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- Advise patients on the evidence for the use of omega-3 PUFA supplementation in the treatment of peripartum major depressive episodes

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

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ABSTRACT

Objective: Several randomized controlled trials (RCTs) investigated omega-3 polyunsaturated fatty acids (PUFAs) (ie, fish oil) in perinatal depression, but their efficacy remains unclear. We performed a meta-analysis of RCTs on omega-3 PUFAs for perinatal depression, comparing a priori defined subgroups: pregnant women vs postpartum women and prevention vs treatment of perinatal depression.

Methods: We searched Web of Science, Embase, PsycINFO, and the Cochrane Library, combining omega-3 PUFAs and perinatal depression terms and including publications up to February 18, 2019, for RCTs on omega-3 PUFAs compared to placebo or any active comparator.

Results: Data from 18 RCTs on 4,052 participants showed an overall significant small beneficial effect of omega-3 PUFAs on depressive symptoms compared to placebo (−0.236 standardized difference in means [SDM]; 95% CI = −0.463 to −0.009; $P = .042$). Heterogeneity was considerable ($I^2 = 88.58$; $P < .001$), with significant subgroup differences explaining 55% of between-study variance ($P = .001$). In depressed women, omega-3 PUFAs showed a medium effect (SDM = −0.545; 95% CI = −1.182 to 0.093; $P = .094$) vs no effect in nondepressed women (SDM = −0.073). Moreover, the effect was medium to large in postpartum women (SDM = −0.656; 95% CI = −1.690 to 0.378; $P = .214$) compared to a negligible effect during pregnancy (SDM = −0.071). RCTs specifically studying postpartum depression showed the largest effect (SDM = −0.886; 95% CI = −2.088 to 0.316; $P = .149$).

Conclusions: Omega-3 PUFAs have an overall significant small beneficial effect on perinatal depression, with important subgroup differences. We advise against prescribing omega-3 PUFAs for the treatment or prevention of depressive symptoms during pregnancy, given a lack of effect with low heterogeneity. In contrast, omega-3 PUFA supplementation may be a promising (add-on) treatment for postpartum depression.

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Clinical Points

- This meta-analysis showed that omega-3 PUFA supplementation has an overall small but significant beneficial effect on perinatal depression, with important subgroup differences.
- Result advise against prescribing omega-3 PUFAs for the treatment or prevention of depressive symptoms during pregnancy but suggest that omega-3 PUFAs can be a promising (add-on) treatment option for postpartum major depressive episodes.
- Based also on data from outside the perinatal period, the use of a supplement with > 50% EPA providing 2,200 mg EPA per day for women with a major depressive episode in the postpartum period is advised.

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Untreated perinatal (or peripartum) major depressive disorder can have long-lasting negative effects on mothers and their children. Depression during pregnancy has been associated with a range of adverse child outcomes later in life. Moreover, depression in the postpartum period is known to have a negative impact on mother-infant bonding. In the most severe cases, postpartum depression can lead to tragic outcomes such as suicide or infanticide.[1–4] Adequate treatment of perinatal depression is therefore a public health priority.

There are no controlled studies on the effect of psychotropic medication for depression during pregnancy, which makes decisions regarding the use of antidepressants complex.[5] Antidepressants are generally considered to be safe to use during pregnancy, but many patients consider tapering their medication before or during pregnancy. Some guidelines advise to continue antidepressants, but most guidelines do not advise on continuation or discontinuation. Ideally, clinicians and patients make a shared decision based on the severity of the mood disorder, comorbidities, previous episodes and previous attempts to taper, and the preference of the patient.[1,5,6] In the postpartum period, selective serotonin reuptake inhibitors are associated with higher response and remission rates of depression compared with placebo.[7] In clinical practice, many women wish to avoid the use of antidepressants both during pregnancy and while breastfeeding, and they prefer alternative treatment options. While psychotherapy has shown to be effective in both the treatment and prevention of depression during the perinatal period, psychotherapy is not widely available for everyone, which makes the search for safe and effective alternatives for both medication and psychotherapy pressing.[1]

A promising option in this regard may be the use of omega-3 polyunsaturated fatty acids (PUFAs), ie, eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA). These PUFAs are essential nutrients, meaning that humans can obtain them only through dietary intake, of (fatty) fish in particular.[8] Outside the perinatal period, both fish intake and omega-3 PUFA concentrations are inversely associated with the incidence of major depressive episodes, which is supported by several meta-analyses[9–11] on beneficial effects of omega-3 PUFA supplementation in patients with major depression. In particular, high dosages of the omega-3 PUFA EPA have shown antidepressant effectiveness, possibly due to the anti-inflammatory properties of its metabolites.[11]

Interestingly, ecological evidence also suggests an inverse association between fish intake and major depressive episodes during the perinatal period.[12] This association was supported by case-control and prospective studies showing associations between low omega-3 PUFA concentrations and perinatal major depressive episode risk,[13–15] which were recently integrated in a meta-analysis.[16] These studies support the idea that supplementation of omega-3 PUFAs may be an effective treatment option for depression specifically during the perinatal period. Further corroborating these findings are the physiological roles of omega-3 PUFAs in the perinatal period. Both pregnancy and the postpartum period are thought to increase omega-3 PUFA requirements, to support fetal brain development.[13] Moreover, the postpartum period is a period of relative immune stimulation, and the anti-inflammatory and neurotrophic effects of PUFAs could be particularly beneficial during this period.[8] It is not surprising that obstetric clinical guidelines advise women to consume up to 3 or 4 servings of (fatty) fish each week.[13] However, very few women actually meet these requirements, with one of the reasons being their concern for mercury poisoning.[13]

Multiple randomized controlled trials (RCTs) tested the effect of omega-3 PUFA supplementation on depressive symptoms in the perinatal period, with various results.[16–34] Prior systematic reviews and meta-analyses have aimed to pool these data, with large variety in methodology and outcomes (see Supplementary Table 1 for an overview). Notably, the number of included RCTs differs greatly between prior meta-analyses, potentially suggesting selection bias. Of note, the largest number of RCTs was included in the oldest meta-analysis,[35] and there is a need for a more contemporary, timely, and extensive meta-analysis. This is especially true because prior studies limited their inclusion based on timing (during pregnancy vs postpartum) or indication (depressive symptoms vs major depressive episode diagnosis). Thus far, all available meta-analyses concluded that the evidence remains inconclusive.[6,35–41]

The absence of recommendations is problematic because omega-3 PUFAs are currently widely used during pregnancy and the postpartum period (both to prevent and to treat depressive symptoms), and women ask their health care professionals for advice with regard to safety and effectiveness. To facilitate clinical decision making, we aimed at continuing the debate on the effectiveness of omega-3 PUFAs for the treatment of perinatal depressive symptoms by performing a meta-analysis of all available RCTs and performing a meta-regression. Following the *DSM-5* view of perinatal depression as a continuum of depressive symptoms associated with the entire perinatal period, we did not limit our search according to timing or indication. Thereby, we were able to include all available evidence and more than doubled the number of pooled RCTs, which substantially increased the available evidence base. Moreover, this provided the opportunity to use meta-regression to statistically test differences according to a priori planned subgroup analyses comparing effects in women diagnosed with a major depressive episode at baseline vs women that were not and in postpartum vs pregnant women.

