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Role of Omega-3 Unsaturated Fatty Acids in the Postpartum Depression: Systematic Review and Narrative Synthesis

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Abstract

Background: Postpartum depression (PPD) is a complex mental health disorder that affects women during their childbearing years. It is a serious medical condition that occurs in approximately 15% of women after birth and has an adverse effect on both the mother and the infant. Hypotheses exist relating dietary deficiencies in a pregnant or postnatal woman's diet may cause postnatal depression. It is unclear whether Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are effective for treating or preventing PPD.

Objectives: To assess the best available evidence to date regarding the effect of n-3 PUFAs on the etiology, prevention and treatment of postnatal depression.

Methods: A systematic review and narrative synthesis was conducted in order to address the gaps in knowledge. For the systematic review, a broad search of electronic databases of published quantitative literature was conducted. The narrative synthesis consists of four elements: 1) developing a theory; 2) developing a preliminary synthesis; 3) exploring relationships in the data; 4) assessing the robustness of the synthesis. Published experimental and observational studies were accepted involving women who were pregnant or who had given birth in the previous six weeks. N-3 PUFAs was the intervention of interest and PPD was the outcome.

Results: Out of 181 potential articles, a total of 17 studies met the inclusion criteria. The overwhelming majority of the studies found that n-3 PUFAs had no inverse association with PPD evaluations. Significant heterogeneity was observed among included studies.

Conclusions: Overall, This systematic review and narrative synthesis failed to find a significant positive association between n-3 PUFAs intake and PPD.

Keywords: maternal mental health, maternal nutrition, narrative synthesis, omega-3 polyunsaturated fatty acids, postpartum depression, systematic review

1. Introduction

Depression is a major cause of disability for all ages and both genders (World Health Organization [WHO], 2008). Women are at the highest risk of depression during their childbearing years; and the birth of a child may precipitate a depressive episode in vulnerable women (Stewart, Robertson, Dennis, Grace, & Wallington, 2003). Postpartum depression (PPD) can affect up to 15% of new mothers during the first year after delivery (Stewart et al., 2003).

In addition to its effects on the mother, untreated PPD negatively affects the social, emotional and cognitive development of the infant (Fisher et al., 2009; Harpham et al., 2005; Logsdon, Wisner, & Pinto-Foltz, 2006). Indeed, in severe cases, it can even lead to maternal suicide or infanticide (Fisher et al., 2009; Harpham et al., 2005).

Although antidepressants may be effective for treating PPD, many women may not want to risk taking drugs that may harm their fetuses or, for breastfeeding mothers, their newborns (Borja-Hart & Marino, 2010; U. S. Food and Drug Administration [FDA], 2014). Taking antidepressants in the third trimester has been associated with several adverse effects, such as transient neonatal withdrawal syndrome, muscle weakness, and respiratory problems (Oberlander et al., 2004).

Thus, it is important to explore the efficacy of alternative, perhaps non-pharmaceutical or nutritional, options for PPD treatment. One such alternative worthy of exploration is supplementation with omega-3 polyunsaturated fatty

acids (n-3 PUFAs).

N-3 PUFAs are necessary for a healthy brain function and structure; they prevent or decrease the inflammatory status occurring during depression and may be important for maintaining healthy mood and controlling mental distress (Bourre et al., 1991; Maes & Smith, 1998; Suarez et al., 2003).

There is evidence to suggest that n-3 PUFAs decrease by 50% during gestation and may not be fully replenished up to 26 weeks postpartum (Al, Van Houwelingen, Kester et al., 1995; Al Van Houwelingen, & Hornstra, 1997; Huang et al., 2013; Holman et al., 1991; Markhus et al., 2015; Otto et al., 1997; Van den Ham et al., 2001). Therefore, mothers may be at a risk of suffering PPD when they become depleted of n-3 PUFAs (Al, Van Houwelingen, Kester et al., 1995; Al Van Houwelingen, & Hornstra, 1997; Hibbeln & Salem, 1995; Huang et al., 2013; Holman et al., 1991; Otto et al., 1997; Van den Ham et al., 2001).

