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Original Research Article

Dietary interventions for perinatal depression and anxiety: a systematic review and meta-analysis of randomized controlled trials

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A B S T R A C T

Background: Dietary interventions are a widely available mediation for depression and anxiety among pregnant and/or postpartum (i.e., perinatal) persons, but their effectiveness is not well known.

Objectives: We performed a systematic review and meta-analysis to assess the effectiveness of dietary interventions for the treatment of perinatal depression and/or anxiety.

Methods: We searched MEDLINE, EMBASE, PsycINFO, CINAHL, and Web of Science from their inception to 2 November, 2022. Studies were included if they were available in English and examined the effectiveness of a dietary intervention for perinatal depression and/or anxiety in a randomized controlled trial.

Results: Our search identified 4246 articles, of which 36 were included and 28 were eligible for meta-analysis. Random-effects meta-analyses were performed. Polyunsaturated fatty acids (PUFAs) were not found to improve symptoms of perinatal depression compared to control conditions [standardized mean differences (SMD): −0.11; 95% CI: −0.26 to 0.04]. These results neither changed when examined during pregnancy or the postpartum period separately nor varied according to the fatty acid (FA) ratio. Elemental metals (iron, zinc, and magnesium) were also not found to be superior to placebo (SMD: −0.42; 95% CI: −1.05 to 0.21), although vitamin D yielded a small to medium effect size improvement (SMD: −0.52; 95% CI: −0.84 to −0.20) in postpartum depression. Iron may help in those with confirmed iron deficiency. Narrative synthesis was performed for studies ineligible for meta-analyses.

Conclusions: Despite their widespread popularity, PUFAs and elemental metals do not appear to effectively reduce perinatal depression. Vitamin D taken in doses of 1800–3500 International Units per day may be, to some extent, promising. Additional high-quality, large-scale randomized controlled trials are needed to determine the true effectiveness of dietary interventions on perinatal depression and/or anxiety.

This study was registered at PROSPERO (registration date: 5 July, 2020; CRD42020208830).

Keywords: nutrients, micronutrients, postpartum depression, postpartum anxiety, nutritional sciences, dietary supplements, vitamin D, polyunsaturated fatty acids, pregnancy

Introduction

The time between conception and 1-y postpartum is frequently referred to as the perinatal period, and may be a phase of increased vulnerability for the development of depression and/or anxiety for mothers and birthing parents. Up to 1 in 5 of these individuals will experience perinatal depression and/or anxiety during this time, with negative consequences for them, their offspring, and their families [1,2]. Despite widespread knowledge of the adverse effects of these difficulties, as few as 1 in 10 receive evidence-based treatment [3,4]. During the perinatal period, a wide range of interventions have been used in an attempt to treat depression and/or anxiety (e.g., psychotherapy, medications, and dietary interventions) [5]. Psychotherapy has a substantial evidence base [6], but can be difficult to access due to low numbers of available therapists, high costs, and a lack of funding and insurance coverage [4]. Psychotropic medications are widely available, but some have concerns regarding the cost, fetal exposure, and their transmission through breast milk [7].

Dietary interventions are perceived to be safe by many pregnant and postpartum persons [8,9], and nutritional imbalances have been

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Abbreviations

BDI	Beck Depression Inventory
DASS	Depression Anxiety Stress Scale
DEN	Daily essential nutrients
EPDS	Edinburgh Postnatal Depression Scale
GHQ	General Health Questionnaire
IDA	Iron deficiency anemia
LNS	Lipid-based nutrient supplement
PHQ	Patient Health Questionnaire
POMS	Profile of Mood States
RCT	Randomized controlled trial
SMD	Standardized mean differences
SRQ	Self-reporting questionnaire
STAI	State-Trait Anxiety Inventory
VAS	Visual analog scale

hypothesized to be involved in the development and persistence of perinatal depression and/or anxiety [10,11], making them popular [12]. Considering the poor availability of psychotherapy and hesitation to take medication, there has been substantial interest in treatments that are considered "natural" (i.e., dietary interventions). Not only these compounds are affordable, but they are also easily accessible without requiring a prescription or healthcare provider visit. Given that over 89% of women reported taking any form of dietary intervention in their third trimester of pregnancy [13], it is important to evaluate whether dietary interventions are effective in treating perinatal depression and/or anxiety. The findings from this review could be used to inform clinical practice guidelines and identify whether dietary interventions are best suited for more or less severe cases, or as adjunct therapies with psychotherapy.

Many randomized controlled trials (RCTs) have examined dietary interventions consisting of macronutrients (most commonly PUFAs) [14–16] as well as various micronutrients (e.g., vitamins, amino acids, and elemental metals) [16–19] for their effect on symptoms of perinatal depression and/or anxiety. However, some have concluded that there is insufficient evidence to support PUFA supplementation to treat perinatal depression [14,20], whereas others have claimed significant benefits [15,21,22]. Some reviews pooled multiple micronutrients and the results of RCTs with studies lacking control groups [23], which can artificially inflate effect estimates [24]. Finally, although there are a number of scattered systematic reviews of some micronutrients and macronutrients, to date, no single review has comprehensively summarized the effects of dietary interventions to inform clinical decision-making for pregnant and postpartum persons and their healthcare providers.

A comprehensive synthesis of the existing data on the putative effectiveness of dietary interventions is needed to support the creation of evidence-based clinical practice guidelines for individuals with perinatal depression and/or anxiety. Therefore, the objective of this systematic review and meta-analysis was to assess the effectiveness of these compounds in treating depression and/or anxiety during pregnancy and/or the postpartum period.

Methods

The study protocol guiding this systematic review and meta-analysis was published in the PROSPERO database on 11 October, 2020 (CRD42020208830). The guidelines and checklists from PRISMA were followed (Supplemental Figure 1) [25].

A systematic search of electronic databases (MEDLINE, EMBASE, PsycINFO, CINAHL, and Web of Science) was conducted from their inception up to 2 November, 2022. Search strategies/terms were developed in collaboration with a health sciences librarian at McMaster University (Supplemental Figure 2). The search strategy included 3 concepts: pregnancy and/or postpartum period, depression and/or anxiety, and dietary interventions. Medical Subject Headings terms and keywords were used in searches when applicable. Reference lists of relevant articles were also hand-searched, and the gray literature was searched using the Grey Matters tool by the Canadian Agency for Drugs and Duck Duck Go.

Studies were included if they *1*) contained a RCT, *2*) included dietary interventions for depression and/or anxiety initiated during pregnancy or up to 1 y postpartum, *3*) included a comparison/control (e.g., placebo) group, *4*) measured depression and/or anxiety using questionnaires and/or validated clinical interviews, *5*) were available in English, and *6*) assessed outcomes during pregnancy or within the first 12 mo postpartum. Studies were excluded if the women had other perinatal mental disorders/comorbidities (i.e., OCD and personality disorders) or they were in the format of systematic reviews or commentaries, although the reference lists of these manuscripts were searched for individual RCTs.

Titles and abstracts of reports assessing dietary intervention effectiveness were screened by 3 independent reviewers (NM, NS, and UT), and any disagreements were adjudicated by a fourth reviewer (ZT). The data were extracted using a standardized form, which was pilot-tested with 5 randomly selected studies to ensure adequate data capture. Information on the study location was extracted, as well as the sample size and other intervention characteristics, mental health outcomes, scores, cut-offs used to define outcomes (if applicable), the timing of outcome assessment, funding sources, and main results in Population, Intervention, Comparator, Outcome, Time format. Study methods were assumed to follow published protocols unless stated otherwise, and intervention details were simplified into dose intake per day.