METHODS

Literature Search

Methods have been described a priori in a protocol in the PROSPERO database (CRD42016044046) following PRISMA guidelines.[42] We conducted a literature search from inception up to February 18, 2019, in Web of Science, the Embase and PsycINFO databases from Ovid, and additionally CENTRAL (the Cochrane database of controlled trials; Cochrane Library). We used a sensitive search strategy combining terms regarding omega-3 PUFAs and perinatal depression (Supplementary Appendix 1: Search). In addition, we searched references of selected studies and earlier reviews for additional relevant studies.

Selection of Studies

DSM-5 defines perinatal depression as a major depressive episode with onset during pregnancy or following delivery, according to the observation that 50% of "postpartum" episodes actually begin prior to delivery.[43] Moreover, although the *DSM-5* uses a cutoff after 4 weeks postpartum, perinatal depression can have an onset "during pregnancy or in the weeks or months following delivery."[43] In line with this view, and in order to include all relevant data in our meta-analysis, we included all studies that investigated the perinatal period as ranging from the beginning of pregnancy until 6 months postpartum. In addition, *DSM-5* describes perinatal major depression as "the more severe part of a spectrum/continuum of depressive symptoms during the perinatal period."[43] In line with this continuum, we applied a dimensional perspective on perinatal depressive symptoms. Specifically, we included studies on the complete spectrum/continuum of depressive symptoms by including RCTs that measured depressive symptoms in participants that do or do not fulfill major depressive episode criteria.

We included studies that used a randomized controlled trial design to study the effect of omega-3 PUFAs (ie, fish oil) compared to placebo or any active comparator available. We did not exclude studies based on concomitant therapy (eg, antidepressants or psychotherapy). Two independent reviewers (K.S./C.R. and R.J.T.M.) performed study selection; discrepancies were resolved by discussion, with a third reviewer (J.A.) when necessary.

Data Extraction

We extracted data in duplicate using a standardized, pre-piloted data extraction form. Extracted data included the number of participants, the number and nature of comparisons in the trial, the number and characteristics of outcomes, the number of time points, the participants' characteristics (pregnant vs postpartum, major depressive episode diagnosis at baseline vs no major depressive episode diagnosis at baseline), study duration, intervention components and dosages, type of analyses performed (intention to treat vs other), concomitant treatment, and study outcome data. The outcome data consisted of all available depression related outcomes for all studies, including the Edinburgh Postnatal Depression Scale (EPDS),[44] Beck Depression Inventory (BDI),[45] Hamilton Depression Rating Scale (HDRS),[46] or Postpartum Depression Screening Scale (PDSS).[47]

Bias and Quality Assessment

We assessed risk of bias for individual studies in duplicate using the Cochrane Collaboration's tool for assessing risk of bias.[48] In addition, we applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology framework to make systematic judgments about quality of evidence.[49] We resolved any possible disagreement through discussion, with a third reviewer (J.A.) where necessary.

Publication Bias

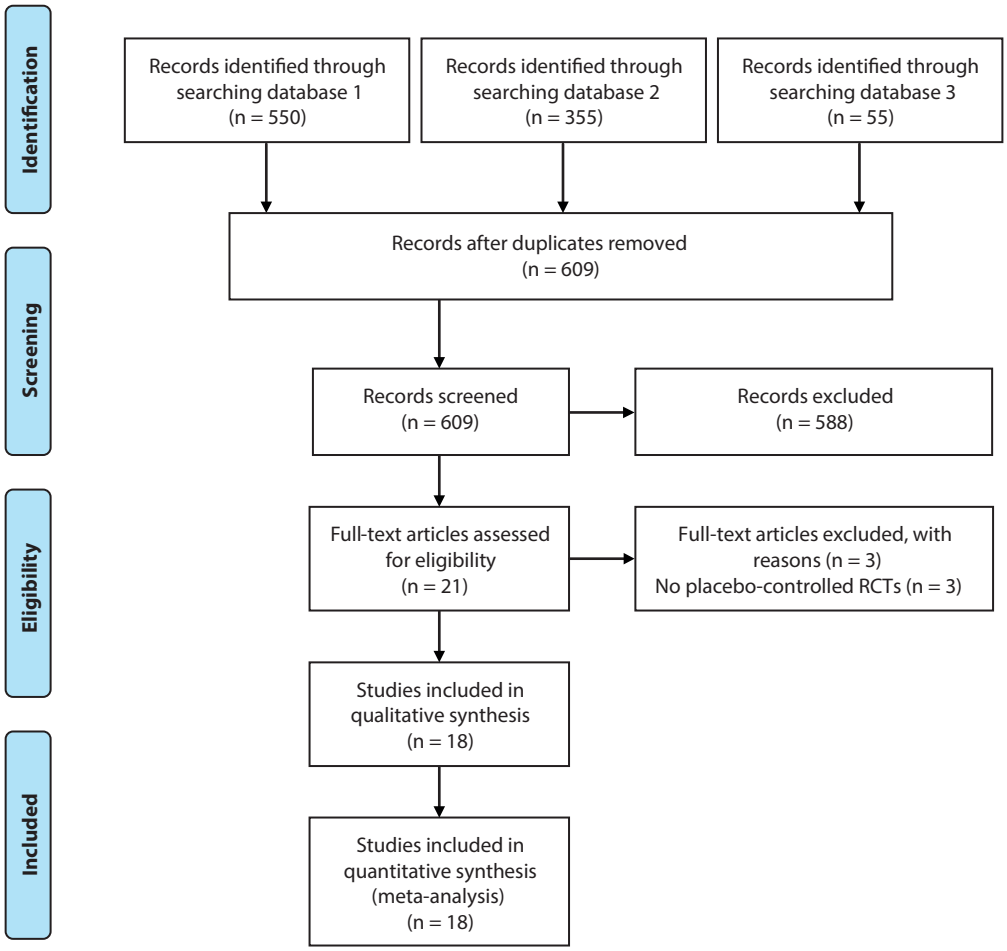
We assessed publication bias by plotting a funnel plot, reporting the classic and Orwin's fail-safe *N*, Begg and Mazumdar rank correlation, and Egger's regression intercept. We used Duval and Tweedie's trim-and-fill method to report adjusted values if applicable.[50]

Procedure for Meta-Analyses

We performed quantitative data synthesis at the study level using Comprehensive Meta-Analysis.[50] We presented random (primary) and fixed (sensitivity) effects meta-analysis results for all studies (ie, combined analysis). We used standardized differences of means (SDM) for continuous outcomes and calculated 95% confidence intervals and 2-sided *P* values for each outcome. We assessed heterogeneity between the studies using the I^2 statistic. We considered an I^2 value greater than 50% indicative of substantial heterogeneity.

