THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Omega-3 Fatty Acid Supplementation for Perinatal Depression: A Meta-Analysis

Author(s): Roel J. T. Mocking, MD, PhD; Katja Steijn, BSc; Carolien Roos, MD, PhD; Johanna Assies, MD, PhD; Veerle Bergink, MD, PhD; Henricus G. Ruhé, MD, PhD; and Aart H. Schene, MD, PhD

DOI Number: 10.4088/JCP.19r13106

List of Supplementary Material for the article

1. Appendix 1 Search
2. Table 1 Overview of Earlier Meta-Analyses
3. Table 2 Quality of the Evidence of the Overall and Subgroup Meta-Analyses on the Effect of Omega-3 Fatty Acids for Perinatal Depression
4. Figure 1 Risk of Bias Summary
5. Figure 2 Depressed and Postpartum: Forest Plot Showing the Meta-Analysis Effects of Included Randomized Controlled Trials on Omega-3 Fatty Acid Supplementation vs Placebo for Postpartum Depression
6. Figure 3 Funnel Plot

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1: Search (fish oils [MeSH Terms] OR fatty acids, omega 3 [MeSH Terms] OR Omega-3 [Title/Abstract] OR polyunsaturated FA [Title/Abstract] OR fish oil [Title/Abstract] OR EPA [Title/Abstract] OR DHA [Title/Abstract] OR eicosapentaenoic acid [Title/Abstract] OR docosahexaenoic acid [Title/Abstract] OR alpha-linolenic acid [Title/Abstract] OR cod liver oil [Title/Abstract] OR n-3 fatty acids [Title/Abstract] OR n3 polyunsaturated fatty acids [Title/Abstract]) AND (postpartum OR post-partum OR "post partum" OR postnatal* OR post-natal* OR "post natal*" OR peripartum* OR peri-partum* OR "peri partum*" OR perinatal* OR peri-natal* OR "peri natal*" OR puerp* OR intrapartum OR intra-partum OR "intra partum" OR antepartum OR ante-partum OR "ante partum" OR pregnan* OR maternity OR birth OR prenatal* OR pre-natal* OR "pre natal*" OR antenatal* OR ante-natal* OR "ante natal*") AND (depressive disorder [MeSH Terms] OR depression [MeSH Terms] OR depression [Title/Abstract] OR depressive disorder [Title/Abstract] OR depressed mood [Title/Abstract] OR dysthymic disorder [Title/Abstract] OR dysthymia [Title/Abstract] OR depress*)

Supplementary table 1. Overview of earlier meta-analyses

First Author	Publication year	Search date	Population	Number of RCTs	Total N	Pooled effect	Conclusion
Jans[35]	2010	December 2009	Pregnant or post-partum, either depressed or non-depressed	7 (Llorente, Krauss-Etschmann, Rees, Freeman, Su, Mattes, Doornbos)	612	-0.03 (95%CI -0.18 to 0.13; P=.76)	The question of whether EPA and DHA administration is effective in the prevention or treatment of perinatal depression cannot be answered yet.
Dennis[36]	2013	January 2013	Pregnant with antenatal depression	2 (Freeman, Su)	55	NA	The evidence is inconclusive to allow us to make any recommendations for omega-3 fatty acids for the treatment of antenatal depression.
Miller[37]	2013	April 2013	Pregnant or given birth in the previous 6 wks, not taking antidepressants, not depressed	1 (Mozurkewich)	126	NA	There is insufficient evidence to conclude that DHA or EPA prevent postnatal depression.
Grosso[38]	2014	August 2013	Women with perinatal depression (including DSM- defined diagnosis of MDD and prevention of post-partum depression)	6 (Freeman, Su, Rees, Llorente, Doornbos, Mozurkewich)	Separate analyses for: Antenatal MDD (N=121) Healthy pregnant women (N=403)	Antenatal MDD: 0.24 SD (95%CI -0.73 to 1.21; P=.63) Healthy pregnant women: −0.05 SD (95%CI -0.24 to 0.15; P=.64)	Analyses led to inconclusive results.
Wei-Hong[39]	2017	April 2015	Pregnant women with MDD and receiving no other treatment than omega-3 fatty acids	4 (Freeman, Su, Rees, Kaviani)	201	0.75 (95%CI 0.47 to 1.04)	Omega-3 fatty acid supplementation resulted in better efficacy than placebo. Evidence is limited due to the small number of studies and participants.

van Ravesteyn[6]	2017	June 2016	Pregnant women with MDD or dysthymic disorder diagnosed during pregnancy using interview	3 (Freeman, Rees, Su)	81	g = -0.51 (95%CI -1.02 to -0.01; P=.06)	The results of omega-3 fatty acids intake are mixed
Middleton[40]	2018	August 2018	Pregnant women, depressed or non-depressed	9 in total (Freeman, Kaviani, Mozurkewich, Rees, Su, Vaz, Carlson, Judge, Makrides) Postnatal depression: 2 (Judge, Mozurkewich)	Postnatal depressio n: 2431	Postnatal depression: average RR 0.99 (95%CI 0.56 to 1.77)	The effects of omega-3 supplementation on perinatal depression cannot be determined due to insufficient evidence.
Smith[41]	2019	March 2018	Pregnant women with depression during the antenatal period	3 (Freeman, Mozurkewich, Su)	172	−0.12 (95%CI −0.76 to 0.52); Z=.37; P=.71	There is insufficient evidence for an effect of fish oil. This may be due to small sample sizes, heterogeneity, high risk of biases and too few studies.