The methodological risk of bias for eligible studies was assessed using the updated Cochrane Risk of Bias 2 (ROB2) scale for RCTs. Selection, confounding, outcome, and classification bias were each graded as low, some concerns, or high risk. Publication bias was assessed visually using funnel plots generated through RevMan 5.4 and statistically assessed using the Egger test.

Random-effects meta-analyses were performed separately for depression and anxiety outcomes to determine the effectiveness of dietary interventions, as preliminary searches identified more than 5 studies and similar existing reviews identified significant heterogeneity. Differences were expressed using standardized mean differences (SMDs) with 95% CIs as many studies used different rating instruments [e.g., Edinburgh Postnatal Depression Scale (EPDS), HAM, and Patient Health Questionnaire (PHQ)] to measure the same outcome (symptoms of depression or anxiety). Heterogeneity was assessed using the Cochrane Q test, and the variation between standardized mean differences was assessed using the Higgins I^2 statistic and described as low ($I^2 < 25\%$), moderate ($I^2 < 26\%$–74%), or high ($I^2 \geq 75\%$) [26].

In accordance with the recommendations of the Cochrane Handbook, study groups were created so that only 2 distinct groups (dietary intervention users compared with nondietary intervention users) were present [26]. Meta-analyses were conducted separately for the types of dietary interventions (e.g., PUFAs, B vitamins, vitamin D, elemental metals, probiotics, and amino acids). A priori subgroup analyses were

also conducted to assess the impact of the reproductive stage (pregnancy compared with postpartum) on the effectiveness of the dietary interventions. As EPA and DHA have been shown to exert different effects and act on different physiological mechanisms [27], we also planned a priori subgroup analysis on the impact of the EPA/DHA ratio ($\geq$1.5 and $<$1.5) on intervention effectiveness. Subgroup analyses were performed based on the type of clinical trial (e.g., parallel compared with crossover) and the presence of comorbid anxiety and depression symptoms. Sensitivity analyses were conducted to assess the impact of the risk of bias. Finally, we completed a narrative synthesis of the results of the studies that were not eligible for meta-analysis.

Results

Our search identified 4246 potentially relevant articles investigating dietary intervention effectiveness for perinatal depression and/or anxiety, and 2811 remained after the removal of duplicates. We identified 143 articles for full-text review and 36 met the inclusion criteria (refer the Supplemental material for a full list of excluded full-text papers). Interrater agreement was high (Cohen's $\kappa = 0.90$). Of the 36 studies included, 28 were eligible for meta-analysis (Figure 1) and the rest were included in our narrative synthesis.

These 36 studies contained a total of 7010 participants, with 3386 individuals receiving a dietary intervention and 3624 controls. Thirteen studies were conducted in Iran; 6 studies were conducted in the United States, 2 studies were conducted in each of Australia, the Netherlands, New Zealand, Brazil, and the United Kingdom; and 1 study was conducted in each of Canada, Taiwan, Kenya, the Netherlands, Malawi, South Africa, and Japan. One study was conducted in both Taiwan and Japan.

All 36 studies assessed depression as their primary outcome. Twenty-seven studies used the EPDS [17,18,28–51], 3 studies used the Hamilton Depression Rating (HAM-D) Scale [31,52,53], and 4 studies used the Beck Depression Inventory (BDI-II) [50,54–56]. The following measurement tools were used by 1 study each: the Center for Epidemiological Studies–Depression (CES-D) scale [57], the self-reporting questionnaire (SRQ) [49], the General Health Questionnaire (GHQ) [36], a visual analog scale (VAS) [19], the Middlesex Hospital Questionnaire (MHQ) [58], the PHQ [59], and a 5-point Likert scale [60].

Eight studies also measured anxiety [40,44,46–48,51,59,60]. Five studies used the State-Trait Anxiety Inventory (STAI) [40,44,47,51,59], 1 study used the Profile of Mood States (POMS) scale [48], and 1 study used a 5-point Likert scale [60]. One used both the Depression

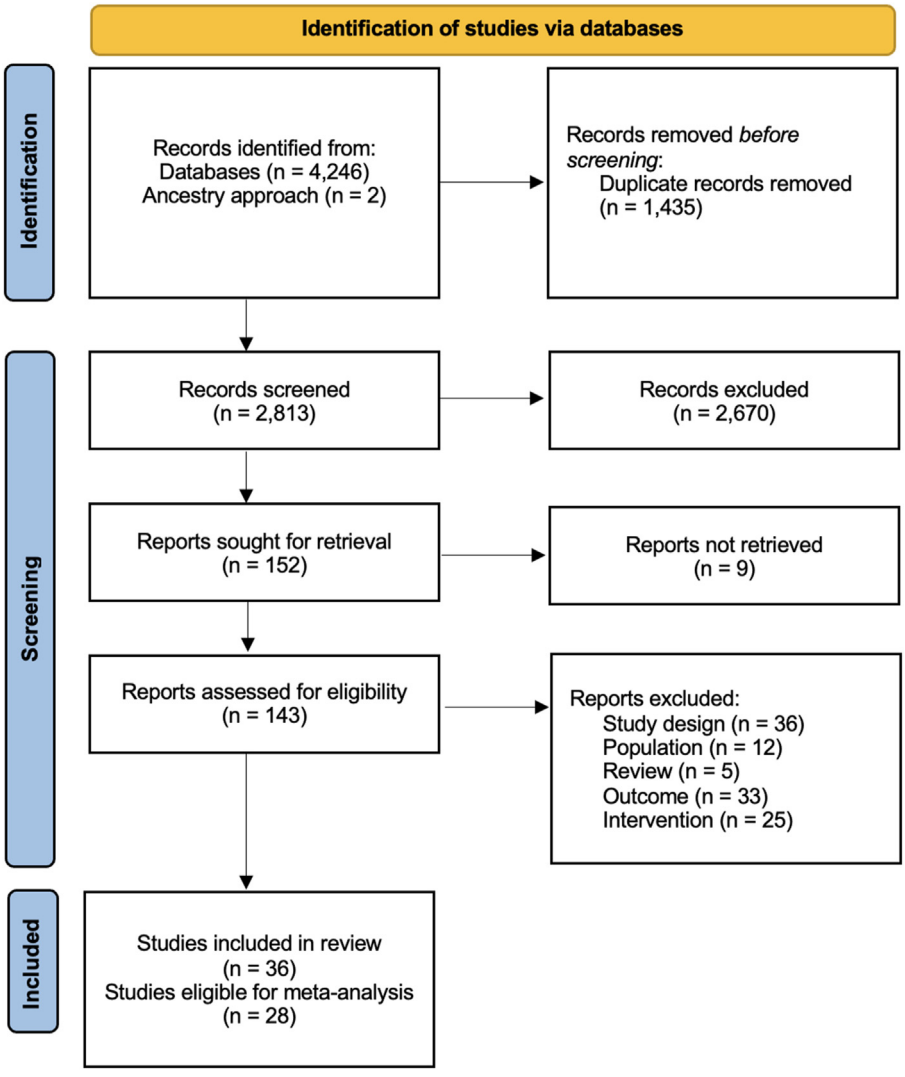

FIGURE 1. PRISMA flowchart of RCTs assessing effectiveness of dietary intervention. RCT, randomized controlled trial.