Several experimental and observational studies evaluated the effectiveness of the n-3 PUFAs on PPD, but there was no current systematic review that has examined all quantitative designs that have been conducted to assess the efficacy n-3 for PPD. There were, however, some brief, non-systematic literature and article reviews which dealt with a broad range of issues related to our topic rather than addressing the n-3 PUFAs and PPD in particular in depth (Borja–Hart & Marino, 2010; Freeman, 2006; Levant, 2010; Jans, Giltay, & Willem Van der Does, 2010; Ramakrishnan, 2011; Wojcicki & Heyman, 2011).

Research indicated that systematic reviews are more transparent than literature and article reviews with a goal of decreasing bias by identifying, appraising, and synthesizing all relevant studies on a specific topic (Uman, 2001).

As no systematic review was conducted on the role of n-3 PUFAs for PPD, the aim of this study was to fill this gap of knowledge and update the current information about the overall published evidence concerning whether n-3 PUFAs exposure in the perinatal and postpartum period are beneficial for treating depression, up to 12 months post-partum.

2. Methods

We employed a systematic review of published evidence, with a narrative synthesis in lieu of statistical meta-analysis (Cochrane Collaboration, 2008; Popay et al., 2006).

2.1 Searching the Literature

With the assistance of a librarian, research papers published in English between 1990 and 2014 were identified via searches of the following databases: Ovid, CINHAL (Cumulative Index of Nursing and Allied Health Literature), Embase, Chochrane, and Google Scholar, using the following keywords, their derivatives and conjugated terms: “fish oils”, OR “omega fatty acids”, OR “omega-3”, OR “fatty acids”, OR “α linolenic acid”, OR “docosahexaenoic acids”, OR “eicosapentaenoic acid” AND “Postpartum depression”, OR “postnatal depression”.

Abstracts, animal studies, and individual case reports were excluded, as were studies that failed to clearly describe the intervention and outcome measures.

2.2 Quality Appraisal

The Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project (EPHPP) was used to assess methodological quality (EPHPP, 2009; Thomas, Ciliska, Dobbins, & Micucci, 2004). This quality assessment tool allows quantitative studies (randomized and nonrandomized trials) to be rated on six components: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts. Each study was rated as “strong,” “moderate,” or “weak” on each of these components. An overall global rating was then given to each study with studies classified as “strong” (at least four strong ratings without any weak ratings), “moderate” (less than four strong ratings and one weak rating), or “weak” (two or more weak ratings).

Concerning the data collection methods, the validity and reliability of the methods were rated in relation to PPD outcome measures only.

2.3 Data Abstraction

The following data were abstracted: study designs, characteristics of the participants and interventions, intervention measurement, outcome measurement, findings and limitations.

2.4 Data Synthesis

A narrative synthesis of the findings about the association between n-3 PUFAs intake and PPD was carried out. This stepwise narrative methodology has been used previously in a wide range of study reviews (Arai et al., 2007; Dennison et al., 2009).

Narrative synthesis is an approach to synthesis findings that relies mainly on the use of words and text to summarize and explain findings. It is typically used when statistical meta-analysis is not suitable. Due to the significant clinical variability (variability in the participants, interventions and outcomes studied also variability in outcome measures) and methodological heterogeneity (variability in study design) between the selected studies of the papers in this study, statistical meta-analysis was contra-indicated, hence our reliance upon narrative methods. The four stages of the narrative synthesis were: (i) developing a theory; (ii) developing a preliminary synthesis; (iii) exploring relationships within and between studies; and (iv) assessing the robustness of the synthesis.

2.4.1 Element 1: Developing a Theory

This part is concerned with "how the intervention works, why, and for whom" (Popay et al., 2006, p.12).The purpose of this part is to develop an understanding of the theory behind the intervention in order to inform decisions about the review question and the types of studies to include. It is also important in "contributing to the interpretation of the review's findings and will be valuable in assessing how widely applicable those findings may be" (Popay et al., 2006, p.12).