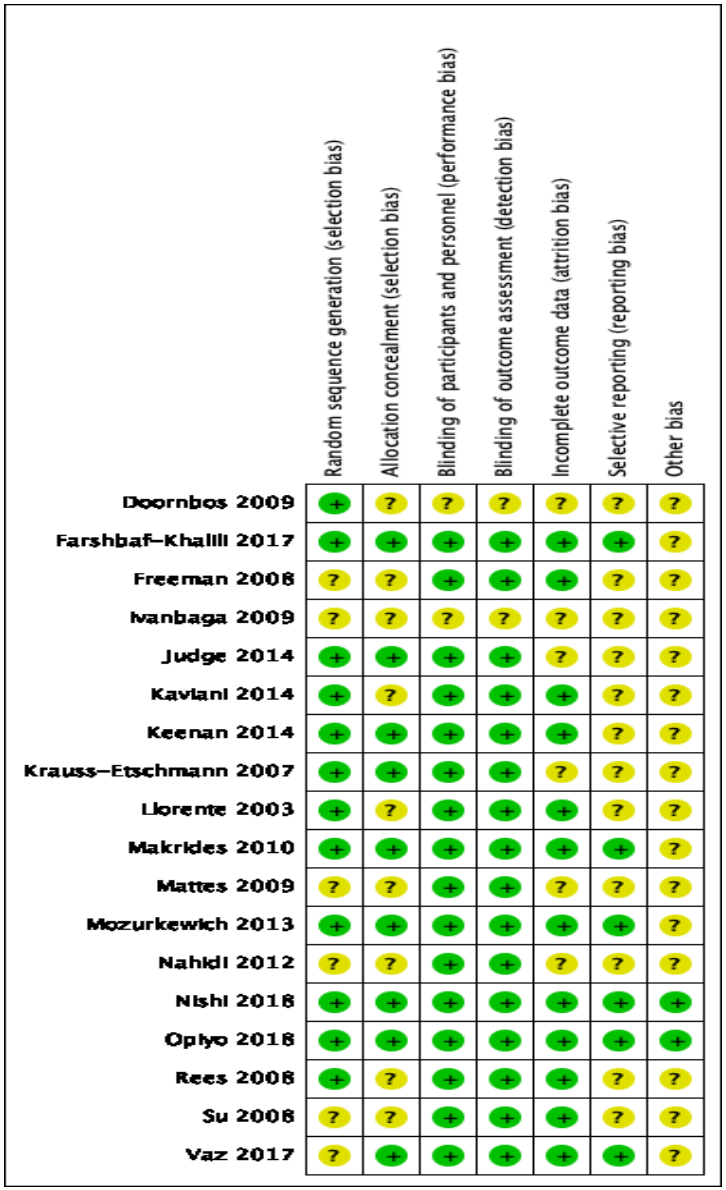
Supplementary table 2. Quality of the evidence of the overall and subgroup meta-analyses on the effect of omega-3 fatty acids for perinatal depression

Subgroup	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	Final GRADE score
Overall	+4, RCTs	-1, other[1]	0[2]	0	-1, imprecision	0, undetected	0	⊕⊕⊖⊖ low
Depressed	+4, RCTs	-1, other[1]	-1, heterogeneity	0	-1, imprecision	0, undetected	0	⊕⊖⊖⊖ very low
Non-depressed	+4, RCTs	-1, other[1]	0, no heterogeneity	0	0	0, undetected	0	⊕⊕⊕⊖ moderate
Pregnant	+4, RCTs	-1, other[1]	0, no heterogeneity	0	0	0, undetected	0	⊕⊕⊕⊖ moderate
Postpartum	+4, RCTs	-1, other[1]	-1, heterogeneity	0	-1, imprecision	0, undetected	0	⊕⊖⊖⊖ very low
Postpartum depressed	+4, RCTs	-1, other[1]	-1, heterogeneity	0	-1, imprecision	0, undetected	0	⊕⊖⊖⊖ very low

[1] Several potential biases remained unclear, e.g. due to the lack of a pre-published protocol.

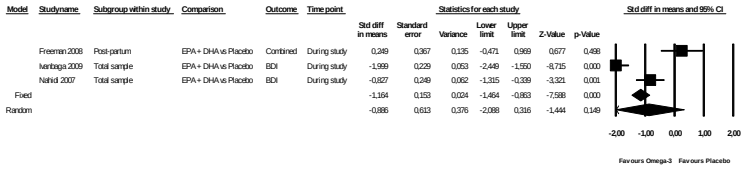
[2] Heterogeneity explained by differences in populations

Supplementary figure 1. Risk of bias summary



Supplementary figure 2. Depressed and postpartum

Forest plot showing the meta-analysis effects of included randomized controlled trials on omega-3 fatty acid supplementation vs. placebo for postpartum depression.



Supplementary figure 3. Funnel plot

The funnel plot showed no clear asymmetry, apart from one positive outlier with a medium sample size (20). Classic and Orwin's fail-safe N's were 65 and 18, respectively. This means that 65 studies must have been missed to bring the P-value to insignificance for the fixed effects main analysis, and 18 studies without an effect must have been missed to bring the effect size to <0.1 SDM. Regarding the Begg and Mazumbar rank-correlation test, Kendall's tau's with and without continuity correction were -0.26 ($P_{2\text{-sided}}$=0.13), and -0.27 ($P_{2\text{-sided}}$=0.12), respectively, indicative of no publication bias. Egger's regression intercept was -0.82 (95%CI=-2.99 to 1.35; $P_{2\text{-sided}}$=0.44), also suggesting no significant publication bias. Duval and Tweedie's trim-and-fill method using random or fixed effects model suggested that no studies were missed to the right of the mean (i.e. that would reduce the overall effect for omega-3 PUFAs vs. placebo).