Anxiety Stress Scale (DASS) and the Generalised Anxiety Disorder-7 scale (GAD-7) [46].

Sixteen studies examined interventions involving macronutrients, including omega-3 FAs, EPAs, DHAs, and primrose oil (an omega-6 FA) [28–37,50,52–55,57]. Fourteen studies examined the impact of micronutrients such as vitamins (B and D) [17,18,38,39,45], elemental metals (calcium, zinc, magnesium, copper, iron, and selenium) [40–44,60], and tryptophan [19,58]. One study examined a combination of macronutrients (FA–rich lipid-based nutrient supplement) and micronutrients (e.g., iron) [46]. Five examined other dietary interventions, including saffron [56], pregerminated brown rice [48], bacterial colonies (i.e., probiotics) [47,51], and flavonoids [59]. Most interventions were administered daily with treatment periods in trials lasting between 4 wk and 6 mo. Three studies contained populations with comorbidities such as diabetes [44], iron deficiency anemia [40], and HIV [54]. Table lists the characteristics of all eligible studies.

Of the 36 studies included, 9 were rated as having a high risk of bias (i.e., having a high risk of bias for any of the key domains on the Cochrane Risk of Bias – refer Supplemental Table) [17–19,33,38,40,43,45,59], 17 were rated as having some concerns of bias (i.e., having a low risk of bias or some concerns for all key domains) [27–30,33,35,39,42,44–48,50–52,59], and 10 were rated as low risk [28,34,36,39,42,51,55–58]. Bias due to deviations from intended intervention and bias due to missing outcome data most often increased the bias scores.

The symmetrical pattern of the funnel plot formed around the SMD of −0.10 for PUFAs is not suggestive of publication bias (Supplemental Figure 3 in the Supplementary Material). Furthermore, formal statistical tests (i.e., the Egger test) suggest that symmetry exists in the funnel plot ($P = 0.95$) and also support an absence of publication bias. Publication bias was not examined for the other outcomes due to an insufficient number of studies.

A meta-analysis of the 13 studies that examined PUFAs showed no statistically significant reduction in symptoms of perinatal depression with the treatment utilizing these compounds (SMD: −0.11; 95% CI: −0.26 to 0.04; Figure 2). Heterogeneity for PUFAs ($I^2 = 23\%$; $P > 0.05$) was low and not statistically significant.

Our meta-analysis of 3 studies similarly failed to show the superiority of elemental metals (iron, zinc, and magnesium) as dietary interventions compared to control conditions (SMD: −0.42; 95% CI: −1.05 to 0.21; Figure 3). However, our meta-analysis of 4 studies examining vitamin D yielded a small to medium effect size (SMD: −0.52; 95% CI: −0.84 to −0.20; Figure 4), suggesting that it may be more effective than control conditions.

Meta-analysis for anxiety outcomes could not be examined due to an insufficient number of studies for individual supplements, but the results of these studies will be discussed in our narrative synthesis below.

Subgroup analyses

Pregnancy compared with postpartum depression

Studies that utilized PUFAs and that were conducted during both pregnancy and postpartum periods were categorized according to when the majority of the intervention took place. However, PUFAs were not associated with reductions in symptoms of depression during pregnancy (SMD: −0.12; 95% CI: −0.32 to 0.07) or after delivery (SMD: −0.12; 95% CI: −0.33 to 0.10) compared to control conditions.

Subgroup analyses for antenatal compared with postpartum depression for all other interventions were not possible as all studies included in the meta-analysis were conducted during the postpartum period.

EPA/DHA ratio in omega-3 FAs

To investigate whether the EPA proportion for PUFA interventions plays a key role in their effectiveness, we classified the ratio of EPA and DHA as ≥1.5 or <1.5. One study did not mention the ratio of EPA/DHA and thus was excluded. In the ratio≥1.5 group of studies, no statistically significant superiority was observed when compared to control conditions (SMD: −0.08; 95% CI: −0.34 to 0.18). Similarly, no statistically significant effects were observed in the ratio<1.5 group (SMD: −0.14; 95% CI: −0.43 to 0.14) (Supplemental Figure 4)

Subgroup analyses could not be performed based on the type of clinical trial (e.g., parallel compared with crossover) as all included studies were parallel clinical trials. The presence of comorbid anxiety and depression symptoms could not be analyzed separately as only 8 studies evaluated both anxiety and depression symptoms, all of which used different interventions.

Sensitivity analyses

Including only studies with a low risk of bias did not significantly change the effect estimates for PUFAs (SMD: −0.34; 95% CI: –0.68 to 0) (Supplemental Figure 5). No sensitivity analyses could be conducted for vitamin D supplementation, as only 1 study was rated low risk [39], and elemental metal supplementation, as none of the studies included in the meta-analysis were rated as low risk.

Narrative synthesis of study results that could not be meta-analyzed

Macronutrients

Judge et al. (2014) administered 0.3 g/d of DHA to mothers for 6 wk starting at 24 weeks of gestation and found that PDSS total scores were significantly lower ($P = 0.016$; 46.03 ± 2.17, intervention compared with 52.11 ± 2.4 placebo) in the intervention group at 6 mo postpartum [57]. Effect sizes could not be generated as a different tool (CES-D) was used to evaluate symptoms at baseline than at follow-up. Makrides et al. (2010) examined supplementing DHA-rich fish oil capsules (800 mg/d of DHA) for the last half of pregnancy and found that the percentage of mothers with high levels of depressive symptoms (EPDS score > 12) during the first 6 mo postpartum did not differ between the DHA and control groups (9.67% compared with 11.19%; $P = 0.09$) [34]. Freeman et al. investigated the effects of combination of supportive psychotherapy plus omega-3 FAs for 8 wk (with follow-ups from pregnancy to 6 mo postpartum) compared with supportive psychotherapy alone, but found no statistically significant differences between EPDS score decreases in these groups [31]. Finally, Nikoomazhab et al. (2018) found that the use of evening primrose oil did not lead to statistically significant decreases in EPDS scores between 4 and 14 d after delivery in the intervention group ($n = 66$; 13.3 ± 3.28 compared with 13.05 ± 2.6) compared to the control group ($n = 66$; 10.5 ± 0.57 compared with 11.7 ± 1.3; effect sizes could not be generated as baseline scores were not reported) [36].

Micronutrients

Two studies examined tryptophan as a dietary intervention [19,58]. Although Harris et al. (1980) did not find that 3 g/d of tryptophan reduced “maternity blues” (evaluated via the Middlesex Hospital Questionnaire) after being administered within 10 h of delivery and over the next 10 d [58], Dowlati et al. (2017) found that administration of 2 g tryptophan for 5 d combined with 10 g tyrosine daily reduced symptoms of postpartum depression on a VAS scale compared to the control group (nothing; SMD: −2.9; CIs not reported) [19].

TABLE
Characteristics of the included studies.