2.4.2 Element 2: Developing a Preliminary Synthesis

The preliminary synthesis provides a description of the results of all included research studies in order to organize findings to provide an initial description of patterns across included studies (Popay et al., 2006). Studies were organized according to design and effects. For each included paper, the following data were extracted and tabulated: type of paper, study location, methodological approach, participant information and inclusion criteria, intervention and outcomes measurement, summary of main study findings, and limitation.

2.4.3 Element 3: Exploring Relationships Within and Between Studies

The purpose of this element is to consider relationship: first between study results and Key aspects for other studies and second the factors across included studies (Popay et al., 2006). The outcomes that emerged from the preliminary synthesis were subjected to further rigorous evaluation to identify any factors that may explain the differences within and across the included studies and to understand how and why n-3 PUFAs have or do not have an effect on PPD.

2.4.4 Element 4: Assessing the Robustness of the Synthesis

Assessing methodological quality is a way to ensure the robustness of the synthesis. The analysis of relationships within and between studies described previously helps in creating a thorough assessment of the strength of the evidence available for drawing conclusions on the basis of a narrative synthesis (Popay et al., 2006).

3. Overall Results in Context with Expectations Arising from the Literature (Narrative Synthesis Element 2: Developing a Preliminary Synthesis)

Our search produced 181 studies, though only 17 met our criteria: eight experimental and nine observational studies. Of the former, six were randomized controlled trials (Doornbos et al., 2009; Freeman et al., 2008; Llorent et al., 2003; Makrides et al., 2010; Mozurkewich et al., 2013; Rees, Austin, & Parker, 2008) and two pilot trials (Freeman et al., 2006; Marangell et al., 2004). The nine observational studies included: one ecological study (Hibbeln, 2002), a cross-sectional study (De Vriese, Christophe, & Maes, 2003), a case-control study (Browne, Scott, & Silvers, 2006), and six cohort studies (da Rocha & Kac, 2012; Markhus et al., 2013; Miyake et al., 2006; Otto, De Groot, & Hornstra, 2003; Parker et al., 2014; Strøm, Mortensen, Halldorsson, Thorsdottir, & Olsen, 2009). The included studies and the results of our quality appraisals are summarized in Table A1, while more detail on the characteristics of the studies is presented in Table A2.

Excluded studies were: review and journal articles (N=113); editorials (N=9); animal studies (N=6); duplicate studies (N=5); abstracts only (N=2); different interventions and outcomes (N=28), lack of sufficient data (N=1).

In terms of methodological quality assessment, our set indicated five strong, nine moderate, and three weak studies. Weak rating scores were given because of a poor study design, lack of controlling confounders, and/or high dropout rates. The most common reasons for a study not receiving a 'strong' rating were a low response rate from eligible participants and high withdrawal/dropout rate.

Significant heterogeneity was observed among included studies, hence justifying our narrative synthesis approach. There are large differences among them in terms of study designs, sample size, population and time period of the study (depressed or healthy participants, pregnant and/or postpartum), characteristics of the intervention in terms of (type, dosage, duration), and choice of measures of predictors and outcomes.

4. Discussion (Narrative Synthesis: Element 3)

We demonstrated that the results of the use omega-3 PUFA as therapeutic and preventative agents for postpartum depression were varied. Many limitations complicated the interpretation of the findings, most prominently the small sample size, as only 17 studies met the inclusion criteria.

Furthermore, clinical and methodological heterogeneity were high. It was noticeable that the heterogeneity between studies may depend on clinical and methodological issues. Intervention trials were varied in terms of characteristics and number of participants, depression scales employed (EPDS, HAM-D, or BDI), baseline depression score, the nature of the intervention (e.g., formulation, dose, duration, timing, etc.), time period of study and supplementation (i.e., antenatal, postnatal or combined antenatal/postnatal), lack of control group, open label trials, low supplement dosages, under-reporting of fatty acid intake, short-term follow-up, unsuitable ratios of EPA:DHA. This considerable variability made the discussion of results more complex.

In addition, most studies measured depression using the EPDS without verification of high EPDS scores with a clinical diagnosis of depression, which can result in biased results since a high EPDS score can be due to anxiety as well as from depression (Stuart, Couser, Schilder, O'hara, & Gorman, 1998).

