Reply to J Morze and L Schwingshackl

Dear Editor:

We thank Morze and Schwingshackl for their interest regarding our paper entitled "Comparing the Effects of Docosahexaenoic and Eicosapentaenoic Acids on Inflammation Markers Using Pairwise and Network Meta-analyses of Randomized Controlled Trials" published recently in *Advances in Nutrition*. Their letter nicely summarizes the intent behind a network meta-analysis (NMA), which represents a significant evolution over traditional methods used in pairwise meta-analyses, allowing researchers to answer questions for which data are often lacking. Morze and Schwingshackl have raised a number of concerns regarding the methodology of our NMA on DHA and EPA, which we wish to address here.

We agree that the most common approach to NMA is to include all interventions that compare, directly or indirectly, the impact of a series of treatments (diet, nutrients) on an outcome (cardiometabolic, clinical or disease). This is, of course, if one wants to answer the question: Which treatment among all possible treatments has the greatest impact on a particular outcome? However, the research question may and should also guide how the NMA is applied and used. Indeed, the new 2019 Cochrane Handbook indicates that "when planning an NMA and upon the researchers' question, the authors can use specific interventions of direct interest." The set of interventions that meets inclusion criteria is referred to as the "decision set" [(1), page 295]. A "supplementary set" (e.g., other interventions) may be included in the NMA for the purpose of improving the inference among the interventions in the decision set. The complete set of interventions, the decision set plus the supplementary set, is referred to as the "synthesis comparator set" (1). The Cochrane Handbook also indicates that expanding a network beyond the stated questions is at times unhelpful [(1), page 296]. Hence, guidelines indicate that the validity of an NMA does not rest solely on the systematic inclusion of all randomized controlled trials (RCTs) comparing all treatments and interventions on specific outcomes.

Our NMA would be flawed if our intention had been to assess which of all fatty acids has the greatest impact on markers of subclinical inflammation. Our intent right from the inception of this project was to examine whether DHA or EPA has the highest impact on inflammation markers, using the totality of the available evidence from RCTs. The decision set included all interventions using DHA and/or EPA, while the supplementary set included the control oil/fatty acid arms of those interventions (excluding DHA or EPA). The synthesis comparator set included the decision and supplementary sets, as recommended in the new Cochrane Handbook. However, and to circle back to the example provided by Morze and Schwingshackl, it would be inappropriate to use data from our NMA to infer differential effects between any of the control oils included in the supplementary set. Indeed, our search strategy focused on DHA and EPA exclusively and, hence, did not yield a comprehensive set of studies on the effects of other oils on inflammation markers (e.g., canola vs. olive oil). This has been clearly stated in the footnotes of Supplemental Figures 11, 12, 13, and 14 of our paper.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension for GRADE (Grading of Recommendations Assessment, Development, and Evaluation) states that authors should "describe inclusion and exclusion criteria for treatment regimens [that is, nodes] and should provide justification when treatment nodes are merged to form single comparators [a practice sometimes described as "lumping" of interventions]". Lumping requires treatments to have similar treatment effects, and although this technique is appropriate in some cases, it should be supported by a clear rationale when performed. Therefore, both Cochrane and PRISMA allow for clearly stated criteria for selection of nodes and lumping of some of these nodes, when appropriate and strongly justified. We cannot find evidence in the literature that inclusion of all possible comparisons is an absolute prerequisite of a valid NMA (2). Consistent with current guidelines on NMA, we therefore believe that the proposed approach was justified in this context.

Regarding the assessment of NMA certainty of evidence, we used the GRADE approach according to the new procedure described by Brignardello-Petersen et al. (3), in which the starting point for the indirect evidence is the lowest rating of the direct evidence from the first-order loop, minus imprecision (if any). The method actually suggests ignoring the imprecision criterion in the loop when grading the indirect evidence to not downgrade twice. Therefore, for direct estimates we included its GRADE, accounting for imprecision, but ignored that imprecision when choosing the rating for the indirect estimate based upon the direct evidence from first-order loop (3). For example, let's say that the lowest rating of the direct evidence from the first-order loop was moderate due to imprecision. The starting point for the indirect evidence ignored this and was set as high when there was no evidence of intransitivity, or downgraded to "moderate" when there was evidence of intransitivity. Because there was no evidence of intransitivity, all indirect evidences were therefore rated as "high certainty," despite the fact that the direct estimates were rated "moderate." We have

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made sure throughout the various iterations of the NMA that our interpretation of these GRADE recommendations was aligned and consistent with Brignardello-Petersen et al.'s own intention and interpretation (3).

The assessment of imprecision in the GRADE approach for pairwise meta-analysis (MA) (direct evidence) is slightly different from that of the direct estimate from NMA. Imprecision in pairwise MA is downgraded if the 95% CI crosses the Minimally Important Difference. It was not the case for IL-6 and TNF-α outcomes in the pairwise MA, thus explaining why imprecision was not downgraded and the evidence was rated as a "high" for these 2 inflammation markers. In the NMA, the ratings for IL-6 and TNF-α were downgraded for imprecision due to wide CIs including the null effect, and the evidence for the direct estimate was thus rated as "moderate."

Despite different doses of EPA and DHA used in the eligible RCTs, the median doses of both fatty acids were similar (~2 g/d), allowing consistent comparisons of DHA vs. EPA in the present meta-analyses. However, the selection of RCTs including the control oil/fatty acid arms for the implementation of the NMA was not based on isocaloric exchange, as assessing the effects of other oils on inflammation markers diverted from the main objective, which was to compare the effects of DHA and EPA on these markers.

In conclusion, we hope that this discussion will help clarify some of the issues raised by Morze and Schwingshackl in their letter. Applying NMA to the field of nutrition research is highly desirable when possible, as it contributes to bringing more credibility to research findings.

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