Study (author, year, country)	Intervention type and amount	Duration of treatment	Treatment group(s) (*n*)	Comparison group(s) (*n*)	Baseline and assessment timepoint(s)	Outcomes' scales	Main results: SMD[1] (95% CI)[2]
Macronutrients							
Omega-3 FAs (DHA + EPA)							
Rees et al., 2008, Australia [29]	Omega-3 FA: 6 g/d (27.3% DHA, 6.9% EPA)	6 wk	Omega-3 FA: 13	Placebo (sunola oil): 13	Baseline: between the third trimester and 6 mo postpartum ATP: weekly for 6 wk	Perinatal depression (EPDS)	EPDS: −0.24 (−1.01 to 0.54)
Su et al., 2008. Taiwan [52]	Omega-3 FA: 3.4 g/d (2.2 g EPA, 1.2 g DHA)	8 wk	Omega-3 FA: 13	Placebo (olive oil ethyl esters): 11	Baseline: between 16 and 32 wk of GA ATP: biweekly for 8 wk	Antenatal depression (HAM-D)	HAM-D: 8 wk: −0.81 (−1.66 to 0.03)
Freeman et al., 2008, United States [31]	Omega-3 FA: 1.9 g/d (1.1 g EPA and 0.8 g DHA) and supportive psychotherapy	8 wk	Omega-3 PUFA: 28	Placebo (corn oil capsule) and supportive psychotherapy: 23	Baseline: 12–32 wk of GA ATP: biweekly, within 6 mo postpartum	Perinatal depression (EPDS + HAM-D)	EPDS: 0.24 (−0.31 to 0.79) HAM-D: 0.26 (−0.29 to 0.82)
Makrides et al., 2010, Australia [34]	Omega-3 FA: (0.8 g/d DHA, 0.1 g/d EPA)	Last half of pregnancy (usually from study entry until birth)	Omega-3 FA: 1197	Three 500-mg vegetable oils (rapeseed, sunflower, and palm oil) capsules (without DHA) per day: 1202	Baseline: ~22 wk of GA ATP: 6 wk and 6 mo postpartum	Postpartum depression (EPDS)	Not applicable (insufficient information to convert relative risk to SMD)
Kaviani et al., 2014, Iran [28]	Omega-3 FA: 1 g/d	6 wk	Omega-3 FA: 40	Placebo (olive oil): 40	Baseline: >20 wk of GA ATP: 6 wk after baseline	Antenatal depression (EPDS)	EPDS: −0.69 (−1.14 to −0.24)
Keenan et al., 2014, United States [32]	Omega-3 FA (0.45 g/d DHA, 0.09 g/d EPA) and vitamin E (15 IU)	9–14 wk (from 16–21 weeks of gestation to 30 weeks of gestation)	Omega-3 FA: 43	Identical placebo pills: 21	Baseline: 16–21 wk of GA ATP: 24 and 30 wk of GA	Postpartum depression (EPDS)	EPDS: 24 wk: 0.94 (−2.24 to 4.12) EPDS: 30 wk: 0.52 (−2.85 to 3.89)
Mozurkewich et al., 2013, United States [55]	EPA group: 1.06 g/d EPA, 0.274 g/d DHA group: 0.9 g/d DHA, 0.18 g/d EPA	12–20 wk of gestation to 6–8 wk postpartum	EPA: 39; DHA: 38	Placebo (soybean oil capsules): 41	Baseline: 12–20 wk of GA ATP: 6–8 wk postpartum	Perinatal depression (BDI and EPDS at baseline, BDI at follow-up)	BDI DHA vs. placebo: −0.23 (−0.67 to 0.21) EPA vs. placebo: −0.11 (−0.55 to 0.33)
Farshbaf-Khalili et al., 2017, Iran [35]	Omega-3 FA: 1 g/d (0.12 g DHA, 0.18 g EPA)	Week 21 of pregnancy to delivery	Omega-3 FA: 75	Placebo (paraffin): 75	Baseline: 16–20 wk of GA ATP: 35–37 wk of GA	Perinatal depression (EPDS)	EPDS: −0.21 (−0.53 to 0.11)
Opiyo et al., 2018, Kenya [54]	Omega-3 FA: 3.17 g/d (2.15 g EPA, 1.02 g DHA)	8 wk	Omega-3 FA: 86	Placebo gels of soybean oil: 96	Baseline: second trimester (14–27 wk of GA) ATP: 8 wk after baseline	Antenatal depression (BDI-II)	BDI-II 8 wk: 0.08 (−0.21 to 0.37)
Nishi et al., 2019, Japan and Taiwan [53]	Omega-3 FA (1.206 g/d EPA and 0.609 g/d DHA)	12 wk	Omega-3 PUFA: 54	Placebo capsules (olive oil and omega-3 FAs): 54	Baseline: 12–24 wk of GA ATP: 12 wk after the start of intervention	Antenatal depression (HAM-D)	HAM-D: 0.05 (−0.33 to 0.42)
dos Santos Vaz et al., 2020, Brazil [30]	Omega-3 FA: 1.8 g/d (1.08 g EPA, 0.72 g DHA)	16 wk	Omega-3 FA: 15	Placebo (6 1-g soybean capsules/d): 17	Baseline: 5–13 wk of GA ATP: 22–24 wk of GA (T1), 30–32 wk of GA (T2), and 4–6 wk postpartum (T3)	Perinatal depression (EPDS)	EPDS T1: 0.27 (−0.43 to 0.97) EPDS T2: 0.43 (−0.28 to 1.13) EPDS T3: −0.09 (−0.79 to 0.60)
Sousa et al., 2022, Brazil [33]	Omega-3 FA (260 mg/d EPA, 1440 mg/d DHA)	16 wk (until delivery)	Omega-3 FA: 30	Olive oil: 30	Baseline: 22–24 wk of GA ATP: 34–36 wk of GA (T1), 1 mo postpartum (T2), 6 mo postpartum (T3)	Perinatal depression (EPDS)	EPDS T1: −0.19 (−0.70 to 0.31) EPDS T2: −0.24 (−0.74 to 0.27)

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TABLE (*continued*)