Moreover, information regarding the pathophysiological nature of depression occurring in patients was lacking. Indeed, none of the studies reviewed evaluated the brain or synaptic DHA levels , while few assessed DHA levels in the plasma (Browne et al., 2006; De Vriese et al., 2003; Doornbos et al., 2009; Makrides et al., 2010; Markhus et al., 2013; Llorent et al., 2003; Mozurkewich et al., 2013; Parker et al., 2014; Rees et al., 2008).

Research showed that regional levels of brain DHA metabolism can be measured in human with Positron Emission Tomography (PET) and following intravenous injection of [1-11C] DHA (Rapoport, Ramadan, & Basselin, 2011; Rapoport, 2013).

It has been hypothesized that n-3 PUFAs affects synaptic function by impacting membrane structure and through cytokine-immuno neuroendocrine interactions (Maes et al., 1998). Other studies stated that plasma levels of fatty acids are not a perfect measure of dietary intake nor a perfect predictor of fatty acid levels in brain tissue (Rapoport, Ramadan, & Basselin, 2011; Shapiro et al., 2012). While Erythrocytes are considered the gold standard to measure the long-term n-3PUFA status, However, several studies have indicated strong correlations between FA content of erythrocytes and plasma; consequently, we can consider the plasma as a valid biomarker to reflect n-3 status over the last month (Harris, 2008; Garneau et al., 2012; Paradis, Pérusse, Godin, & Vohl, 2008) Such theories could explain the lack of association found in some of the studies reviewed here between n-3 PUFAs supplementation and prevention of PPD.

Lastly, some important issues concerning the delivery of the intervention have been explored in recent meta-analyses, which showed that the positive effects of n-3 PUFAs on depressive symptoms appeared to depend more on EPA administration rather than DHA, severity of depression, and study quality (Bloch & Hannestad, 2012). However, some concerns regarding these findings still persist (Lin et al., 2012). The findings regarding the different efficacy of EPA compared to DHA and EPA-DHA combinations were confirmed by Grosso et al., (2014) in a meta-analysis in which the researchers grouped RCT's based on the type of n-3 PUFAs administered. Whether EPA is more effective than DHA, in improving depression, the different effects of the types of n-3 PUFAs is challenging for convincing explanation since DHA is a major structural constituent of neuronal membranes (Grosso et al., 2014). Thus, that increasing its dietery intake would be valuable on brain function, rather than EPA, which exists at lower levels (Arterburn, Hall, & Oken, 2006; Grosso et al., 2014).

Although heterogeneity among included studies makes it difficult to synthesize the findings, our narrative approach indicates a null benefit of n-3 PUFAs on depressive symptoms postpartum, as only one small pilot trial (Freeman et al., 2006), one weak ecological study (Hibbeln, 2002), and four small cohort and cross-sectional studies (da Rocha & Kac, 2012; De Vriese, Christophe, & Maes, 2003; Markhus et al., 2013; Otto, De Groot, & Hornstra, 2003) reported promising results, whilenone of the RCTs identified in this review showed an association of n-3 PUFAs with a decreased risk for maternal PPD.

In short, the only studies showing positive associations were of small sample size and comparatively weak designs.

Future research should focus on identifying the specific molecular mechanisms underlying the function of n-3 PUFAs in the brain. Moreover, factors related to the pathophysiological nature of the depression should be considered.

Our findings should not marginalize the other significant benefits of n-3 PUFAs. Many studies suggested an important role of n-3 PUFAs for fetal development including neuronal, retinal, and immune function (Dunstan et

al., 2004; Greenberg, Bell, & Van Ausdal, 2008; Swanson, Block, & Mousa, 2012).

Research indicated that women during pregnancy and lactation are not getting enough n-3 PUFAs (Denomme, Stark, & Holub, 2005; Jia et al., 2015). In June, 2014, The Food and Drug Administration (FDA) issued an updated statement advising women to eat more fish during pregnancy and breastfeeding to aid in fetal growth and development. The FDA's recommendations are consume 8 to 12 ounces of a variety of fish each week from choices that are lower in mercury during pregnancy and breastfeeding (U. S. Food and Drug Administration, 2014).

