Peer-Review comments and authors responses

Reviewer 1:

Recommendation*: Accept Submission*

Comments for authors*:*

The authors conducted a systematic review evaluating the effects of Omega-3 supplementation on Children with ADHD. The authors found that the studies included were highly heterogeneous and that there is no evidence to support the use of Omega-3 supplementation on children with ADHD. Please see below for several comments:

> ***INTRODUCTION****: Well-written section. Recommend further clarifying/defining what the authors mean when they say "population of children."*
>
> Thank you for your positive feedback on the introduction and for pointing out the need for clarification. In response to the comment, we have revised the term "population of children" in the introduction section of the abstract. Specifically, we refer to children aged from 6-18 years who have been diagnosed with ADHD, as stated in the methods section of the abstract. Thank you again for your constructive feedback.
>
> ***METHODS****: The authors report that they searched MEDLINE, Embase, and Web of Science through May 1st, 2024; however, there's no explicit statement as to the start date for the search. Additionally, the authors mentioned that they only included studies that were done over the past 30 years — that being said, it would be essential to discuss/appraise the results of this study within the context of changes in the diagnostic tools and criteria for ADHD (as these have changed over the span of 30 years). Moreover, the authors mention that the full search strategy would be located in the supplemental materials; however, this was not included.*
>
> Thank you for the valuable feedback. In response to your comment regarding the search period, we have clarified in the Methods section that the literature search was conducted from April 17th to May 1st, 2024. Our articles span between 2003 and 2022. We agree with the reviewer that the evolving diagnostic criteria for ADHD over the last 30 years could influence our findings. In 2013, the new DSM V broadened its criteria. This may account for over diagnosing as autism is no longer an excluding criteria, for example. Another important aspect during this time span is the increased public and physician awareness of the diagnosis, which may also lead to over or misdiagnosis. These factors may cause a larger sample heterogeneity and therefore patients with different neuro-genetic-environmental baseline characteristics that could explain a varied response to interventions. (Abdelnour, E., Jansen, M. O., & Gold, J. A. (2022). ADHD Diagnostic Trends: Increased Recognition or Overdiagnosis? *Missouri medicine*, *119*(5), 467–473.). This comment has been added to our discussion

Additionally, we apologize for the oversight regarding the full search strategy. This information, including the specific MeSH terms and keywords used, has now been added to the Materials and Methods section to enhance the study's reproducibility and transparency. Thank you again for helping us strengthen the rigor and clarity of our manuscript.

RESULTS*: In the "Description of the studies" section, the authors provide an average sample size with the standard deviation — Recommend reconsidering the use of mean/SD in this situation as the coefficient of variation of 0.475 was high. Median/IQR might be better suited. In addition, when reporting the median duration of treatment, I recommend maintaining the same units (currently reported as weeks and then months, which makes it confusing for the reader). I recommend further clarifying the use of "...independent t-tests indicated differences..." in the "Overall symptom assessment" section, as its relevance in this portion remains uncertain. The risk of bias section needs to be further developed.*

Thank you for the insightful suggestions to improve the clarity and rigor of our Results section. In response to the recommendation regarding the sample size reporting, we have recalculated and presented the sample size using the median and interquartile range (IQR) rather than the mean and standard deviation (SD). This change aligns with the data's high coefficient of variation, as noted by the reviewer, and provides a more representative summary. We also appreciate the suggestion to standardize the units when reporting treatment duration. The treatment duration is now consistently presented in weeks throughout the text to avoid confusion for readers. Regarding the "Overall symptom assessment" section, we have revised this portion to clarify the relevance of the independent t-tests. Specifically, we now explain how these tests were used to assess group differences in symptom improvement and detail the context of their inclusion in our analysis. Finally, we agree with the reviewer that the risk of bias section would benefit from additional elaboration. We have expanded this section by providing a more detailed discussion of the specific domains assessed, as well as a breakdown of the risk levels across studies to support transparency in evaluating the reliability of our findings. Thank you again for these constructive comments, which have significantly enhanced the clarity and thoroughness of our manuscript.

DISCUSSION*: Overall, this is a well-written section; however, the authors need to unify their message. Here, the authors mention that the included studies spanned between 2003 and 2022 — as previously mentioned, it is imperative to discuss how the changes in the diagnostic criteria/tools may shape/affect the results of these studies. Moreover, the authors mention "... suggesting that Omega-3 may not have a significant effect on ADHD management." In this setting, my question to the authors is whether they can draw this conclusion with the current level of evidence that they have — One way to look at this is to think whether the absence of evidence is evidence of absence. Additionally, the authors mention the "flawed statistical analysis" of the studies included, but there's no mention as to what the impact of this may be and/or how they were flawed.*

Thank you for the insightful feedback and for highlighting areas where the discussion section can be improved. We have revised the discussion to present a more cohesive narrative. We now explicitly address how the changes in diagnostic criteria and tools for ADHD over the study period (2003-2022) may have influenced the findings, particularly in terms of heterogeneity of the population and diagnostic variability. We appreciate the reviewer's thoughtful question about whether the absence of evidence equates to evidence of absence. We have rephrased out conclusions to acknowledge the limitations of the current evidence and have emphasized the need for further high-quality studies to assess the effects of Omega-3 supplementation on ADHD management. We also recognize the importance of discussing the flawed statistical analyses of the included studies and their potential impact. We have expanded this section as well to describe the types of statistical flaws encountered and discussed how these issues may limit the reliability and generalizability of the findings. Thank you again for these valuable suggestions which have greatly improved the discussion section of our manuscript.