Study (author, year, country)	Intervention type and amount	Duration of treatment	Treatment group(s) (*n*)	Comparison group(s) (*n*)	Baseline and assessment timepoint(s)	Outcomes' scales	Main results: SMD[1] (95% CI)[2]
							EPDS T3: −0.12 (−0.63 to 0.38)
DHA only							
Llorente et al., 2003, United States [50]	DHA (0.2 g/d)	First 4 mo postpartum	DHA: 44	Placebo: 45	Baseline: 37–38 wk of GA ATP: 3 wk, 2 mo, and 4 mo postpartum	Postpartum depression (BDI at baseline, BDI and EPDS at follow-up)	BDI 3 wk: 0.03 (−0.39 to 0.45) 2 mo: 0.08 (−0.33 to 0.50) 4 mo after delivery: 0.05 (−0.37 to 0.47)
Doornbos et al., 2009, the Netherlands [37]	DHA (0.22 g) or DHA + AA (0.22 g each) daily	From enrollment until 3 mo after delivery	DHA: 42; DHA + AA: 41	Soybean oil (placebo):36	Baseline: 14–20 wk of GA ATP: week 36 pregnancy and week 6 postpartum	Perinatal depression (EPDS)	EPDS 36 wk of GA: Placebo vs. DHA: −0.09 (−0.48 to 0.30) Placebo vs. DHA +AA: 0.00 (−0.45 to 0.45) Week 6 postpartum: Placebo vs. DHA: 0.00 (−0.45 to 0.45) Placebo vs. DHA +AA: 0.07 (−0.38 to 0.52)
Judge et al., 2014, United States [57]	DHA (0.3 g/d)	6 wk	DHA: 20	Placebo (1 corn oil capsule/d for 5 d a week): 22	Baseline: 24 wk of GA ATP: 2 wk, 6 wk, 3 mo, and 6 mo postpartum	Postpartum depression (CES-D for baseline, PDSS for follow-ups)	Not applicable (baseline and follow-up used different measurement tools)
Other macronutrients							
Nikoomazhab et al., 2018, Iran [36]	Evening primrose oil (1 g/d)	From 37 weeks of gestation to delivery and the second component of study from delivery to 2 wk postdelivery	Evening primrose oil: 66	Placebo capsules: 66	Baseline: 37 wk of GA ATP: 4, 10, and 14 d postpartum	Perinatal depression (GHQ at baseline and EPDS for follow-ups)	Not applicable (baseline data was not reported)
Micronutrients							
Vitamin D							
Vaziri et al., 2016, Iran [38]	Vitamin D3 (2000 IU/d)	From 26 to 28 weeks of gestation until childbirth	Vitamin D3: 78	Placebo (2 starch pills daily): 75	Baseline: 26–28 week of GA ATP: 38–40 wk of GA, 4–8 wk postpartum	Postpartum depression (EPDS)	EPDS: 4 wk: −0.22 (−0.54 to 0.09) EPDS: 8 wk: −0.26 (−0.58 to 0.06)
Rouhi et al., 2018, Iran [18]	Vitamin D3 (1000 IU daily)	6 mo (4–10 mo postpartum)	Vitamin D3: 40	Placebo pills (containing lactose, starch, and microcrystalline cellulose): 40	Baseline: 4 mo postpartum ATP: 10 mo postpartum	Postpartum depression (EPDS)	EPDS: −0.96 (−1.43 to −0.50)
Dabbaghmanesh et al., 2019, Iran [39]	Vitamin D3 (2000 IU daily)	26th to 28th week of gestation until birth	Vitamin D3: 46	Placebo tablets: 52	Baseline: 26–28 wk of GA ATP: 4 wk postpartum	Postpartum depression (EPDS)	EPDS: −0.59 (−0.99 to −0.19)
Amini et al., 2020, Iran [61]	Vitamin D3 + calcium: 3500 IU/d + 500 mg/d calcium carbonate Vitamin D + calcium placebo: 3500 IU/d + placebo of calcium carbonate/d	8 wk	Vitamin D3 + Ca: 26	Placebo of vitamin D3 fortnightly + placebo of calcium carbonate: 26 Placebo: 24	Baseline: 8 wk before the start of intervention ATP: 8 wk after the start of intervention (intervention started at 1–6 mo postpartum)	Postpartum depression (EPDS)	EPDS: vitamin D + Ca vs. control: −0.31 (−0.86 to 0.25) EPDS: vitamin D + Ca placebo vs. control: −0.78 (−1.34 to −0.21)

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Elemental metals							
Harrison-Hohner et al., 2001, United States [42]	Elemental calcium (2 g/d)	From between 11 and 21 weeks of gestation up to until childbirth	Calcium: 239	Placebo: 229	Baseline: 11–21 wk of GA ATP: 6 and 12 wk postpartum	Perinatal depression (EPDS)	Not applicable (baseline data not reported)
Beard et al., 2005 , South Africa [40]	Mothers with IDA: vitamin C (25 mg/d) and folic acid (10 μg/d; IDA-placebo) Mothers with IDA: $FeSO_4$ (125 mg/d), vitamin C (25 mg/d), and folic acid (10 μg/d; IDA-Fe)	10 wk postpartum to 9 mo postpartum	IDA-placebo: 21 IDA:Fe: 30	CN (nothing): 30	Baseline: 10 wk postpartum ATP: 9 mo postpartum	Postpartum depression and anxiety (EPDS, STAI)	Depression (EPDS): IDA-PL vs. CN: 0.48 (−0.08 to 1.05) IDA-Fe vs. CN: −1.00 (−1.54 to −0.46) Anxiety (STAI): IDA-PL vs. CN: −1.44 (−2.06 to −0.81) IDA-Fe vs. CN: −0.86 (−1.39 to −0.33)
Mokhber et al. 2011, Iran [43]	Selenium (100 μg/d)	6 mo during pregnancy	Selenium: 44	Placebo: 41	Baseline: <12 wk of GA ATP: within 8 wk of delivery	Postpartum depression (EPDS)	Not applicable (baseline data not reported)
Sheikh et al., 2015, Iran [41]	One ferrous sulfate tablet (50 mg of elemental iron/d)	Delivery to 6 wk postpartum	Iron: 35	Placebo/cellulose tablets: 35	Baseline: before the start of intervention ATP: 6 wk after the start of intervention	Postpartum depression (EPDS)	EPDS: −0.97 (−1.46, −0.47)
Fard et al., 2016, Iran [44]	Zinc group: elemental zinc (11 mg/d) Magnesium group: elemental magnesium (64.6 mg/d)	First 8 wk of the postpartum period	zinc group: 31, magnesium group: 31	Placebo (lactose, starch, microcrystalline cellulose, and magnesium stearate): 33	Baseline: within 48 h of the postpartum period ATP: 8 wk after baseline	Postpartum depression (EPDS) Postpartum anxiety (STAI)	Depression (EPDS): Zinc: 0.06 (−0.43 to 0.55) Magnesium: 0.20 (−0.29 to 0.69) Anxiety (STAI): Zinc: −0.33 (−0.83 to 0.16) Magnesium: −0.34 (−0.83 to 0.15)
Kashanian et al., 2016, Iran [60]	Copper supplement (1 g/d)	17th wk GA to delivery	Copper: 127	Placebo: 111	Baseline: 17 wk of GA ATP: 2nd and 3rd trimester	Postpartum depression (Likert scale) Postpartum Anxiety (Likert scale)	Not applicable (baseline data not reported)
Other micronutrients							
Harris, 1980, United Kingdom [58]	L-tryptophan (3 g/d)	10 d	L-tryptophan: 27	Placebo: 28	Baseline: 12 h postpartum ATP: daily for 10 d	Postpartum depression (Middlesex Hospital Questionnaire)	Not applicable (baseline data not reported)
Dowlati et al, 2017, Canada [19]	Tryptophan (2 g), tyrosine (10 g), blueberry juice + blueberry extract daily	5 d postpartum	Tryptophan + tyrosine + blueberry extract: 21	Nothing: 20	Baseline: after delivery ATP: 5 d postpartum	Postpartum depression (VAS)	VAS: −2.9 (CI's not reported)
Khodadad et al. 2018, Iran [45]	During pregnancy: vitamin B6 (80 mg/d) After delivery: vitamin B6 (40 mg/d)	From week 28 of pregnancy to 1 mo postpartum	Vitamin B6: 40	Placebo (starch): 41	Baseline: 28 wk of GA ATP: 6 wk after childbirth	Postpartum depression (EPDS)	EPDS: −1.63 (−2.14 to −1.13)
Rucklidge et al., 2022, New Zealand [46]	Full dose of multinutrient (MN) formula (DEN) per day	12 wk	MN: 42	Active control containing iodine and riboflavin: 52	Baseline: 12–24 wk of GA ATP: 2–12 wk after enrollment, 1, 6, and 12-mo postpartum	Perinatal depression (EPDS) Perinatal anxiety (DASS and GAD-7)	Not applicable (baseline data not reported)