5. Reflecting Critically on the Synthesis Process (Narrative Synthesis Element 4: Assessment of the Robustness of the Synthesis)

This is the first narrative synthesis systematic review on n-3 PUFAs and PPD literature. The use of defined eligibility criteria, the application of a rigorous search strategy, and the quality assessment of the studies and systematic analysis of the findings made this review transparent. However, there are some limitations to the approach taken in this systematic review and narrative synthesis.

First of all, the different designs of included studies increased heterogeneity. Also, the diversity of outcomes that result from different contexts and the heterogeneous research studies limited the extent to which clear conclusions could be drawn about the usefulness of n-3 PUFAs in PPD. One systematic review and synthesis cannot overcome these complexities alone, but can provide some clarity about the research evidence and its implications for practice and further research.

In addition, since the review yielded a small sample size, it is possible that the aim of the present research may not have been adequately addressed, particularly with relation to the ability to decide whether n-3 PUFAs components are effective for PPD.

The literature search required screening in the most potential databases using a robust search strategy and undertaking empirical checks on the inclusiveness of the search strategy results. However, only studies in the English language were included. It is unknown what other relevant materials in other languages was missed due to this limitation.

Overall, the narrative synthesis methodology used in this review facilitated the understanding and acknowledgement of the broader influences of theoretical and contextual variables when it was challenging to interpret multiple forms of heterogeneous studies. This method was suitable for integrating quantitative research findings and important as a mechanism for drawing messages from research in order to draw our own recommendations for future implication.

6. Conclusion

The majority of the studies found that PUFA had no association with PPD. The minority that reported a beneficial effect were of poor quality. In conclusion, n-3 PUFAs cannot be considered to be an empirically supported treatment or method for the prevention of PPD. However, since there are other benefits for n-3 PUFAs, then there is no harm in including them in prenatal/postnatal care.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Appendix

Appendix A: Tables

Table A1. Relevant Features of Included Studies

Characteristics of the 17 Included Studies	Summary of Results		
Country	6 USA 3 Australia 3 The Netherlands	1 Norway 1 Denmark 1 Japan	1 Brazil 1 New Zealand
Design	6 RCTs 2 Pilot trials	1 Ecological 1 Cross-sectional	1 Case-control 6 Cohort
Sample Size	Experimental 7-2399 Observational 48-54202		
Participants	12 Healthy pregnant women	3 Depressed women	2 History of depression
Objective	3 Treatment	5 Prevention	9 Prevalence risk
Intervention (clinical trials: 0.2-6g)	7 EPA + DHA 3 Pure DHA 1 DHA + AA	1 EPA, DHA, ALA 3 n-3/n-6 ratios	2 total fatty acids
Intervention Period (clinical trials)	6 Perinatal 2 Postpartum		
Fatty Acids Measurement	4 Blood test + FFQ 6 only blood test	4 only FFQ 1 Breast milk	1 Cord blood
Depression Measurement	7 EPDS 1 HAM-D	2 DSM 4 EPDS + HAM-D	2 BDI 1 EPDS + DSM
Quality Appraisal	5 Strong	9 Moderate	3 Weak

Table A2. Characteristics of Eligible Studies N-3 PUFAs for PPD/ Experimental studies

