Letter to the Editor on "Comparing the Effects of Docosahexaenoic and Eicosapentaenoic Acids on Inflammation Markers Using Pairwise and Network Meta-Analyses of Randomized Controlled Trials"

Dear Editor:

We read with great interest the systematic review authored by Vors and colleagues (1). The authors aimed to compare the effect of DHA and EPA on several markers of systemic inflammation by pairwise and network meta-analyses (NMAs) of randomized controlled trials (RCTs). They concluded that results from pairwise and NMAs suggest that supplementation with either DHA or EPA does not differentially modify systemic markers of subclinical inflammation. Overall, we congratulate the authors for using state-of-the-art methods such as study protocol registration in PROSPERO, providing a reproducible search strategy, assessing risk of bias by using the Cochrane Risk of Bias tool, rating the certainty of evidence, and by applying the innovative method of NMA. However, we have major concerns regarding the implementation of the NMA and, thus, conclusions made in the paper.

NMA is an evidence-synthesis method, which allows comparing multiple interventions simultaneously (2, 3). There is a growing number of published NMAs in nutrition research (4–6), but the methodological quality varies (3). The NMA model combines data from direct comparisons (existing trials comparing different arms) and indirect comparisons (estimated using common comparators). This property enables to interfere on contrasts not evaluated in a physical trial. Additionally, NMA provides measures for relative ranking on treatment efficacy [e.g., surface under the cumulative ranking curves (SUCRA)]. Their value is between 0 and 1, where 0 means that a treatment is always worst and 1 means that a treatment is always best compared with the other treatments in the network. NMA offers the opportunity to synthesize large amounts of data relating to clinical outcomes and might improve the precision of the effect estimates. Moreover, NMA has a potential to advance knowledge in the field of nutrition because it gives insights that cannot be obtained by individual trials or pairwise meta-analysis, and provides an important basis for the design of novel trials (3).

Usually, a researcher intends to run the NMA to answer the question "Which intervention is the best for particular health outcomes?" Therefore, a vital issue is that all relevant data on comparisons between interventions of interest were identified (7). The authors, however, identified only RCTs that compared DHA with EPA or either of those 2 with a different fatty acid or oil (e.g., olive or canola oil). The network plot (their Figure 2) of the Vors and colleagues' NMA shows nicely that only direct comparisons are considered between DHA, EPA, or either of those 2 with a different fatty acid or oil, but not between other oils, although such evidence is available (e.g., coconut vs canola oil) (8). In that case, the constructed network misses important contrasts between nodes regarded as control, and thus violates the assumption on the availability of all data. The authors justify the use of the NMA by the potential to extend pairwise meta-analysis between DHA and EPA with the use of indirect comparisons. The NMA also assumes that any missing comparison in the network has occurred completely at random (7). In their present systematic review, a lack of pairwise comparisons between different oils is not random. This is a substantial gap in the body of evidence, which is negatively influencing the reliability of NMA results, and is not a strength of the study as stated by the authors. Even as presented NMA estimates have up to 50% contribution from indirect comparisons, they can be biased by the fact that they do not consider all available data. In such a setting, NMA shows no benefit over pairwise meta-analysis, which is also reflected in the presented results. It may also sometimes provide potentially invalid results as shown in the authors' Supplemental Table 12, where sunflower oils strongly increased IL-6 compared with canola, coconut, corn, and olive oil.

With regard to the NMA certainty of evidence assessment, we were surprised that all indirect estimates were judged as "high certainty," whereas none of the direct estimates was rated with a "high certainty" of evidence. As suggested by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group (9), the indirect estimate should be rated as "lowest of the ratings of the 2 direct comparisons forming the most dominant first order loop" (9), which was rated never as "high certainty" by the authors. In this regard, there also seems to be an inconsistency between the grading of the pairwise meta-analysis (direct evidence) (the authors' Supplemental Table 7), where the certainty of evidence was rated as "high" for the outcomes IL-6 and TNF-α for the comparison of DHA versus EPA but only "moderate" for the direct estimate (the authors' Supplemental Tables 9–10).

Finally, an additional limitation of the present NMA is that the authors did not take into account isocaloric comparisons (e.g., 3 g/d of DHA were compared with 7.5 g/d of olive oil) within and across the eligible RCTs, as suggested previously (10).

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In summary, although we highly applaud the authors for using NMA, it might have been better to include direct evidence from all relevant comparisons to minimize the risk of potentially invalid results. Raising awareness of conducting high-quality NMAs shows promise for it to become a benchmark in nutrition evidence synthesis.

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References

1. Vors C, Allaire J, Mejia SB, Khan TA, Sievenpiper JL, Lamarche B. Comparing the effects of docosahexaenoic and eicosapentaenoic acids on inflammation markers using pairwise and network meta-analyses of randomized controlled trials. Adv Nutr 2021;12(1):128–40.
2. Schwingshackl L, Buyken A, Chaimani A. Network meta-analysis reaches nutrition research. Eur J Nutr 2019;58(1):1–3.
3. Schwingshackl L, Schwarzer G, Rücker G, Meerpohl JJ. Perspective: network meta-analysis reaches nutrition research: current status, scientific concepts, and future directions. Adv Nutr 2019;10(5):739–54.
4. Schwingshackl L, Nitschke K, Zähringer J, Bischoff K, Lohner S, Torbahn G, Schlesinger S, Schmucker C, Meerpohl JJ. Impact of meal frequency on anthropometric outcomes: a systematic review and network meta-analysis of randomized controlled trials. Adv Nutr 2020;11(5):1108–22.
5. Schwingshackl L, Neuenschwander M, Hoffmann G, Buyken AE, Schlesinger S. Dietary sugars and cardiometabolic risk factors: a network meta-analysis on isocaloric substitution interventions. Am J Clin Nutr 2019;111(1):187–96.
6. Schwingshackl L, Krause M, Schmucker C, Hoffmann G, Rücker G, Meerpohl JJ. Impact of different types of olive oil on cardiovascular risk factors: a systematic review and network meta-analysis. Nutr Metab Cardiovasc Dis 2019;29(10):1030–9.
7. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Syn Meth 2012;3(2):80–97.
8. Neelakantan N, Seah JYH, van Dam RM. The Effect of coconut oil consumption on cardiovascular risk factors: a systematic review and meta-analysis of clinical trials. Circulation 2020;141(10):803–14.
9. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, Hazlewood GS, Alhazzani W, Mustafa RA, Murad MH, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol 2018;93:36–44.
10. Schwingshackl L, Bogensberger B, Benčič A, Knüppel S, Boeing H, Hoffmann G. Effects of oils and solid fats on blood lipids: a systematic review and network meta-analysis. J Lipid Res 2018;59(9):1771–82.