(*continued on next page*)

TABLE (*continued*)

Study (author, year, country)	Intervention type and amount	Duration of treatment	Treatment group(s) (*n*)	Comparison group(s) (*n*)	Baseline and assessment timepoint(s)	Outcomes' scales	Main results: SMD[1] (95% CI)[2]
Combined macronutrients and micronutrient							
Stewart et al., 2016, Malawi [49]	FA–rich lipid-based nutrient supplement (LNS; 20 g/d) and multiple micronutrients (including iron, 20 mg/d)	From enrollment (no more than 20 weeks of gestation) to delivery for IFA group and an additional 6 mo postpartum for MMN and LNS group	LNS: 339	Iron folate (IFA): 362 Multiple-micronutrient (MMN) capsules (IFA + 16 additional micronutrients): 356	Baseline: within 21 d of enrollment ATP: 6 mo postpartum	Postpartum depression (SRQ at baseline, SRQ and EPDS at follow-up)	SRQ: LNS vs. IFA: 0.38 (−0.38 to 1.13) MMN vs. IFA: 0.04 (−0.71 to 0.79)
Other dietary interventions							
Sakamoto et al., 2007, Japan [48]	Pregerminated brown rice (238.0 ± 35.3 g/d)	2 wk	Brown rice: 21	White rice: 20	Baseline: between 2 and 11 mo postpartum ATP: 2 wk after start of intervention	Postpartum depression and anxiety (POMS)	Depression: −0.6 (−2.39 to 1.12) Anxiety: −0.1 (−2.47 to 2.27)
Tabeshpour et al., 2017, Iran [56]	Saffron (30 mg/d)	8 wk in postpartum period	Saffron: 30	Placebo (2 identical pills): 30	Baseline: unspecified but in postpartum period ATP: 4 wk and 8 wk after baseline	Postpartum depression (BDI-II)	BDI-II: 4 wk: −0.57 (−1.09 to −0.05) BDI-II: 8 wk: −0.84 (−1.37 to −0.31)
Slykerman et al., 2017, New Zealand [47]	HN001 in capsules at a dose of 6×10^9 CFU/g per d	From enrollment (14–16 wk of gestation) until birth and from birth up to 6 mo post-birth while breastfeeding	Probiotic *Lactobacillus rhamnosus* HN001: 193	Placebo (corn-derived maltodextrin) capsule: 187	Baseline: 14–16 wk of gestation ATP: when the child was 6 mo and/or 1 y old	Postpartum depression (EPDS) Postpartum anxiety (STAI)	Depression (EPDS): −0.20 (−0.82 to 0.41) Anxiety (STAI): −0.67 (−1.30 to −0.04)
Browne et al., 2021, the Netherlands [51]	Probiotic multispecies mixture (2.5×10^9 CFU/g)	From 26–30 wk of GA until delivery	Probiotic group: 20	Placebo (identical looking pills): 20	Baseline: 26–30 wk of GA ATP: 8 wk after baseline (T1), 4 wk postpartum (T2)	Perinatal depression (EPDS) Perinatal anxiety (STAI)	Depression (EPDS): T1: 0.31 (−0.31 to 0.94) T2: 0.10 (−0.52 to 0.72) Anxiety (STAI): T1: 0.27 (−0.35 to 0.90) T2: 0.08 (−0.54 to 0.70)
Barfoot et al., 2021, United Kingdom [59]	≥1 high flavanoid food item/d	2 wk	Flavanoid group: 21	Control (no change to diet): 20	Baseline: 5–48 wk postpartum ATP: 2 wk after baseline	Postpartum depression (PHQ) Postpartum anxiety (STAI)	Depression (PHQ): −0.13 (−0.74 to 0.49) Anxiety (STAI): −0.85 (−1.49 to −0.20)

AA, amino acid; ATP: assessment time point(s); BDI, Beck's Depression Inventory; CES-D: Center for Epidemiological Studies for Depression Scale; CFU: colony forming unit; DASS, Depression Anxiety Stress Scale; DEN, daily essential nutrients; EPDS, Edinburgh Postnatal Depression Scale; GA, gestational age; GAD-7, Generalised Anxiety Disorder Assessment; GHQ, General Health Questionnaire; HAM-D, Hamilton Depression Rating Scale; HN001, *Lactobacillus rhamnosus*; IDA, iron-deficient anemia; IFA, iron folate; IU, International Units; MMN, multiple micronutrient; PHQ, Patient Health Questionnaire; POMS, Profile of Mood States scale; SRQ, self-reporting questionnaire; STAI, State-Trait Anxiety Inventory; VAS, visual analog scale.

[1] At the study endpoint unless otherwise stated.

[2] All values are SMDs. Negative values indicate that treatment is better than control.

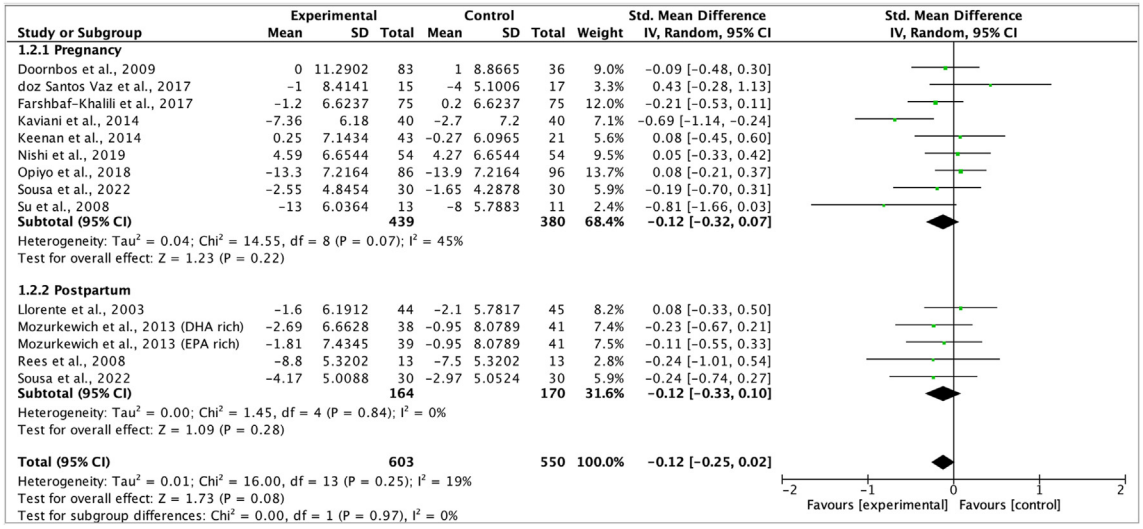

FIGURE 2. Forest plot of RCTs examining the effectiveness of PUFAs for perinatal depression. The random-effects model was used, and figures were generated using RevMan. RCT, randomized controlled trial.