In light of concerns of publication bias in previous meta-analyses on omega-3 fatty acid supplementation, we included

Figure 1. PRISMA Flow Diagram



Abbreviation: RCT = randomized controlled trial.

fixed effects sensitivity analyses in our protocol (as published in PROSPERO) since fixed effects models are thought to be less sensitive to publication bias, given that they assign less weight to smaller/imprecise studies.[51] Nevertheless, because we found no evidence for publication bias, primary results and conclusions are based solely on random effects models.

We performed a priori planned subgroup analyses comparing effects of omega-3 PUFAs vs placebo in participants that were diagnosed with a major depressive episode at baseline vs participants that were not, according to scores above cutoff on depression questionnaires or diagnostic interviews. A study sample was defined as depressed when baseline scores were 12.5 (EPDS), 14 (BDI), 8 (HDRS), 60 (PDSS), or higher.[44–47] In addition, we performed a priori planned subgroup analyses of studies performed in postpartum vs pregnant women. We used method of moment meta-regression to assess the amount of variance that could be explained by subdivision according to these subgroups, expressed as R^2. The power for additional meta-regression for supplementation omega-3 PUFA dose and add-on vs single therapy was insufficient.

RESULTS

Selection of Studies

The literature search produced a set of 609 articles. Based on title and abstract, 588 articles were excluded. After full-text assessment of the remaining 20 articles, 18 could be included in the meta-analysis (Figure 1). There was no apparent overlap between the investigated samples.

Study Characteristics

The 18 RCTs included a total of 4,052 participants (median = 84.5, interquartile range = 58). Thirteen RCTs started supplementation during pregnancy, 3 started postpartum, and 2 included a mixed sample. Seven RCTs included patients with a major depressive episode, 3 included nondepressed participants, and 8, a mixed sample. Two RCTs specifically included postpartum women with a major depressive episode. The EPA doses ranged from 0–2,200 mg/d, and DHA doses, from 120–1,638 mg/d. Most studies used supplements with both DHA and EPA. Three studies supplemented DHA only, and no studies

Table 1. Data Extraction Table Providing Study Characteristics of Included Studies

First Author	Year	Population	N	Intervention	Control	Supplementation Length	Outcome	Analyses	Other
Doornbos[17]	2009	Apparently healthy, pregnant 14–20 (mean 16.5) wk	Total: 119 DHA: 42 DHA + AA: 41 C: 36	220 mg of DHA or DHA and AA (220 mg each)	Soybean oil	Until 3 mo postpartum	Mean EPDS scores 36 wk gestation and 6 wk postpartum	PP	
Farshbaf-Khalili[18]	2017	Pregnant 16–20 wk, EPDS < 20, no MDD	Total: 150 I: 75 C: 75	120 mg of DHA, 180 mg of EPA, and 400 mg of ALA	1,000 mg of liquid paraffin	From the end of the 20th week gestation until 1 month after birth	Mean EPDS score 26–30, 35–37 wk and 30–45 days postpartum	ITT	According to the psychiatrists' examination, no participants received antidepressant intervention during the study
Freeman[27]	2008	Pregnant 12–32 wk or < 6 mo postpartum, MDD (if postpartum onset within 4 wk), EPDS ≥ 9	Total: 51 I: 28 C: 23	1,100 mg of EPA and 800 mg of DHA	Corn oil	8 wk	Mean EPDS and HDRS score every 2 wk, during supplementation	mITT (> 1 FU visit)	Current users of antidepressants excluded. Concomitant psychotherapy. Subgroups for pregnant and postpartum
Ivanbaga[28]	2009	2 wk–3 mo postpartum, postpartum depression (onset within 2–12 wk), EPDS ≥ 11	Total: 116 I: 58 C: 58	1,000 mg of omega-3 fatty acids	330 mg of starch	8 wk	BDI weekly, during supplementation	PP	"No tendency to use antidepressants." Dutch translation from Persian manuscript
Judge[29]	2014	Healthy, pregnant 24 wk, no medical history	Total: 42 I: 20 C: 22	300 mg of DHA, 5 days a week	Corn oil	From 24 wk gestation until delivery	PDSS 2 and 6 wk and 3 and 6 mo postpartum	PP	
Kaviani[30]	2014	Pregnant > 20 wk, mild depression, BDI 14–19	Total: 80 I: 40 C: 40	1,000 mg of omega-3 fatty acids	1,000 mg olive oil	6 wk	BDI 6 wk	ITT	No antidepressants or psychological consultations
Keenan[31]	2014	Pregnant 16–21 wk, African American	Total: 63 I: 43 C: 20	450 mg of DHA; 40 mg of docosapentaenoic acid and eicosatetraenoic acid; 90 mg of EPA; and 15 IU vitamin E	Corn and soybean oil	Up to 30 wk gestation	EPDS 24 and 30 wk gestation	PP	Users of psychotropic medications excluded. Depression was not set as an exclusion or inclusion criterion
Krauss-Etschmann[32]	2007	Apparently healthy, pregnant < 20 wk	Total: 270 I PUFA: 69 I PUFA + MTHF: 64 C: 72 C MTHF: 65	500 mg of DHA and 150 mg of EPA, 2 × 2 combined with 400 µg of 5-MTHF	Milk-based sachet	From 22 wk gestation until delivery	EPDS at delivery, continuous and dichotomous	PP	Only *P* values reported
Llorente[33]	2003	Pregnant women	Total: 89 I: 44 C: 45	200 mg of DHA	Identical placebo	4 mo, starting < 1 week after delivery	BDI 3 wk, 2 and 4 mo; EPDS 18 mo; SCID-CV 4 and 18 mo	PP	
Makrides[19]	2010	Pregnant < 21 wk, mixed MDD and non-MDD	Total: 2,399 I: 1,197 C: 1,202	800 mg of DHA and 100 mg of EPA	500 mg vegetable oil (grapeseed, sunflower, and palm) without DHA	Until delivery	Events for EPDS > 12, 6 wk and 6 mo postpartum	ITT	Separate outcome reporting for women without current or previous MDD
Mattes[20]	2009	Pregnant < 20 wk	Total: 75 I: 37 C: 38	4,000 mg of 56% DHA and 27.7% EPA (< 4% n-6)	4,000 mg olive oil	From 20 wk gestation until delivery	BDI in first week postpartum	PP	Only *P* values reported, results from earlier meta- analysis
Mozurkewich[21]	2013	Pregnant 12–20 wk, risk for MDD with EPDS 9–19 or history of MDD	Total: 118 I EPA: 39 I DHA: 38 C: 41	1,060 mg of EPA and 274 mg of DHA, or 900 mg of DHA and 180 mg of EPA	98% soybean oil and 1% each of lemon and fish oil	Until 6–8 wk postpartum	BDI 6–8 wk postpartum	mITT	No MDD or antidepressant use at study entrance

(continued)

Table 1 (continued).

