, lines 39-40 (in marked copy file): The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been clarified (Ref\*).

Also, we added the appropriate reference for this sentence as following:

Ref\*: Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, et al. The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. *Endocrine reviews*. 2012;33:456-92.

C8: For the sentence starting in line 13 page “Since...” the authors should also provide a reference.

R: Agreed and added the appropriate reference for this sentence as following:

Page 5, lines 42-44 (in marked copy file): Since childhood and adolescence life cycles increase vitamin requirements for the growth of muscle and bone, vitamin D deficiency is also significantly observed during this period(Ref\*)

Ref\*: Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2011;96:1911-30.

C9: The authors should consider if they use the term “various/different doses” instead of the term “variable doses” (page 5 line 29). If they change the term they should use the same term throughout the whole manuscript.

R: Agreed. We used the term “various doses” instead of the term “variable doses” as following:

Page 5, lines 56-58 (in marked copy file): Although many trials have evaluated the effects of vitamin D supplementation on clinical outcomes, few attempts have been made for evaluating the influence of various doses of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents.

Also, after changing this term, we used the same term throughout the whole manuscript.

C10: Typo in line 45; page 5 should be corrected to “achieving”

R: Agreed and corrected this term as following:

Page 6, lines 63-66 (in marked copy file): This controversy may be explained by the fact that IOM recommendations are based on achieving the target level of  $\geq 20$  ng/ml for 25-hydroxyvitamin D, while the Endocrine society recommendation is based on achieving  $\geq 30$  ng/ml.

C11: The sentence on page 5 line 50 ff should be corrected “...adolescents at risk of vitamin D deficiency such as obesity” is grammatically incorrect.

R: Agreed and modified this sentence grammatically as following:

Page 6, lines 66-69 (in marked copy file): The Society for Adolescent Health and Medicine suggests 600 IU vitamin D for healthy adolescents and at least 1000 IU for those at risk of vitamin D deficiency, such as obese ones, emphasizing the differences in recommendations of these two scientific societies.

C12: Authors should provide a reference for the statement starting on page 6 line 6-10 “Exposure...”

R: Agreed and added the appropriated reference for this sentence as following:

Page 5, lines 49-51 (in marked copy file): Exposure to sunlight is the most important factor in the synthesis of vitamin D, which is dependent on skin color, latitude, season, lifestyle, and dress codes based on the cultural beliefs of individuals (Ref\*\*).

Ref\*\*: Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2011;96:1911-30.

C13: The authors should revise the sentence starting with “Supplementation...” (page 6 line 10). The should mention dietary intake as the second source for vitamin D and supplementation as the third one. In addition, some example e.g., fatty fish should be named as dietary sources of vitamin D. Again, a reference for this statement is missing.

R: Agreed and revised this sentence as following:

Page 5, lines 51-53 (in marked copy file): Dietary intake of limited foods such as fatty fish, egg yolk, cheese, and fortified foods with vitamin D and also supplementation of vitamin D may increase 25-hydroxyvitamin D concentrations (Ref1 and Ref 2).

Ref 1: Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. The American journal of clinical nutrition. 2008;87:1952-8.

Ref 2: Smith TJ, Tripkovic L, Damsgaard CT, Molgaard C, Ritz C, Wilson-Barnes SL, et al. Estimation of the dietary requirement for vitamin D in adolescents aged 14-18 y: a dose-response, double-blind, randomized placebo-controlled trial. The American journal of clinical nutrition. 2016;104:1301-9.

C14: Authors should consider introducing an abbreviation for 25-hydroxyvitamin D using 25(OH)D.

R: Agreed. We used 25(OH)D as an abbreviation for introducing 25-hydroxyvitamin D in manuscript.

C15: As obesity is only one possible factor that is discussed to influence vitamin D levels, and this is not the main topic of the manuscript, I would prefer shortening this section and only mention in a single sentence that previous studies have shown that obesity might also influence 25(OH)D levels (followed by a respective reference).

R: Agreed. We have shortened this section and only mention in a single sentence as following:

Page 6, lines 70-71 (in marked copy file): Previous studies have shown that obesity might also influence 25(OH)D, 1,25-hydroxyvitamin D, and parathyroid hormone levels

C16: In the sentence “Recently...”(page 6 lin36) the authors should delete the word “optimal” here.

