Fatty acids in context
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**Discussion**

**Summary of our findings**

By using meta-analysis to pool available studies on omega-3 fatty acid supplementation in MDD, we observed a medium sized overall effect, that was larger for studies that supplemented higher EPA dose and used supplements in addition to antidepressants in an add-on design. In peripartum depression, our other meta-analysis showed that studies performed for postpartum depression had a large overall effect, compared to no or negligible effects of supplementation antepartum or for depressive symptoms not fulfilling MDD criteria. This suggests that interventions targeted at fatty acid metabolism hold clinical promise, and can be applied to relieve the burden of (postpartum) MDD. Nevertheless, (long-term) biological effects of the manifold and possibly harmful oxidative derivatives of fatty acids (i.e. oxylipins) remain yet largely unknown, providing reasons for caution.

By pooling available studies in a third meta-analysis on the effect of omega-3 fatty acid supplementation on oxidative stress in humans, we showed that - while there was no overall effect - potentially important subgroup differences emerged. In subjects with CVD-risk omega-3 fatty acids decreased oxidative stress, while higher EPA dose in healthy participants had the potentially harmful effect of increasing oxidative stress. This stresses the importance of personalized nutritional or nutraceutical therapy, in order to find the optimal balance between beneficial and harmful effects for each individual.

**Relation with other literature**

Parallel to our meta-analyses, several other efforts have been made to pool evidence on omega-3 fatty acid supplementation for depression, resulting in an ongoing debate. Overall, meta-analytic standardized mean differences for omega-3 fatty acids compared to placebo for depression generally range from 0.11 to 0.56. However, a recent Cochrane meta-analysis of omega-3 fatty acid supplementation for depression observed an overall effect size of 0.30 (95%CI = 0.10-0.50). However, the authors conclude that this statistically significant small-to-modest effect size has small clinical significance because the approximate reduction in Hamilton depression rating scale (HDRS)-score of 2.1 points remains under the National Institute for Health and Care Excellence (NICE)-limit of 3 points for clinically meaningful effects. In addition, the authors are critical in their qualification of study quality. For example, studies that did not add a small amount of fish oil to the placebo to mask a possible fishy aftertaste were judged to be at high risk of bias.

Nevertheless, in the Cochrane meta-analysis the authors acknowledge that the overall effect size for omega-3 fatty acids is comparable to that of antidepressants. However, the authors suggest that the comparable small-to-modest overall effect for both omega-3 fatty acids and antidepressants merely shows the need for other effective treatments. While there obviously is a need for other more effective treatments, given that omega-3 fatty acid are generally thought to have a more beneficial side effect and tolerability profile than antidepressants, these outcomes could also be interpreted in a way suggesting that omega-3 fatty acids indeed have a role as (add-on) treatment for depression.
Moreover, the Cochrane meta-analysis shows stronger beneficial effects in the subgroup of studies supplementing solely or predominantly EPA, and in studies that did not use the omega-3 fatty acid α-linolenic acid (the precursor of EPA and DHA) as placebo. Our a priori specified meta-regression analysis showing a linear dose-response relationship for EPA corroborates this finding. In addition, our meta-regression analysis suggests that omega-3 fatty acids are more effective when given in addition to antidepressants, i.e. augmentation/add-on studies. Furthermore, the pooled effect size for omega-3 fatty acid supplementation specifically for women with post-partum depression was substantially larger in our meta-analysis.

An extra potential advantage is that omega-3 fatty acid supplementation might have a parallel beneficial effect on comorbid (cardiovascular) conditions as well. Similar as in MDD, compared to a healthy diet, fatty acid supplements seem to have less or no primary preventive effects on CVD. However, omega-3 fatty acid supplementation is recommended as an effective secondary preventive intervention against new CVD events in CVD patients. The decreasing effect of omega-3 fatty acids on oxidative stress as shown in our meta-analysis may explain these beneficial clinical effects.

The above line of thought has not yet been implemented in routine clinical practice. Guidelines and handbooks on depression often do not even mention omega-3 fatty acids. This may have to do with the relatively small sample sizes of the performed studies (total N of the Cochrane meta-analysis = 1438), resulting in relatively wide confidence intervals. However, confidence intervals for most meta-analytic outcomes of omega-3 fatty acids for depression (including the Cochrane’s) do not cross zero, and despite that these confidence intervals of overall meta-analytic outcomes include negligible effects, they also include relatively large effects. Concerns that have been raised of publication bias and distortion due to sponsoring seem at most comparable to that for antidepressants. Nevertheless, the adage primum non nocere may withhold clinicians from clinical implementation. Additional final evidence could come from larger but well-executed, long-term, clinical trials that (I) supplement EPA in an add-on design and (II) have attention for biochemical and clinical potential side effects including largely yet unknown long-term biological effects of oxylipins. These trials may convince clinicians and guideline-makers to implement omega-3 fatty acid supplementation for depression in clinical practice.

Conclusion
In conclusion, with (I) an overall effect size equal to that of antidepressants, (II) a side effect profile that is considered to be relatively safe and tolerable, (III) relative low-costs, and (IV) a larger effect size in studies supplementing EPA next to antidepressants, omega-3 fatty acids may hold clinically meaningful potential, especially when prescribing EPA as an augmentation strategy in MDD. Additional final evidence could convince clinicians to implement fatty acid supplementation for MDD in daily care.
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