Reviewer 2:

Recommendation*: Revisions Required*

Comments for authors*:*

Really great systematic review on a difficult topic, whose presentation in form of a mini-review is understandably complicated due to a relatively large number of reviewed/included studies. Therefore, sometimes the reader goes a little bit lost due to the bulk of reported information from 31 studies included. The reviewer therefore advises to strictly follow, wherever possible, a comprehensible structure starting with a rough overview right at the outset of the respective issue/section, and then followed, if relevant, by further details regarding the individual studies.

Please see more detailed comments of the reviewer in this respect. In any case the reviewer recommends reflecting again the stringency and completeness of important information in the ***Abstract*** *(by keeping the word limit) and to supplement both the Abstract and the main text as well with relevant statistical values indicating either the statistical significance (p-value) and/or the clinical importance/significance (effect size) of the presented results. This would give the reader an even better idea on the magnitude of the findings, if any.*

Thank you for the positive feedback and for recognizing the challenges associated with summarizing such a large number of studies in a mini-review format. We appreciate the suggestion to enhance the structure and readability of the manuscript by starting each section with a rough overview, followed by more detailed information where relevant. To address this, we have revised each section to provide an introductory summary, giving readers a clear, high-level understanding before delving into the details of individual studies. In response to the recommendation regarding the Abstract, we have carefully reviewed it for stringency and completeness. While we recognize a report of p-values and effect sizes would be clinically relevant, our mini-review did not aim to report them this time as primary outcomes were too heterogeneous: some reported effects on the three areas of ADHD, others one general score, and they all used different scales. It would be interesting to systematically analyze these calculations and others in a future

metanalysis. Thank you again for these suggestions, which have helped us improve the organization and clarity of our manuscript for readers.

Reviewer 3:

Recommendation*: Resubmit for Review*

Comments for authors*:*

Dear authors, thank you for this wonderful manuscript and the opportunity to review it, entitled "Omega-3 Polyunsaturated Fatty Acids in Children with Attention Deficit Hyperactivity Disorder: a Systematic Review".
I left some comments inside the draft.

Overall, I would suggest revising the ***abstract section*** *and condense it.*

INTRODUCTION*: please shorten it and review my comments in the document. Methods section: please add there the search strategy as I couldn't find it. add the Mesh terms you used to do it.*

RESULTS*: please, summarize the results. I don't think you need to add all the scales the authors employed to measure the outcomes. Try to summarize the findings of the studies instead, what they found. You can mention the similar findings of the studies you included in your review in groups, instead of going all over to each measurement they did.*

I believe your manuscript will have a high impact and it's a very interesting topic. Great points with the limitations of the studies you included, but I highly suggest you summarize that part

I appreciate the quality of the presentation of the bias risk assessment. Congratulations on your manuscript, I hope you can modify as suggested.

Thank you for the encouraging feedback and thoughtful suggestions to improve the quality and impact of our manuscript. We appreciate the advice to condense the Abstract and have revised it to focus on the key findings while ensuring it remains succinct and informative. In response to the comments on the Introduction, we have shortened this section to provide a more focused background and aligned it with the specific objectives of the review. We have also incorporated your in-text feedback to further enhance clarity and conciseness. Regarding the Methods section, we apologize for the missing search strategy. We have now added the complete search strategy, including the specific MeSH terms and keywords used, to ensure transparency and reproducibility. In the Results section, we have streamlined our findings by summarizing the main outcomes of the included studies. While we appreciate the reviewer’s perspective on not including all the scales the authors employed to measure the intervention effect, we respectfully disagree with this suggestion as we believe it reflects another source of heterogeneity between study

designs and how difficult it is to summarize the data. Additionally, we have condensed the discussion of study limitations to provide a clear yet concise overview, as recommended. Thank you once again for your constructive feedback, which has been invaluable in enhancing the clarity, structure, and overall impact of our manuscript.

Reviewer 4:

Recommendation*: Revisions Required*

Comments for authors:

Specific comments were made in the manuscript text. In general terms, the authors should consider improvements in grammar/syntax and style.

Thank you for the helpful recommendations to enhance the manuscript. In response, we have carefully reviewed the entire manuscript to address the grammatical errors and improve the overall readability of the text. Specific comments made in the manuscript have also been addressed accordingly. We appreciate your feedback, which has helped us improve the quality and presentation of our work.

Reviewer 5:

Recommendation*: Accept Submission*

Comments for authors:

Well done! Congratulations on the hard work. Please, remember to add the references whenever you mention a study. Excellent figures and tables, very complete! Please, consider adding more information regarding the gap knowledge and the bias assessment. Good job! Looking forward to see the final manuscript.

Thank you so much for your kind words and thoughtful feedback. We are glad that you found the figures and tables comprehensive, and the overall work well done. We conducted a thorough review to confirm that every cited study is accompanied by its corresponding reference. Additionally, we expanded the discussion section to provide more detailed information on the knowledge gap, as well as the implications of these gaps for future research. A clarification on the bias assessment regarding the different evaluated domains was included, as well as a more comprehensive analysis of the findings. Your suggestions mean a lot to us, and we're excited to finalize the manuscript as well. Thank you again for your support.