First Author	Year	Population	N	Intervention	Control	Supplementation Length	Outcome	Analyses	Other
Nahidi[34]	2012	2–3 wk postpartum, postpartum depression, EPDS ≥ 13	Total: 70 I: 35 C: 35	1 g omega-3 capsule (12% DHA and 18% EPA)	330 mg starch	4 wk	BDI	Unknown	English abstract, Persian manuscript with Dutch translation
Nishi[22]	2018	Pregnant 12–24 wk, depressive symptoms, EPDS ≥ 9	Total: 108 I: 55 C: 53	1,206 mg of EPA and 609 mg of DHA	320 mg of olive oil and 9.9 mg of omega-3 fatty acids	12 wk	HDRS 12 wk	ITT	
Opiyo[23]	2018	Pregnant 14–27 wk, HIV-seropositive, BDI ≥ 14	Total: 182 I: 86 C: 96	2,150 mg of EPA and 1,020 mg of DHA	Soybean oil	8 wk	BDI 4 and 8 wk	PP	Participants were on antiretroviral therapy. Participants who had used antidepressants 2 wk prior to the study were excluded. Some participants attended support group meetings during the study
Rees[24]	2008	From third trimester to 6 mo postpartum, MDD	Total: 26 I: 13 C: 13	6,000 mg fish oil: 27.3% DHA, 6.9% EPA (total omega-3 fatty acids 35.6%) and 3.3% omega-6 fatty acids, monounsaturated fats and a small amount of saturated fat	Sunola oil	6 wk	EPDS, HDRS, MADRS	ITT, LOCF	No antidepressant or psychological therapy
Su[25]	2008	Pregnant 16–32 wk, MDD	Total: 36 I: 18 C: 18	2,200 mg of EPA and 1,200 mg of DHA	Olive oil	8 wk	HDRS 2, 4, 6, and 8 wk	mITT	1 month no psychotropics
Vaz[26]	2017	Pregnant 5–13 wk, history of depression or baseline EPDS ≥ 9, no chronic diseases	Total: 60 I: 32 C: 28	1,080 mg of EPA and 720 mg of DHA	Soybean oil	16 wk, from 22 to 24 wk gestation	EPDS 22–24, 30–32 wk of gestation and 4–6 wk postpartum	ITT	Psychiatric or psychological treatment exclusion criterion

Abbreviations: AA = arachidonic acid, BDI = Beck Depression Inventory, C = control group (placebo), DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, EPDS = Edinburgh Postnatal Depression Scale, FU = follow-up, HDRS = Hamilton Depression Rating Scale, I = intervention, ITT = intention to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, mITT = modified intention to treat, MTHF = methyltetrahydrofolic acid, PP = per protocol, PPD = perinatal depression, PPDS = Postpartum Depression Screening Scale, SCID = Structured Clinical Interview for *DSM* Diagnoses.

supplemented only EPA. Not all studies had depression as a primary outcome; for example, Doornbos et al[17] primarily studied infant neurodevelopment. All RCTs compared omega-3 PUFAs to placebo. Table 1 shows detailed characteristics of all included studies, and Supplementary Figure 1 and Supplementary Table 2 show quality assessments. While none of the studies showed concrete evidence for high risk of bias, several potential biases remained unclear, for example, due to the lack of prepublished protocols.

Main Analyses

Random effects meta-analysis of all studies combined provided a significant main effect of −0.236 (SDM; 95% CI = −0.463 to −0.009; Z value = −2.036; P = .042; Figure 2). This shows that overall, the decreasing effect of omega-3 PUFAs on perinatal depression was significantly greater than that of placebo. There was significant heterogeneity (I^2 = 88.58; Q = 78.81; P < .001). The a priori specified fixed effects sensitivity analyses resulted in a main effect of −0.158 (SDM; 95% CI = −0.240 to −0.076; Z value = −3.776; P < .001).

Subgroup Analyses

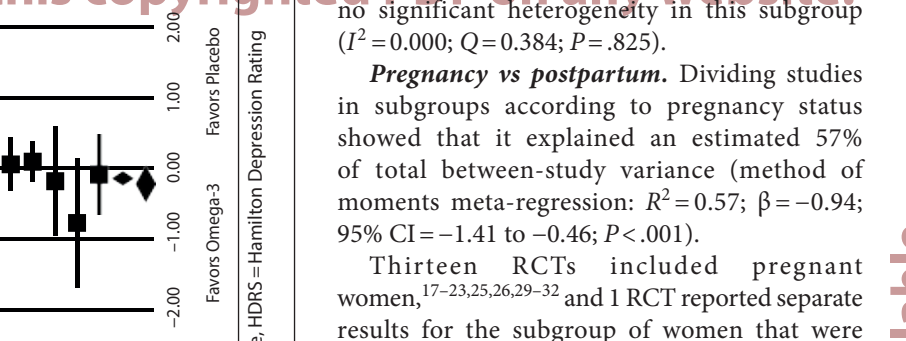
Depressed vs nondepressed participants. Dividing studies into subgroups according to baseline depression status showed that it explained no between-study variance (method of moments meta-regression: R^2 = 0.00; β = −0.53; 95% CI = −1.49 to 0.43; P = .28).

Seven RCTs included only depressed patients.[23–25,27,28,30,34] Meta-analysis in this a priori defined subgroup resulted in medium effect sizes (Figure 3; random: −0.545 [SDM; 95% CI = −1.182 to 0.093]; Z value = −1.673; P = .094; fixed: −0.452 [SDM; 95% CI = −0.628 to −0.276]; Z value = −5.043; P < .001). There was still significant heterogeneity in this subgroup (I^2 = 91.40; Q = 69.78; P < .001).

