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Relationships of 25-Hydroxyvitamin D Levels and Non-Alcoholic Fatty Liver Disease in Obese Children: A Possible Strategy to Promote Early Screening of NAFLD

Jeanette Irene Christiene Manoppo*, Vivekenanda Pateda, Cindy Prayogo, Fima L. F. G. Langi, [Fahrul Nurkolis](#) and [Apollinaire Tsopmo](#)

Opinion, *Front. Nutr. – Nutrition and Metabolism*
Received on: 22 Aug 2022, Edited by: [Marc Poirot](#) ✉
Manuscript ID: 1025396
Research Topic: [Sterols, Nutrition, and Health](#)
Keywords: Child, NAFLD, Liver, obese, 25-hydroxyvitamin D, Vitamin D

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- Editor Active
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Handling Editor: Marc Poirot
Received date: 22 Aug 2022
Editorial assignment start date: 08 Sep 2022
Independent review start date: 14 Sep 2022
Interactive review activated date: 29 Sep 2022
Review finalized date: 29 Sep 2022
Final validation date: 11 Oct 2022

Revised Manuscript Resubmitted

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History Editor Active Reviewer 1 Finalized A-I-R-A

Reviewer 1
Independent review report submitted: 26 Sep 2022
Interactive review activated: 29 Sep 2022
Review finalized: 29 Sep 2022

Initial recommendation to the Editor: Major revision is required

EVALUATION

Q 1 Please list your revision requests for the authors and provide your detailed comments, including highlighting limitations and strengths of the opinion. If you have additional comments based on O2 and O3 you can add them as well.

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Reviewer 1 | 26 Sep 2022 | 16:52 #1

The authors should improve some parts of the work and do more detailed research on the topic so that the opinion gets the quality corresponding to the journal category.

- In section Introduction, the part related to vitamin D needs to be supplemented and changed. For example, in lines 53–54: „Once absorbed from the intestine, vitamins D2 and D3 are metabolized in the liver and then form 25–hydroxyvitamin D [25(OH)D],...“ here, the authors do not distinguish between the sources of vitamin D2 and D3,... do not state that the primary source of vitamin D3 is exposure to the sun because vitamin D3 is primarily synthesized in the skin, while a smaller part is taken from dietary sources. Also, terminology such as a classical and non–classical function for vitamin D (lines 57–58) is not common (skeletal and extra–skeletal function would be more correct)
- The pathophysiology of NAFLD is oversimplified. First, NAFLD is much more than steatosis and includes a whole spectrum of diseases (according to EASL–EASD–EASO Clinical Practice Guidelines for the management of non–alcoholic fatty liver disease from 2016. NAFLD includes two pathologically distinct conditions with different prognoses: non–alcoholic fatty liver (NAFL) and non–alcoholic steatohepatitis (NASH); steatosis is only the first stage of the disease. Also, the basis of pathophysiology is the complex interaction among hormonal, nutritional and genetic factors whereby hyperinsulinemia and insulin resistance takes a central place in NAFLD pathophysiology
- Most of the cited papers examined the relationship between vitamin D levels in children and adolescents with NAFLD but failed to establish a direct link between vitamin D status and histologic NAFLD severity. Also, authors should refer to the limits of the cited studies and meta–analysis, first of all to the fact that most of the included papers were observational studies, which cannot easily explain the causality.
- In addition, the authors do not list other potential risk factors for vitamin D deficiency that should be critically reviewed before concluding, such as multiple host–, environment–, and heritability–related factors regulating vitamin D synthesis and metabolism. Among them, the most critical factors are limited sun exposure (due to the predominant sedentary lifestyle) and/or poor nutrition, which is also seen in obese children, among whom the highest prevalence was found in NAFLD. Moreover, a significant number of cross–sectional studies investigating the relationship between vitamin D levels and NAFLD/NASH originated from East and Middle East Asia countries where wearing concealing clothing is commonly practised...
- In addition to all of the above, it is necessary to correct some of the sentences that are difficult to understand or confusing, such as:
 - Lines 27–29: New functions of vitamins are still being discovered. Some examples include the role of the kidney in acute respiratory distress syndrome and the regulation of the microbiota (Bakke et al., 2018; Erol et al., 2019).
 - Moreover, lines 20– 21: „The physiological roles of vitamins are generally grouped into water–soluble vitamins (or B vitamins) and fat–soluble roles are diverse.“
 - Lines 23–24: Most vitamins also ask as signally molecules through phosphatases, kinases, or transcription factors
 - lines 33–34 The active form of vitamin D (1,25–dihydroxy vitamin D) has been demonstrated in experimental experiments to exhibit immunologic effects on several constituents of the components of the immune system, as well as the integrity of the endothelial membrane.
- Also sentences in lines 93–99 (not clear which of the mentioned studies the mentioned study refers to): „Several