R: Agreed and deleted the term “Optimal” in this sentence as following:

Page 6, lines 73-75 (in marked copy file): Recently a review study from the Middle East and North Africa (MENA) region showed that intakes of intermediate vitamin D dose of 1000–2000 IU daily may be necessary to facilitate for achievement of 25(OH)D level of 20 ng/ml in children and adolescents.

C17: As a general comment authors should also consider revising the current structure of their introduction. I would prefer that the paragraph on prevalence rates of vitamin D deficiency should be followed by the paragraph on 25-hydroxyvitamin D (Currently starting on page 6 line 3). As the paragraph ends with supplementation the paragraph starting currently on page 5 line 24 “Although many trials...” would fit next. Afterwards the paragraph starting with the sentence on page 6 line 31 “A systematic review...” could follow.

R: Agreed. We re-arranged the various sections of introduction in manuscript according to comment of the referee.

Methods:

C18: Is it by default that the objectives have to be stated in the methods? Otherwise I would replace the last paragraph of the introduction by these objectives to avoid repeating them.

R: Agreed. We provide the objectives of the current study in the last paragraph of the introduction as following:

Pages 6-7, lines 80-84 (in marked copy file): This review will therefore aim at determining the effectiveness of various doses of vitamin D supplementation in children and adolescents for improving serum 25(OH)D concentrations and assessing the graded response to vitamin D supplementation. Secondly, we aimed to determine if the effect of vitamin D supplementation on serum 25(OH)D varies by baseline vitamin D status, sex, body mass index, puberty status, or the type of vitamin D given.

C19: As already indicated in the abstract the authors should clarify the different study types included in more detail.

R: Agreed and clarified the different study types included in more detail as following:

Methods: Page 7, lines 87-91 (in marked copy file): We will include randomized controlled trials of vitamin D supplementation with placebo, no intervention control, or comparative arm studies.

Comparative arm is an arm type in which a group of participants receives another dose of vitamin D, or fortified foods with vitamin D, or other micronutrients such as vitamin E during the clinical trial. Also, all of included studies must have reported 25-hydroxyvitamin D level at baseline and at the end of the study.

C20: Could the authors give one or two examples of mild diseases? (see line 6, page 8).

R: Agreed. We added some examples of mild diseases in this section as following:

Page 7, lines 93-95 (in marked copy file): Healthy children and adolescents (aged  $\leq 18$  years old) given vitamin D as a preventive measure of certain diseases or individuals with mild diseases (such as flu, obesity, asthma, hypertension, and etc.) that have no reason to have altered vitamin D metabolism.

C21: As the role of obesity was very prominent in the introduction section, a statement on including or excluding children/adolescents with obesity should be provided.

R: Agreed. We will include the studies on children/adolescents with obesity for the current study as following:

Page 7, lines 93-95 (in marked copy file): Healthy children and adolescents (aged  $\leq 18$  years old) given vitamin D as a preventive measure of certain diseases or individuals with mild diseases (such as flu, obesity, asthma, hypertension, and etc.) that have no reason to have altered vitamin D metabolism.

C22: Authors should provide the meaning of NYHA (see page 8 line 24)

R: Agreed and clarified. NYHA is abbreviation of term "New York Heart Association" that is used as a standard index for functional classification of heart failure.

Page 7, lines 100-101 (in marked copy file): Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or below 30 ml/min), liver disease, heart failure (New York Heart Association class 3 or more).

C23: What is meant by "active" vitamin D supplementation? Could the authors please clarify.

R: Agreed and clarified. 1,25-dihydroxyvitamin D is an active form of vitamin D that is prescribed in some diseases, such as chronic kidney disease. We also clarified this term in manuscript as following:

Page 8, lines 110-111 (in marked copy file): Studies that used active vitamin D supplementation (1,25-dihydroxyvitamin D) as this type of supplementation is not recommended for the general population.

C24: In the sentence "We will perform..." (page 9, line 15) the word "intervention" should be replaced by "supplementation"

R: Agreed. We replaced the word "intervention" by "supplementation" as following:

Page 8, lines 117-119 (in marked copy file): We will perform a systematic search of published randomized trials on vitamin D supplementation in subjects aged  $\leq 18$  years old in PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to 27-Sep-2017.