Two RCTs included only participants with no major depressive episode diagnosed at baseline,[17,33] and 1 RCT reported separate results for the subgroup of participants without depression.[19] Meta-analysis in this a priori defined subgroup resulted in no effect of omega-3 PUFAs on depressive symptoms (random: −0.073 [SDM; 95% CI = −0.255 to 0.108]; Z value = −0.793; P = .428; fixed: −0.073 [SDM; 95% CI = −0.255 to 0.108]; Z value = −0.793; P = .428). There was

Figure 2. Forest Plot Showing the Overall Meta-Analysis of Included Randomized Controlled Trials on the Effect of Omega-3 Fatty Acid Supplementation vs Placebo for Perinatal Depression

Model	Study Name	Subgroup Within Study	Comparison	Outcome	Time Point	Statistics for Each Study							Std Diff in Means and 95% CI
						Std Diff in Means	Standard Error	Variance	Lower Limit	Upper Limit	Z Value	P Value	
	Doornbos 2009[17]	Total sample	Combined	EPDS	Combined	0.022	0.242	0.059	−0.452	0.497	0.092	.926	
	Farshbaf-Khalili 2017[18]	Total sample	EPA + DHA + ALA vs placebo	EPDS	Combined	−0.199	0.164	0.027	−0.520	0.122	−1.213	.225	
	Freeman 2008[27]	Combined	EPA + DHA vs placebo	Combined	During study	0.312	0.284	0.080	−0.244	0.868	1.100	.271	
	Ivanbaga 2009[28]	Total sample	EPA + DHA vs placebo	BDI	During study	−1.999	0.229	0.053	−2.449	−1.550	−8.715	.000	
	Judge 2014[29]	Total sample	DHA vs placebo	PDSS	2–24 wk postpartum	−0.777	0.320	0.103	−1.405	−0.149	−2.426	.015	
	Kaviani 2014[30]	Total sample	EPA + DHA vs placebo	BDI	During study	−0.433	0.226	0.051	−0.876	0.010	−1.914	.056	
	Keenan 2014[31]	Total sample	DHA vs placebo	EPDS	Combined	0.149	0.294	0.086	−0.427	0.725	0.506	.613	
	Krauss-Etschmann 2007[32]	Total sample	Combined	Combined	During study	0.000	0.172	0.030	−0.338	0.338	0.001	.999	
	Llorente 2003[33]	Total sample	DHA vs placebo	Combined	Combined	0.048	0.324	0.105	−0.587	0.684	0.149	.881	
	Makrides 2010[19]	Combined	DHA + EPA vs placebo	Combined	Combined	−0.101	0.062	0.004	−0.221	0.020	−1.631	.103	
	Mattes 2009[20]	Total sample	EPA + DHA vs placebo	BDI	During study	0.241	0.232	0.054	−0.213	0.695	1.040	.298	
	Mozurkewich 2013[21]	MDD risk	Combined	Combined	6–8 wk postpartum	0.014	0.416	0.173	−0.800	0.828	0.034	.973	
	Nahidi 2007[34]	Total sample	EPA + DHA vs placebo	BDI	During study	−0.827	0.249	0.062	−1.315	−0.339	−3.321	.001	
	Nishi 2018[22]	Combined	EPA + DHA vs placebo	HDRS	12 wk	0.055	0.193	0.037	−0.323	0.432	0.283	.777	
	Opiyo 2018[23]	Total sample	EPA + DHA vs placebo	BDI	Combined	0.094	0.147	0.022	−0.194	0.382	0.640	.522	
	Rees 2008[24]	Total sample	EPA + DHA vs placebo	Combined	During study	−0.183	0.393	0.155	−0.954	0.588	−0.466	.642	
	Su 2008[25]	Total sample	EPA + DHA vs placebo	Combined	During study	−0.774	0.468	0.219	−1.692	0.144	−1.653	.098	
	Vaz 2017[26]	Total sample	EPA + DHA vs placebo	Combined	Combined	−0.086	0.291	0.085	−0.656	0.484	−0.296	.767	
Fixed						−0.158	0.042	0.002	−0.240	−0.076	−3.776	.000	
Random						−0.236	0.116	0.013	−0.463	−0.009	−2.036	.042	



Abbreviations: ALA = alpha-linolenic acid, BDI = Beck Depression Inventory, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, EPDS = Edinburgh Postnatal Depression Scale, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, PDSS = Postpartum Depression Screening Scale, std diff = standardized difference.

no significant heterogeneity in this subgroup ($I^2 = 0.000$; $Q = 0.384$; $P = .825$).

Pregnancy vs postpartum. Dividing studies in subgroups according to pregnancy status showed that it explained an estimated 57% of total between-study variance (method of moments meta-regression: $R^2 = 0.57$; $\beta = -0.94$; 95% CI = −1.41 to −0.46; $P < .001$).

Thirteen RCTs included pregnant women,[17–23,25,26,29–32] and 1 RCT reported separate results for the subgroup of women that were pregnant.[27] Meta-analysis in this a priori defined subgroup resulted in negligible effect sizes (Figure 4A; random: −0.071 [SDM; 95% CI = −0.188 to 0.045]; Z value = −1.204; $P = .229$; fixed: −0.078 [SDM; 95% CI = −0.165 to 0.009]; Z value = −1.765; $P = .078$). There was no significant heterogeneity in this subgroup ($I^2 = 18.977$; $Q = 16.045$; $P = .247$).

Three RCTs included postpartum women,[28,33,34,52] and 1 RCT reported separate results for the subgroup of participants that were postpartum.[27] Meta-analysis in this a priori defined subgroup resulted in medium to large effect sizes: (Figure 4B; random: −0.656 [SDM; 95% CI = −1.690 to 0.378]; Z value = −1.243; $P = .214$; fixed: −0.942 [SDM; 95% CI = −1.213 to −0.670]; Z value = −6.795; $P < .001$). There was significant heterogeneity in this subgroup ($I^2 = 92.736$; $Q = 41.301$; $P < .001$).

Postpartum depression. Including the depressed vs nondepressed, pregnancy vs postpartum subdivisions and their interaction explained an estimated 55% of between study variance in total (method of moments meta-regression: $R^2 = .55$; $Q_{\text{test of model}} = 10.88$, $df = 3$, $P = .012$; $Q_{\text{goodness of fit}} = 18.19$, $df = 4$, $P = .001$).

Meta-analysis of the 2 RCTs that specifically included postpartum women with a major depressive episode and the 1 RCT that reported separate results for the subgroup of postpartum women with a major depressive episode[27,28,34,52] showed the largest pooled effect (Supplementary Figure 2; random: −0.886 [SDM; 95% CI = −2.088 to 0.316]; Z value = −1.444; $P = .149$; fixed: −1.164 [SDM; 95% CI = −1.464 to −0.863]; Z value = −7.588; $P < .001$), with considerable heterogeneity ($I^2 = 93.305$; $Q = 29.873$; $P < .001$).

Publication Bias

The different approaches to assess publication bias showed no indication for any publication bias (Supplementary Figure 3).