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Q 2 Check List

 **Reviewer 1** | 26 Sep 2022 | 16:52 #1

- a. Is the quality of the figures and tables satisfactory?
- Yes
- b. Does the reference list cover the relevant literature adequately and in an unbiased manner?
- Yes
- c. Does this manuscript refer only to published data? (unpublished or original data is not allowed for this article type)
- Yes
- d. Is the opinion supported by evidence?
- Yes

 **Submitting Author: Fahrul Nurkolis** | 29 Sep 2022 | 17:05 #2

Thank you for your constructive input on our manuscript. We appreciate your input.

 **Reviewer 1** | 29 Sep 2022 | 19:36 #3

The authors satisfactorily addressed all comments and significantly improved the quality of manuscript so it can be approved for publication.

QUALITY ASSESSMENT

Q 3 Rigor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q 4 Quality of the writing	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q 5 Overall quality of the content	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q 6 Interest to a general audience	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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History

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Reviewer 1

Finalized

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Reviewer 1

Independent review report submitted: 26 Sep 2022

Interactive review activated: 29 Sep 2022

Review finalized: 29 Sep 2022

Initial recommendation to the Editor: Substantial revision is required

▼ EVALUATION

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Fahrul Nurkolis

Peer Reviewer of HELIYON; Clinical Nutrition ESPEN; F1000Research; Journal of Food Biochemistry; Open Access Macedonian Journal of Medical Sciences; Future Foods; Journal of Functional Food; Current Research in Food Science; Clinical Nutrition Open Science; BioMed Research International; and Life Sciences.

No WhatsApp/Telegram/Phone: +62822-3264-2477; Web of Science ResearcherID: <https://www.webofscience.com/wos/author/rid/AAI-1874-2021>; ORCID: <https://orcid.org/0000-0003-2151-0854>

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Submitting Author: Fahrul Nurkolis | 29 Sep 2022 | 17:05

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 - Also sentences in lines 93-99 (not clear which of the mentioned studies the mentioned study refers to): „Several other studies that have been conducted have found that a decrease in 25 (OH)D levels in the body increases the occurrence of NAFLD. The study found a negative association between vitamin D status with NAFLD, fibrosis, and NASH in adolescents and children. Furthermore, vitamin D insufficiency was also found to be more common in obese patients than in those of normal weight (Shanshan et al., 2019; Yodoshi et al., 2020; Ahmed et al., 2016; Fang et al., 2018).“
- The way of citing references is not following the requirements of the journal

Submitting Author: Fahrul Nurkolis | 29 Sep 2022 | 17:05

#2

September 29, 2022

Ref No/Manuscript ID: 1025396

Title: Relationships of 25-Hydroxyvitamin D Levels and Non-Alcoholic Fatty Liver Disease in Obese Children: A Possible Strategy to Promote Early Screening of NAFLD

Dear *Prof. Johannes le Coutre*,
Prof. Marc Poirot,
 Frontiers in Nutrition

Dear **Prof. Marc Poirot** and **Reviewer**, thank you very much for taking the time to handling and review on our manuscript. We greatly appreciate your careful assessment and insightful comments on our manuscript, as well as your recognition of the importance of our study. We have revised extensively and thoroughly, the manuscript with highlights re-submitted. We believe that the manuscript in the revised version is substantially and technically improved as well. Please find below a point-by-point response to the reviewer comments and clarify the important points

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1. In section Introduction, the part related to vitamin D needs to be supplemented and changed. For example, in lines 53-54: "Once absorbed from the intestine, vitamins D2 and D3 are metabolized in the liver and then form 25-hydroxyvitamin D [25(OH)D],..." here, the authors do not distinguish between the sources of vitamin D2 and D3,... do not state that the primary source of vitamin D3 is exposure to the sun because vitamin D3 is primarily synthesized in the skin, while a smaller part is taken from dietary sources. Also, terminology such as a classical and non-classical function for vitamin D (lines 57-58) is not common (skeletal and extra-skeletal function would be more correct).