C25: The authors should delete the sentence on page 9 line 31 "Inclusion criteria will be  $\leq 18$ ..." as this was already mentioned in the inclusion criteria and also in the first sentence of the paragraph (line 15)

R: Agreed. We deleted the sentence “Inclusion criteria will be the  $\leq 18$  years (children and adolescents) age group” from this section.

C26: Could the authors please clarify what is meant by “excess relevant keywords”.

R: Agreed. We removed this term from the section of “Electronic searches”

C27: I would recommend revising the sentence on other resources accordingly (see line 48, page 9): We use snowballing techniques to complement the database searches by screening the reference lists of included articles for relevant studies” or something like this.

R: Agreed and modified the “Searching other resources” section as following:

Page 9, lines 130-131 (in marked copy file): To complete the data bank, we will use snowballing techniques to complement the database searches by screening the reference lists of included articles for relevant studies.

C28: Authors should delete “review” and just write “two authors” (see page 10 line 6, line 25, and line 42).

R: Agreed. We removed the term “review” from sentence in L134, L142, and L154 (in marked copy file).

C29: I would switch the order of the terms “title” and “abstract” (page 10, line 9)

R: Agreed and switched the order of the terms “title” and “abstract” as following:

Page 9, lines 134-136 (in marked copy file): Two authors (G.A., H.F.) will independently determine studies that should be evaluated further by scanning the title, abstract, or both, of every study retrieved based on inclusion/exclusion criteria.

C30: Authors should clarify what is meant by “...extract data based on inclusion and exclusion criteria” (page 10, 26ff) do they mean “select”. But although if they mean select I do not understand the meaning of the whole paragraph. Especially the sentence “In first the review authors will select articles by keywords...” gets not clear to me. I recommend revising the whole paragraph.

R: Agreed. We modified this paragraph as following:

Page 10, lines 142-147 (in marked copy file): In the first step, two authors (G.A., H.F.) will independently select articles by title and abstract or search reference lists of relevant studies, and in the second, full texts of selected articles will be retrieved and screened using inclusion and exclusion criteria (study design, participants, and intervention). Finally, in the third step, we will extract the relevant data from the selected articles in a structured data bank (G.A., H.F.). We will resolve any disagreement through consensus or consultation with a third author for resolving differences (F.H.).

C31: On page 11 line 21 the term “population studies” appears for the first time. But in the previous sections authors talk about including only “clinical trials”. If this is not the case, this has to be made clear in all previous sections of the manuscript. Or do the authors mean “study population”? Please clarify

R: Agreed and clarified. We changed the phrase “population studies” to the correct form that is study population as following:

Page 10, lines 159-160 (in marked copy file): We will present data of all included studies and provide a description of results, including study population, interventions, and outcome in details in both summary tables and the text.

C32: Authors should not report in the protocol that they will conduct a meta-analysis. Especially, as they are expecting high heterogeneity, it is not clear, if conducting a meta-analysis is appropriate.

R: Regarding to variable of interest (25-hydroxyvitamin D), we expect to conduct meta-analysis. If heterogeneity would be significant and high in the current review, we conduct random-effects model meta-analysis; if not, we conduct fixed-effect model meta-analysis. Also, to overcome heterogeneity, we will assess the individual study and subgroup characteristics and perform a sensitivity analysis to clarify the reasons of this heterogeneity.

C33: As the first two sentences in the discussion section repeat content of the introduction, I would delete these sentences and start with "The findings..." Perhaps it is also possible to delete the caption "discussion" or replace it by "Summary statement".

R: Agreed. We replaced the caption "discussion" by "Summary statement". Also, we modified this section as following:

Page 13, lines 208-212 (in marked copy file): The findings of this review will provide the existing evidence regarding the effectiveness of various doses of vitamin D supplementation in children and adolescents for improving serum 25(OH)D concentrations. Our research will also provide guidance to general practitioners, nutritionist, and researchers on the skeletal and extra-skeletal outcomes and the long term safety of supplementation of various doses of vitamin D in this age group.

C34: In general, I do not know if there are any author guidelines on writing a discussion section of a study protocol. But if yes, would expect also dealing in the discussion on potential limitation. As I do not know the guidelines the discussion section had no influence on my decision of accepting the study or not.

R: Agreed. We replaced the caption "discussion" by "Summary statement" based on previous comment of the referee. Also, it is worth mentioning that, we mentioned the strengths and limitations of this study in separate section after abstract section according to author guidelines of BMJ Open journal (Page 4).