DISCUSSION

This meta-analysis pooled all 18 available RCTs (n = 4,052 women) regarding the effect of omega-3

Figure 3. Forest Plot Showing Meta-Analyses of Included Randomized Controlled Trials on the Effect of Omega-3 Fatty Acid Supplementation vs Placebo for Perinatal Depression, Studies Subgrouped According to Depression Status (Depressed vs Nondepressed)

Model	Group By MDD?	Study Name	Subgroup Within Study	Comparison	Outcome	Time Point	Statistics for Each Study: Std Diff in Means	Standard Error	Variance	Lower Limit	Upper Limit	Z Value	P Value
	No	Doornbos 2009[17]	Total sample	Combined	EPDS	Combined	0.022	0.242	0.059	−0.452	0.497	0.092	.926
	No	Llorente 2003[33]	Total sample	DHA vs placebo	Combined	Combined	0.048	0.324	0.105	−0.587	0.684	0.149	.881
	No	Makrides 2010[19]	No previous or current MDD	DHA + EPA vs placebo	EPDS > 12	Combined	−0.104	0.105	0.011	−0.311	0.102	−0.991	.321
Fixed	No						−0.073	0.093	0.009	−0.255	0.108	−0.793	.428
Random	No						−0.073	0.093	0.009	−0.255	0.108	−0.793	.428
	Yes	Freeman 2008[27]	Combined	EPA + DHA vs placebo	Combined	During study	0.312	0.284	0.080	−0.244	0.868	1.100	.271
	Yes	Ivanbaga 2009[28]	Total sample	EPA + DHA vs placebo	BDI	During study	−1.999	0.229	0.053	−2.449	−1.550	−8.715	.000
	Yes	Kaviani 2014[30]	Total sample	EPA + DHA vs placebo	BDI	During study	−0.433	0.226	0.051	−0.876	0.010	−1.914	.056
	Yes	Nahidi 2007[34]	Total sample	EPA + DHA vs placebo	BDI	During study	−0.827	0.249	0.062	−1.315	−0.339	−3.321	.001
	Yes	Opiyo 2018[23]	Total sample	EPA + DHA vs placebo	BDI	Combined	0.094	0.147	0.022	−0.194	0.382	0.640	.522
	Yes	Rees 2008[24]	Total sample	EPA + DHA vs placebo	Combined	During study	−0.183	0.393	0.155	−0.954	0.588	−0.466	.642
	Yes	Su 2008[25]	Total sample	EPA + DHA vs placebo	Combined	During study	−0.774	0.468	0.219	−1.692	0.144	−1.653	.098
Fixed	Yes						−0.452	0.090	0.008	−0.628	−0.276	−5.043	.000
Random	Yes						−0.545	0.325	0.106	−1.182	0.093	−1.673	.094

Abbreviations: BDI = Beck Depression Inventory, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, EPDS = Edinburgh Postnatal Depression Scale, MDD = major depressive disorder, std diff = standardized difference.

PUFAs on perinatal depression. Pooled results showed an overall significant small beneficial effect. Results differed significantly between predefined subgroups: studies in postpartum women showed a beneficial effect of omega-3 PUFA supplementation (with large effect size), compared to lack of effect for studies that started supplementation during pregnancy. In addition, studies that included depressed patients showed a beneficial effect for omega-3 PUFA supplementation (medium effect size), compared to no effect on depressive symptoms in nondepressed participants. The RCTs that specifically enrolled postpartum women with a major depressive episode showed the largest pooled effect size. Overall quality of the evidence was low due to imprecise and heterogeneous outcomes and variability in study quality, but there was no concrete evidence for bias in individual studies or publication bias.

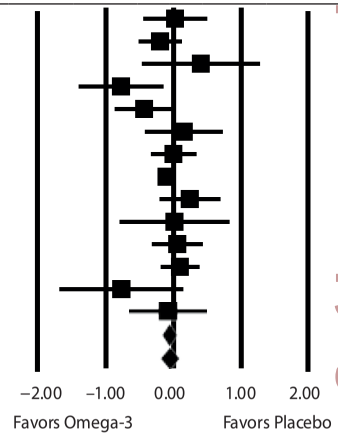
These results are in line with findings for depression outside the perinatal period, where omega-3 PUFA supplementation appears more effective in patients with an actual major depressive episode compared with patients who have subclinical depressive symptoms.[11,53] In addition, results of the present meta-analysis corroborate ideas of differences in pathophysiology between depression during pregnancy vs depression postpartum.[54] The postpartum period is particularly characterized by activation of the immune system,[55] which may explain the effectiveness of omega-3 PUFAs in this time window, given their anti-inflammatory effect. In support of this theory, higher omega-6 concentrations (which have a proinflammatory effect) and a higher omega-6/omega-3 ratio have been found to be associated with a formal diagnosis of perinatal depression.[16] Given the balance between proinflammatory effects of omega-6 fatty acids versus the proposed anti-inflammatory effects of omega-3 fatty acids, these findings support the idea that inflammatory dysregulation plays a role in the pathophysiology of postpartum depression.

We observed considerable heterogeneity between studies, both in methodology and outcomes. Division in a priori defined subgroups significantly and considerably explained variance between studies, and mostly led to more homogeneous pooled effects. Because of substantial differences between subgroups, meta-regression with a continuous predictor (eg, to find dose-response effects for EPA and DHA) on the total number of studies was considered inapplicable due to a small number of RCTs per subgroup resulting in limited power. It therefore remains to be determined whether EPA shows a dose-response effect in perinatal depression, such as was found for major depressive episodes outside the perinatal period.[11] This could further support the idea that EPA is of greater importance than DHA in omega-3 PUFA supplementation in major depression.

Figure 4. Forest Plot Showing Meta-Analyses of Included Randomized Controlled Trials on the Effect of Omega-3 Fatty Acid Supplementation vs Placebo for Perinatal Depression, Studies Subgrouped According to Pregnancy Status