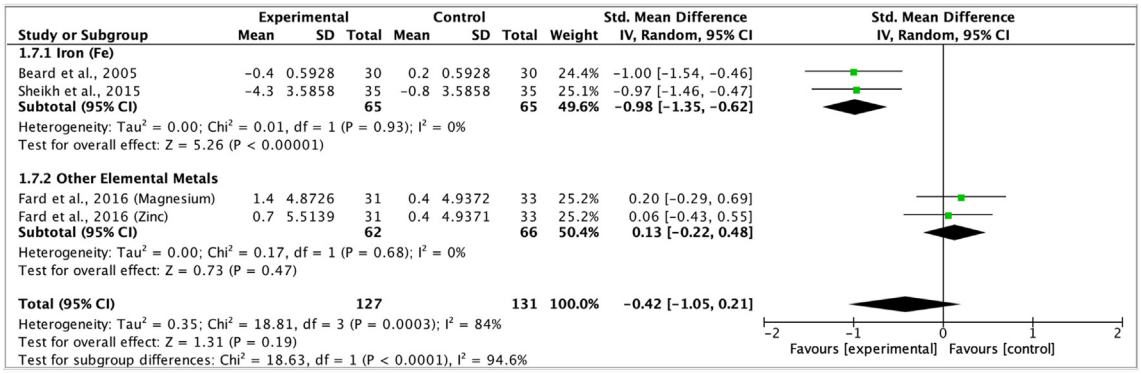

FIGURE 3. Forest plot of RCTs examining the effectiveness of elemental metals for postpartum depression. The random-effects model was used, and figures were generated using RevMan. RCT, randomized controlled trial.

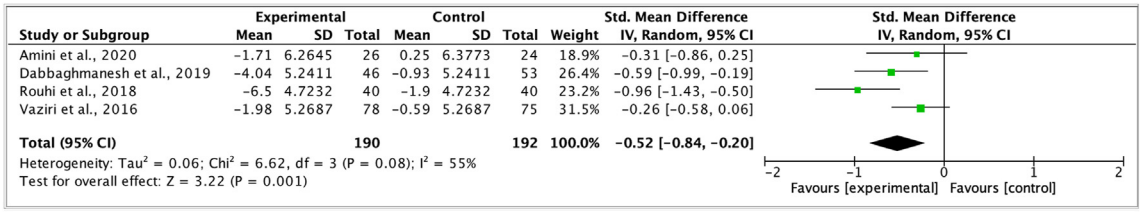

FIGURE 4. Forest plot of RCTs examining the effectiveness of vitamin D for postpartum depression within 8 wk postpartum. The random-effects model was used, and figures were generated using RevMan. RCT, randomized controlled trial.

Three studies examined elemental metals as dietary interventions [42,43,60]. Harrison-Hohner et al. (2001) provided 2 g/d of elemental calcium during pregnancy (from 11 to 21 weeks of gestation to birth) and found that among the 247 women evaluated at 12 wk postpartum, there were fewer occurrences of depression (EPDS $<$ 14) in calcium-supplemented women compared to placebo although relative risks were not reported ($P < 0.05$) [42]. Mohkber et al. (2011) provided selenium to a group of 83 women and found that compared to the placebo group ($n = 83$), after 6 mo of supplementation during pregnancy, the mean EPDS score in the selenium group (8.8 ± 5.1) was statistically significant but not clinically meaningfully lower than the placebo yeast tablet control group (10.7 ± 4.4) [43]. However, neither baseline EPDS scores nor changes in scores after supplementation were evaluated, and hence, effect sizes could not be calculated. Similarly, 1 g/d of copper supplementation from the 17th week of gestation to delivery was found to improve the mood status of women in the supplementation group ($n = 127$) compared to the placebo group ($n = 111$) [60]. Evaluated on a 5-point Likert scale, Kashanian et al. (2016) reported a 75% and 90% decrease in the levels of depressive symptoms in the second trimester and third trimester in the supplemented group ($n = 127$), respectively [60]. In addition, there was a 45% and 80% decrease in anxiety symptoms in the second and third trimesters in the supplemented group.

One study used 40–80 mg/d of vitamin B6 from 24 weeks of gestation to 1 mo postpartum, and it was found to reduce symptoms of

postpartum depression (evaluated via EPDS) in the intervention group compared to placebo (SMD: −1.63; 95% CI: −2.14 to −1.13) [45].

Rucklidge et al. (2022) administered a full dose of a multinutrient (MN) formula called "daily essential nutrients" (DEN) composed of broadspectrum of micronutrients per day to 42 mothers for 12 wk starting between 12 and 24 weeks of gestation [46]. However, compared with an active control containing iodine and riboflavin (n = 52), the intervention group scores did not differ significantly on the EPDS (no effect size was reported).

Combined macronutrients and micronutrients

Stewart et al. (2016) delivered both macronutrients (FA–rich lipid-based nutrient supplement, 20 g/d) and micronutrients (including iron, 20 mg/d) throughout pregnancy and 6 mo postpartum [49]. There were no statistically significant differences in changes between the lipid-based nutrient group (n = 339) and the multiple-micronutrient group (n = 356) on SRQ or EPDS scores.

Other dietary interventions

One study delivered 30 mg/d of saffron for 8 wk during the postpartum period to mothers suffering from mild-to-moderate postpartum depressive disorder (BDI-II score ≤ 30) and found that depression symptoms were statistically significantly reduced in the intervention group (n = 30) compared to the placebo group (n = 30; SMD: −0.84; 95% CI: −1.37 to −0.31) [56]. In another study, however, provision of 238.0 ± 35.3 g/d of pregerminated brown rice for 2 wk for mothers was not found to be more effective in reducing symptoms of either anxiety or depression compared to provision of white rice [48].

Two studies used probiotics to treat symptoms of depression [47,51]. Slykerman et al. (2017) found that an HN001 (probiotic *Lactobacillus rhamnosus*, 10^9 CFU/g per capsule) colony delivered in 6 capsules from 14 to 16 weeks of gestation until up to 6 mo postpartum reduced the intervention group's (n = 193) symptoms of both depression and anxiety compared to the placebo group (n = 187) although the impact on depression was small (SMD: −0.20; 95% CI: −0.82 to 0.41; STAI SMD: −0.67; 95% CI: −1.30 to −0.04) [47]. However, Browne et al. (2021) found that supplementing 2 g/d of the probiotic multispecies mixture (2.5×10^9 CFU/g daily) from 26–30 weeks of gestation up to delivery did not significantly reduce the intervention group's (n = 20) EPDS scores (SMD: 0.10; 95% CI: −0.52 to 0.72) or STAI scores (SMD: 0.08; 95% CI; −0.54 to 0.70) compared with the placebo group (n = 20) when evaluated at 4 wk postpartum [51].

Finally, Barfoot et al. found that mothers that consumed ≥1 high flavonoid food item per day for 2 wk postpartum (n = 21) had reduced symptoms of anxiety on the STAI scale compared to the control group (n = 20) who did not make changes in diet (SMD: −0.85; 95% CI: −1.49 to −0.20) [59]. However, depression scores that were evaluated on the PHQ did not decrease (SMD: −0.13; 95% CI: −0.74 to 0.49).

Discussion

This systematic review and meta-analysis identified 36 RCTs that assessed the effectiveness of dietary interventions in the treatment of perinatal depression and/or anxiety. Overall, we found that PUFAs were not effective in treating depression during pregnancy or the postpartum period, and this did not differ for EPA/DHA ratios that were greater than or equal to 1.5. Similarly, pooled results of RCTs that examined elemental metals including iron, zinc, or magnesium were not effective in treating postpartum depression. However, 1000–3500 International Units (IU) per day of vitamin D did appear to lead to small effect size reductions in symptoms of postpartum depression (SMD: −0.37; 95% CI: −0.60 to −0.15). There are also scattered trials of other individual nutrients; however, they were mostly of low quality and have not been replicated, as discussed in our narrative review. It was not possible to conduct meta-analyses for perinatal anxiety due to the very small number of trials.