Study Design and Site	Objectives	Sample size Treatment/ Placebo	Population	Duration of the Intervention	Intervention	Control	N-3 PUFA Measurement	Depression Measurement	Main findings	Limitation
RANDOMIZED CONTROLLED TRIALS-Treatment										
Freeman (2008) RCT USA	To assess the efficacy of Omega-3 PUFAs in the treatment of perinatal depression beside of psychotherapy	Total 51 (31/28) Postpartum depression (14/16)	Pregnancy (after 12 weeks) and postpartum period (before 6 months); current major depressive disorder	8 weeks	1.9 g/day EPA and DHA (1.1 g EPA and 0.8 g DHA) + both groups were given psychotherapy	Placebo (corn oil)	–	EPDS, HAM-D, CGI biweekly for 8 weeks	Insignificant changes in depression scores based on whether control or intervention arm using the EPDS, HAM-D and CGI	Small sample size, short duration and low dosage Lack of supportive psychotherapy Randomization did not equalize subjects
Rees (2008) RCT Australia, Sydney	To assess the efficacy of Omega-3 PUFAs in the treatment of perinatal depression	26 women (12 antenatal; 14 postnatal)	Women aged >21years Perinatal period (third trimester to 6 months postpartum); episode of MDD or dysthymia	6 weeks	6 g/day fish oil (27.3% DHA; 6.9% EPA) in intervention group	Placebo (sunola oil)	Blood test at baseline and at the end of the trial.	EDPS, HAM-D, MADRS at baseline and week 6 postpartum	No difference in depression scores at week 6 based on EPDS, HAM-D and MADRS.	Small sample size The large placebo response and/or automatic remissions that may affected any n-3 beneficial effect
RANDOMIZED COMTROLLED TRIALS-Prevention										
Doornbos (2009) RCT The Netherlands	To assess the efficacy of omega-3 (DHA or DHA+AA) on maternal mental health and sleep quality	119 (DHA 42, DHA + AA 41/36) and placebo	Healthy pregnant women, first time mothers	From week 16 of pregnancy until 3 months post-partum	DHA (220 mg/day) or DHA (220mg/day) + AA (220 mg/day)	Placebo	Blood samples at 16 and 36 weeks of gestation. Food surveys throughout study	EDPS at week 16 and 36 of pregnancy and 6 weeks postpartum And a blues questionnaire at 1st week postpartum	Scores on EPDS did not differ based on group status at 36 weeks and 6 weeks postpartum	-Small sample size Inability of EPDS to assess effects of interventions

Table A2. *Continued (Experimental studies)*

Study Design and Site	Objectives	Sample size Treatment/ Placebo	Population	Duration of the Intervention	Intervention	Control	N-3 PUFA Measurement	Depression Measurement	Main findings	Limitation
RANDOMIZED CONTROLLED TRIALS-Prevention										
Llorent (2003) RCT USA	To determine if DHA supplementation increase plasma phospholipids DHA content and prevent PPD in women who breastfeed	89 (44/45)	Pregnant women, 18–42 years, who planned to breastfeed for at least 4 months	4 months	Daily dose of Omega-3 PUFAs DHA ≈ 200 mg	Placebo	Blood fatty acid levels were measured at baseline (37–38 weeks gestation) and 4 months postpartum	BDI late 3rd trimester, 3 weeks, 2 months and 4 months postpartum	An increase in serum DHA levels but no difference in BDI depression scores between groups at 4 mo.	Small sample size Short study duration Low DHA dosage
Makrides (2010) RCT Australia	To assess the efficacy of DHA during the last half of pregnancy in reducing PPD and enhance the neurodevelopment outcome of children	2399	Pregnant women > 21 weeks of gestation	From week 21 of pregnancy until 6 months postpartum	Daily dose of omega-3 (DHA= 800mg EPA= 100mg)	Placebo (Vegetable oil: rapeseed, sunflower and palm)	The levels of DHA in cord blood was measured through capillary gas chromatography	EPDS at 6 weeks and 6 months postpartum	No difference in EPDS high scores between the DHA and control group	Lack of clinical diagnosis for high EPDS scores Lack of assessment of intake of omega-3
Mozurkewich (2013) RCT USA	To assess the efficacy of omega-3 in the prevention of depression during and after pregnancy among women under risk of depression	126	Pregnant women >12-20 weeks pregnancy and aged more than 18 years old with a past history of depression	From early pregnancy until 8 weeks postpartum	EPA or DHA rich fish oil (1060 mg EPA + 274 mg DHA or 900 mg DHA + 180 mg EPA)	Placebo (Soy oil)	Blood sample at enrolment and 34-36 weeks' gestation	BDI and MINI at 26-28 weeks, 34-36 weeks of pregnancy and at 6-8 weeks postpartum	No difference between groups in depression scores during or after pregnancy	Lack of clinical diagnosis for high depression scores Lack of adherence Presence of fish oil in placebo