#Response: Thank you for suggesting constructive inputs on our manuscript. We have added additional explanations on vitamin D2 and D3, while also changing the "classical and non-classical functions" to "skeletal and extra-skeletal functions" as per your suggestions.

2. The pathophysiology of NAFLD is oversimplified. First, NAFLD is much more than steatosis and includes a whole spectrum of diseases (according to EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease from 2016. NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); steatosis is only the first stage of the disease. Also, the basis of pathophysiology is the complex interaction among hormonal, nutritional, and genetic factors whereby hyperinsulinemia and insulin resistance takes a central place in NAFLD pathophysiology

#Response: Thank you for your suggestions, we believe this will be an exceptional improvement on our manuscript. We have added a more complete discussion about the pathophysiology of NAFLD. Thank you for your constructive input on our manuscript. We appreciate your input.

3. Most of the cited papers examined the relationship between vitamin D levels in children and adolescents with NAFLD but failed to establish a direct link between vitamin D status and histologic NAFLD severity. Also, authors should refer to the limits of the cited studies and meta-analysis, first of all to the fact that most of the included papers were observational studies, which cannot easily explain the causality.

#Response: Thank you for highlighting a very important implication from the papers we used as our references. Subsequently, we have added the limitation on the end



5. In addition to all of the above, it is necessary to correct some of the sentences that are difficult to understand or confusing, such as:

-Lines 27-29: New functions of vitamins are still being discovered. Some examples include the role of the kidney in acute respiratory distress syndrome and the regulation of the microbiota (Bakke et al., 2018; Erol et al., 2019).

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#Response: Thank you for your insights, we have revised the grammar and writing on these specific parts and the overall manuscript. We appreciate your input.

6. The way of citing references is not following the requirements of the journal.

#Response: Thank you, we have changed the reference style of the manuscript. We appreciate your input.

We believe these actions address the deficiencies and comments noted by the reviewers. We hope that you will be pleased with this revision and that the revised manuscript will better meet the requirements of the 'Frontiers in Nutrition' for publication. If any changes need to be made, don't hesitate to contact us again. Your kind help in this submission is highly appreciated!

Actually, this manuscript is an opinion, not a review, systematic review or comprehensive review. So, we hope that by being revised extensively and thoroughly, this manuscript opinion can be considered further and the limitations as a manuscript opinion can be accepted and understood.

Your decision is much appreciated!

Kind Regards,

Assoc. Prof. Dr. Jeanette Irene Christiene Manoppo., MD., Sp.A(K)

Prof. Apollinaire Tsopmo, PhD (Chemistry, Carleton University, 1125 Colonel By Drive, Ottawa, K1S5B6, Canada.; Associate Editor for Heliyon Scopus Q1 by Elsevier-Cell Press)

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History

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Handling Editor: Marc Poirot

Received date: 22 Aug 2022

Editorial assignment start date: 08 Sep 2022

Independent review start date: 14 Sep 2022

Interactive review activated date: 29 Sep 2022

Review finalized date: 29 Sep 2022

Final validation date: 11 Oct 2022

Revised Manuscript Resubmitted

Submitting Author: Fahrul Nurkolis | 29 Sep 2022 | 17:19

#1

September 29, 2022

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Your decision is much appreciated!

AA

review.frontiersin.org

X





Prof. Apollinaire Tsopmo, PhD (Chemistry, Carleton University, 1125 Colonel By Drive, Ottawa, K1S5B6, Canada.; Associate Editor for Heliyon Scopus Q1 by Elsevier-Cell Press)

Fahrul Nurkolis

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▼ Final Decision Status?

Submitting Author: Fahrul Nurkolis | 30 Sep 2022 | 07:54

#1

Dear Prof. Marc Poirot,

Thank you for handling and edited on our manuscript.

I hope you can make a decision as soon as possible because we have been asked by our institution to immediately report the final decision (Related to APC funding assistance for this manuscript).

Your decision is highly appreciated.

I hope to hear good news from you soon.

Thank you very much.

Have a nice day!

Kind Regards,

Assoc. Prof. Dr. Jeanette Irene Christiene Manoppo., MD., Sp.A(K)

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▼ Final Decision Status of Article?

Submitting Author: Fahrul Nurkolis | 06 Oct 2022 | 16:21

#1

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