Our findings on PUFAs do differ from some previous systematic reviews that suggested that PUFAs may be effective in reducing symptoms of perinatal depression [20]. However, Mocking et al. noted a significant heterogeneity between studies in terms of results (I^2 = 89%; Q = 79; P < .001) [14], which was likely due to the fact that they included studies whereby multiple interventions (including PUFAs) were given simultaneously. Another systematic review and meta-analysis by Zhang et al. did not include several studies that would have been eligible in their inclusion criteria and meta-analyses [15].

Why PUFA supplementation does not appear to be superior to control conditions in the treatment of perinatal depression is not clear. Given the number of participants (N = 1153) in this meta-analysis, it seems less likely that this is due to a lack of statistical power, but it is conceivable that differences in dosages or the duration of administration could contribute to the variability among studies. Interventions' duration varied between 4 wk and 6 mo, and longer treatment times could allow more time for the intervention to take effect. Moreover, very few studies evaluated compliance, although it is unlikely that compliance would be better outside of the context of a study. Furthermore, some studies with smaller effect sizes noted that their study participants did not experience higher levels of depression severity, which may have led to a floor effect impacting their results [29,53,54].

To our knowledge, no previous systematic reviews have described the effectiveness of elemental metals in perinatal or general population samples, even though some have speculated that iron and zinc deficiencies may play a role in perinatal depression and anxiety pathogenesis [62]. However, our results suggest that these compounds are unlikely to represent effective treatments for these disorders (SMD: −0.42; 95% CI: −1.05 to 0.21), although the number of studies is low, and so, further research may be warranted. It is important to note that Beard et al. [40] and Sheikh et al. [41] reported significant reductions in symptoms of depression and anxiety when supplementing iron to mothers with iron deficiency anemia (IDA). This is consistent with the literature, as iron supplementation for iron deficiencies has been shown to improve symptoms of depression [63,64].

Our findings suggest that vitamin D may be an effective treatment for perinatal depression. Several studies have showed that vitamin D deficiency alters neurotransmitters that are known to be involved in depressive symptoms [65,66]. Based on our results, 1000–3500 IU per day of vitamin D for 8 wk–6 mo significantly reduced symptoms of postpartum depression (SMD: −0.52; 95% CI: −0.84 to −0.20) in mothers with baseline EPDS scores of >12. This is consistent with a review that found that the intake of >2800 IU of vitamin D per day for at least 8 wk is most likely effective [67], as well as current clinical recommendations of 2000–4000 IU per day during pregnancy and postpartum. In this review, we doubled the number of RCTs meta-analyzed (4) relative to the number of studies included in the previous meta-analysis of vitamin D for postpartum depression (two [61]).

The current systematic review and meta-analysis were restricted to RCTs to help inform maternal choice and clinical decision-making using the most rigorous evidence possible. Very few existing reviews

have looked at the specific timing of interventions (pregnancy or postpartum) or examined specific micronutrients (elemental metals and vitamins) and synthesized narratively other dietary interventions (e.g., probiotics and saffron). We were able to include 13 studies in our meta-analysis of PUFAs with low heterogeneity. Furthermore, based on our findings of our vitamin D meta-analysis, we are able to suggest an appropriate dosage range to clinicians. Using the GRADE approach, we have evaluated our quality of evidence to be moderate. Thus, our assessment of the existing evidence for dietary interventions for perinatal anxiety and/or depression can provide clinically relevant guidance for expectant and new mothers, as well as clinicians and researchers.

However, limitations of this review include a lack of studies for meta-analyzing perinatal anxiety outcomes and methodological limitations of individual studies. There were a small number of studies for interventions other than PUFAs, and we only included studies available in English. Most sample sizes were small, and few studies have evaluated participants' compliance with treatment. The baseline nutritional status was not considered (i.e., measured by biomarkers) for most studies despite the role they could play in depression and anxiety. Eligibility criteria, validated cut-offs for depression and anxiety scores, and reporting of baseline data differed among studies. This is important as the severity of symptoms at baseline will clearly affect the magnitude of the improvements that might be possible. Several studies did not report baseline data scores completely and could not be included in the meta-analyses as effect sizes could not be calculated. Unfortunately, the doses and duration of treatment used in studies were quite disparate, which can make it difficult to pinpoint optimal treatment regimens. Few studies reported longer-term outcomes after the treatment ended, and many reported significant sources of bias (deviations from intended intervention and missing outcome data), with only 10 studies rated as low risk of bias. Many studies also lacked consistencies in scale use to evaluate symptoms of perinatal depression at baseline and follow-up assessments. Overall, studies used various regimens, doses, duration, center settings, and populations enrolled, calling for cautious interpretation of the results.

As nonpharmacological interventions become more common and the relative effectiveness of these is compared with one another, researchers should examine these using network meta-analyses as a means of further guiding clinical practice. Future studies should clearly articulate doses and treatment duration, and utilize clinically meaningful periods of follow-up. More studies should assess the association between nutrient deficiencies and supplementation and subsequently their impact on symptoms of perinatal depression and anxiety, including comorbid depression and anxiety. They should also consider utilizing structured diagnostic interviews in order to determine whether these treatments are effective in those with full-syndrome psychiatric diagnoses (e.g., major depressive disorder and general anxiety disorder). Studies should also examine comprehensive dietary interventions (i.e., those that aim to address more overall diet quality) as recent research has found correlations between healthy diets and lower risks of all-cause mortality and cancer [68]. Given the findings on vitamin D dosages, additional evidence is also needed to determine the role of clinicians in recommending vitamin D supplementation during pregnancy or postpartum and in monitoring potential excessive vitamin D intake in pregnant women. These conditions need to be met in order for clinicians to be able to confidently provide evidence-based recommendations for pregnant and postpartum persons, as well as for these individuals to make confident decisions about whether they should select dietary interventions as a part of their journey to recovery. The role of these interventions as monotherapy or as augmentation agents for other treatments (e.g., antidepressants and psychotherapy) is still not clear.

In summary, this systematic review and meta-analysis of effectiveness studies of dietary interventions for perinatal depression and/or anxiety suggest that PUFAs may not have a meaningful clinical impact on reducing symptoms of perinatal depression compared with evidence-based treatments (e.g., antidepressants and psychotherapy), given the observed negligible effect with low heterogeneity. Iron supplements for those with iron deficiency and vitamin D supplements in general at doses of 1000–3500 IU are quite promising, although the effect sizes are small. Additional high-quality, large-scale RCTs are needed to accurately assess the effectiveness of dietary interventions on perinatal anxiety and/or depression and their potential as clinically meaningful treatment options so that those who are affected can select the treatments that are likely to be most effective for them.

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Authors' Contributions

The authors' responsibilities were as follows – ZT, RV, SO: designed and conducted the research, and provided essential materials; NS, UT, NM: conducted the research; ZT, SO, NS, UT, RV: wrote the paper; ZT, RV: take primary responsibility for the final content; and all authors read and approved the final manuscript.

Conflict of Interest

The authors report no conflicts of interest.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the study and the Supplemental Material. Raw data that supports the finding of the study are available from the corresponding author, upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.03.025.

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