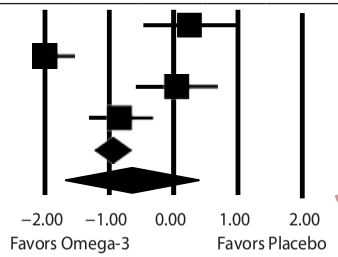
A. Pregnant

Model	Study Name	Subgroup Within Study	Comparison	Outcome	Time Point	Statistics for Each Study: Std Diff in Means	Standard Error	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value
	Doornbos 2009[17]	Total sample	Combined	EPDS	Combined	0.022	0.242	0.059	−0.452	0.497	0.092	.926
	Farshbaf-Khalili 2017[18]	Total sample	EPA + DHA + ALA vs placebo	EPDS	Combined	−0.199	0.164	0.027	−0.520	0.122	−1.213	.225
	Freeman 2008[27]	Pregnant	EPA + DHA vs placebo	Combined	During study	0.404	0.446	0.199	−0.469	1.278	0.908	.364
	Judge 2014[29]	Total sample	DHA vs placebo	PDSS	2–24 wk postpartum	−0.777	0.320	0.103	−1.405	−0.149	−2.426	.015
	Kaviani 2014[30]	Total sample	EPA + DHA vs placebo	BDI	During study	−0.433	0.226	0.051	−0.876	0.010	−1.914	.056
	Keenan 2014[31]	Total sample	DHA vs placebo	EPDS	Combined	0.149	0.294	0.086	−0.427	0.725	0.506	.613
	Krauss-Etschmann 2007[32]	Total sample	Combined	Combined	During study	0.000	0.172	0.030	−0.338	0.338	0.001	.999
	Makrides 2010[19]	Combined	DHA + EPA vs placebo	Combined	Combined	−0.101	0.062	0.004	−0.221	0.020	−1.631	.103
	Mattes 2009[20]	Total sample	EPA + DHA vs placebo	BDI	During study	0.241	0.232	0.054	−0.213	0.695	1.040	.298
	Mozurkewich 2013[21]	MDD risk	Combined	Combined	6–8 wk postpartum	0.014	0.416	0.173	−0.800	0.828	0.034	.973
	Nishi 2018[22]	Combined	EPA + DHA vs placebo	HDRS	12 wk	0.055	0.193	0.037	−0.323	0.432	0.283	.777
	Opiyo 2018[23]	Total sample	EPA + DHA vs placebo	BDI	Combined	0.094	0.147	0.022	−0.194	0.382	0.640	.522
	Su 2008[25]	Total sample	EPA + DHA vs placebo	Combined	During study	−0.774	0.468	0.219	−1.692	0.144	−1.653	.098
	Vaz 2017[26]	Total sample	EPA + DHA vs placebo	Combined	Combined	−0.086	0.291	0.085	−0.656	0.484	−0.296	.767
Fixed						−0.078	0.044	0.002	−0.165	0.009	−1.765	.078
Random						−0.071	0.059	0.004	−0.188	0.045	−1.204	.229



B. Postpartum

Model	Study Name	Subgroup Within Study	Comparison	Outcome	Time Point	Statistics for Each Study: Std Diff in Means	Standard Error	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value
	Freeman 2008[27]	Postpartum	EPA + DHA vs placebo	Combined	During study	0.249	0.367	0.135	−0.471	0.969	0.677	.498
	Ivanbaga 2009[28]	Total sample	EPA + DHA vs placebo	BDI	During study	−1.999	0.229	0.053	−2.449	−1.550	−8.715	.000
	Llorente 2003[33]	Total sample	DHA vs placebo	Combined	Combined	0.048	0.324	0.105	−0.587	0.684	0.149	.881
	Nahidi 2007[34]	Total sample	EPA + DHA vs placebo	BDI	During study	−0.827	0.249	0.062	−1.315	−0.339	−3.321	.001
Fixed						−0.942	0.139	0.019	−1.213	−0.670	−6.795	.000
Random						−0.656	0.528	0.278	−1.690	0.378	−1.243	.214



Abbreviations: ALA = alpha-linolenic acid, BDI = Beck Depression Inventory, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, EPDS = Edinburgh Postnatal Depression Scale, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, PDSS = Postpartum Depression Screening Scale, std diff = standardized difference.

Research Implications

We consider the results of this meta-analysis promising as they justify further investigations into the efficacy of omega-3 PUFA supplementation for perinatal depression. Given the differential effects in our subgroup analyses, with the largest effect in postpartum women with a major depressive episode and no effect in pregnant women, we suggest that future research should primarily focus on supplementation in patients with postpartum major depressive episodes. Together with evidence outside the perinatal period, our findings show that omega-3 PUFAs are particularly effective in patients with a formal major depressive episode diagnosis in contrast to subclinical depressive symptoms.[11] Moreover, we advise focusing on EPA instead of DHA, because studies in major depression outside the perinatal period suggest that EPA is more effective than DHA.[11] The anti-inflammatory properties of EPA could be particularly beneficial in the postpartum period.

Importantly, interventions in the perinatal period should additionally be assessed for their effects on the infant, both in utero and during lactation, outcomes that remain beyond the scope of the current meta-analysis.[56,57] Finally, it may be interesting to also study the effect of omega-3 PUFA addition to the regular treatment and/or prevention of postpartum psychosis.[58–60]

Another interesting aspect in future research may be regional differences. Several Iranian studies included in the present meta-analysis showed relatively large effect sizes.[18,28,34,52] Particularly the study of Ivanbaga et al[28] showed a relatively large effect size. One factor possibly explaining these regional differences may be low background consumption of omega-3 fatty acids in Iran.[18] Of note, excluding these studies may result in important differences in the outcomes of our meta-analysis, which potentially affects generalizability. Further study of regional differences and investigation of baseline factors, including omega-3 fatty acid consumption, assessing the omega-3 index,[14] and inflammatory status, as potential explanations for these differences may identify specific subgroups of patients that may particularly benefit from omega-3 PUFA supplementation.

Clinical Implications

On the basis of results of our meta-analysis, we advise against prescribing omega-3 PUFA supplements for the treatment or prevention of depressive symptoms during pregnancy. For this subgroup, we observed a negligible effect of < 0.1 SMD with no heterogeneity. Prescription of omega-3 PUFAs during pregnancy for other indications, eg, preterm birth, child neurodevelopment, or allergy,[61] can be considered, although effects on the child are incompletely understood and beyond the scope of the current review, with some evidence even suggesting harmful effects.[56,57]

In contrast, based on the currently best available evidence pooled in our meta-analysis, omega-3 PUFA supplementation as an (add-on) treatment for major depressive episodes pre- and especially postpartum could be considered. We observed a large effect in postpartum major depression, albeit with a lower quality of evidence due to large heterogeneity and insufficient power. Omega-3 PUFA supplementation postpartum has not been associated with serious adverse effects for the mother or infant,[38,61–63] although long-term follow-up and study of PUFA metabolites remain scarce.[57] Moreover, concerns have been raised regarding supplement purity and quality, particularly due to the effects of oxidative stress.[8]

A recent guideline based on a literature review, expert panel, and Delphi process suggests a role for omega-3 PUFA supplementation for perinatal major depressive episodes but does not provide dose recommendations.[64] Given the theoretical differential effect for EPA vs DHA, with more anti-inflammatory activity and more clinical efficacy for major depressive episode outside the perinatal period for EPA, we would advise a relatively high EPA content. The advice for major depressive episodes outside the perinatal period is to use a supplement with > 50% EPA providing 2,200 mg EPA per day, while there is no benefit described for DHA-predominant formulas.[65] Because we could not perform dose-response meta-regression analyses due to limited power, there is currently no clear evidence that this dose should be adjusted for the perinatal period.

Limitations and Strengths

While there was no evidence for individual study bias or publication bias, several biases remained unclear because not all studies described their methodology in sufficient detail. Future studies in this field should adhere to all available guidelines for designing and reporting RCTs. Moreover, there were several differences between the included trials in methodology, which may limit standardizability. Future Bayesian or individual patient meta-analyses may better account for this heterogeneity.

Omega-3 PUFA supplementation RCTs have some inherent issues that could influence the quality of meta-analysis outcomes.[66] One of them may be unblinding due to fishy aftertaste. Although most studies reported measures to overcome this issue (eg, a small amount of fish oil in the placebo or purified, deodorized, and/or flavored supplements), blind guess rates were rarely reported.[66]

Major strengths of our study are the highest number of included RCTs and participants to date. This provided the opportunity to use meta-regression and statistically show important differences in prespecified subgroups. This way, this meta-analysis provides a more rational evidence base to guide clinical decisions on omega-3 PUFA supplementation for depression in the perinatal period.

CONCLUSION

Omega-3 PUFA supplementation has a small but significant beneficial overall effect on perinatal depression, with important subgroup differences. Study quality, between-study heterogeneity, precision of effect estimates, and study

issues such as potential unblinding could be improved in future studies. Timing (postpartum vs pregnancy) significantly influenced the effect size of omega-3 PUFA supplementation for perinatal depression. Consequently, we advise against prescribing omega-3 PUFAs for the treatment or prevention of depressive symptoms during pregnancy, given the observed negligible effect with low heterogeneity. Alternatively, omega-3 PUFA supplementation appears a promising (add-on) treatment option for postpartum major depressive episodes.

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Author contributions: Drs Mocking and Roos and Ms Steijn performed the literature search and data collection; Dr Mocking and Ms Steijn performed the analyses and drafted the figures; and all authors contributed to the study design, data interpretation, and writing of the manuscript.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

For the CME Posttest, see next page.

POSTTEST

To obtain credit, go to PSYCHIATRIST.COM **(Keyword: October CME) to take this Posttest and complete the Evaluation.** A $10 processing fee is required.

1. **Beatrix, a 30-year-old pregnant woman, asks you for information about the effects of omega-3 polyunsaturated fatty acid (PUFA) supplementation for depressive symptoms during pregnancy and the postpartum period. In response to her questions, you can tell her:**
   a. Omega-3 PUFA supplementation has limited effect in the treatment of depressive symptoms during pregnancy, but may be helpful to prevent depressive symptoms during pregnancy and to treat postpartum depression
   b. Omega-3 PUFA supplementation has limited effect in the treatment or prevention of depressive symptoms during pregnancy, but may be helpful in the treatment of postpartum depression
   c. Omega-3 PUFA supplementation has limited effect in the treatment of postpartum depression, but may be helpful in the treatment or prevention of depressive symptoms during pregnancy
   d. Omega-3 PUFA supplementation should not be advised for the treatment or prevention of depressive symptoms or episodes either during pregnancy or in the postpartum period
2. **Which statement best reflects the current knowledge on effects of omega-3 fatty acid in peripartum depression?**
   a. Eicosapentaenoic acid (EPA) may be more effective than docosahexaenoic acid (DHA) due to its anti-inflammatory metabolites
   b. EPA may be more effective than DHA due to its better uptake in the brain
   c. DHA may be more effective than EPA due to its anti-inflammatory metabolites
   d. DHA may be more effective than EPA due to its better uptake in the brain
3. **Omega-3 fatty acids cannot be used in combination with antidepressants to treat major depressive disorder.**
   a. True
   b. False

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Supplementary Material

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

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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.

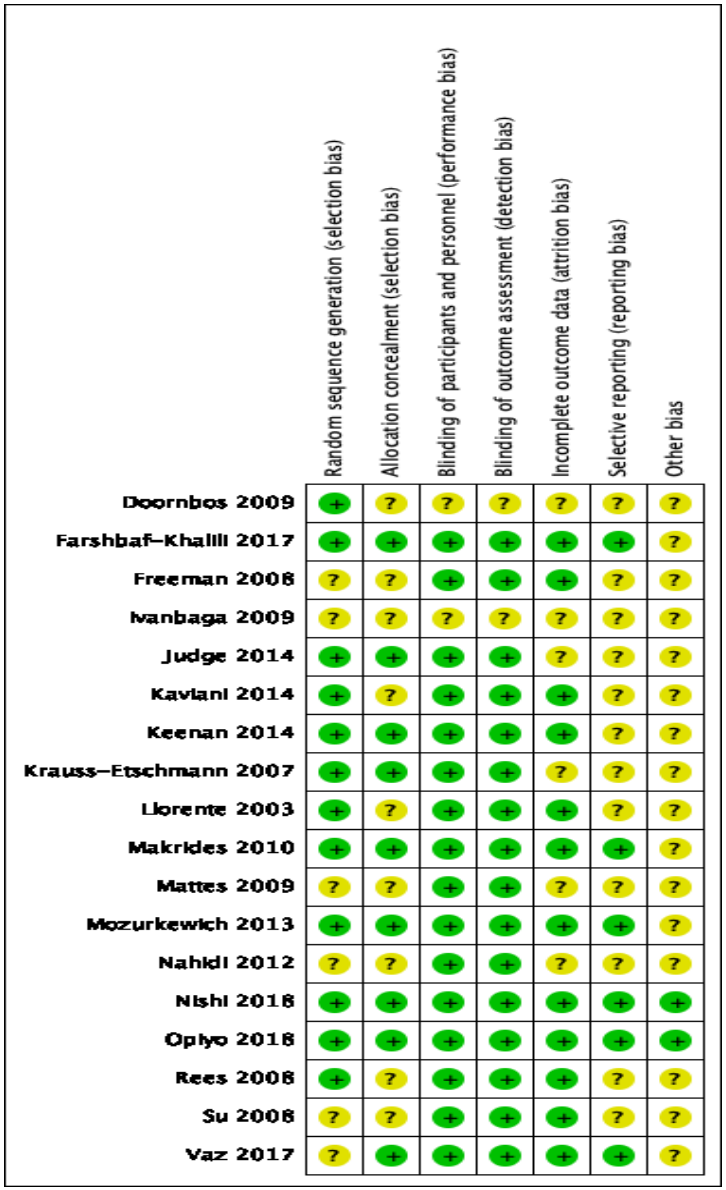
Supplementary table 2. Quality of the evidence of the overall and subgroup meta-analyses on the effect of omega-3 fatty acids for perinatal depression

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.

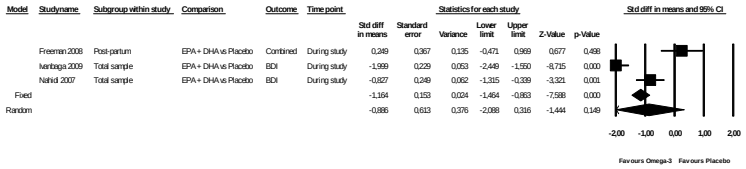
[2] Heterogeneity explained by differences in populations

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).