Table A2. *Continued (Experimental studies)*

Study Design and Site	Objectives	Sample size Treatment/ Placebo	Population	Duration of the Intervention	Intervention	Control	N-3 PUFA Measurement	Depression Measurement	Main findings	Limitation
PILOT TRIALS-Treatment										
Freeman (2006) Open Label USA	To determine the effect of Omega-3 PUFAs in the treatment of PPD	16	Women, aged between 15–45 years, and between 2-14 weeks post-partum participants met criteria for major depressive episode by 1 month postpartum	8 weeks	3 groups: 0.5 g/day; 1.4 g/day or 2.8 g/day of omega-3s (ratio EPA: DHA was 1.5:1)	None	N/A	EPDS and HAM-D at baseline, and weeks 1, 2, 4, 6, 8 postpartum	Decrease on 2 depression measures (EPDS, HAM-D) at 8 weeks compared with baseline by 51.5% and 48.8%	Small sample size Lack of placebo group Randomization did not equalize subjects Lack of inclusion of fatty acids' plasma levels
PILOT TRIALS-Prevention										
Marangell (2004) Open Label USA	To assess the efficacy of Omega-3 PUFAs in the prevention of postpartum depression among women at risk of depression	7	Pregnant women, aged >18 years, From 34 to 36 weeks in pregnancy to 12 weeks postpartum; history of postpartum depression	From week 34–36 of pregnancy until 12 weeks post-partum	2960 mg/day fish oil with 173 mg EPA and 123 mg DHA (ratio EPA:DHA was 1:4)	N/A	Dietary questionnaire	HAM-D, EPDS, adverse experiences log, daily mood diary at baseline and weeks 2, 4, 8 and 12 postpartum	No benefits of omega-3 in the prevention of PPD knowing that 4/7 had relapse of postnatal depression as measured by the HAM-D and the EPDS	Small sample size Lack of control group Unknown optimal dose of Omega-3 PUFAs

Table A2.*Continued (Observational studies)*

Study Design and Site	Objectives	Sample Size	Population	Duration of the Study	N-3 PUFA Assessment	Depression Assessment	Adjustment of Potential Confounders	Main findings	Limitation
ECOLOGICAL STUDIES									
Hibbeln (2002) Ecological USA	To assess if DHA status in mothers' milk and seafood consumption would predict prevalence rates of PPD across countries	n =14 532 mothers	–	–	DHA, EPA and AA data (analysed from breast milk) extracted from reports across 23 countries	EPDS data were reanalysed from 41 studies	Low socioeconomic status, single mothers, secondary education, sample time postpartum, geographical latitude	Higher levels of DHA in breast milk and greater seafood consumption were both associated with lower levels of PPD	Data on potentially confounding factors were not uniformly available for all countries
CROSS SECTIONAL STUDIES									
De Vriese (2003) Cross-sectional The Netherlands	Investigate whether the postpartum fatty acid profile of maternal Serum phospholipids (PL) and cholesteryl esters (CE) differs in women who develop postpartum depression compared to controls	n = 48 10 with PPD, 38 without	Healthy pregnant women	Pregnancy to 10 months postpartum	Blood samples extracted shortly after delivery and assayed for serum phospholipids and cholesteryl esters	SCID interview between 3 and 12 months postpartum	–	Fatty acid concentration was lower in women with depression than in those not depressed	Cannot distinguish temporality whether low fatty acid precede depression or visa versa Lack of control of confounders

Table A2.*Continued (Observational studies)*

Study Design and Site	Objectives	Sample Size	Population	Duration of the Study	N-3 PUFA Assessment	Depression Assessment	Adjustment of Potential Confounders	Main findings	Limitation
CASE CONTROL STUDIES									
Browne (2009) Case control New Zealand	To determine whether prenatal fish consumption and omega-3 status after birth were associated with postnatal depression	n = 80 case = 41 controls =39	First time mothers	Pregnancy to 6 months postpartum	- Blood sample at 6 months postpartum - Food-frequency questionnaire (FFQ) during pregnancy	EDPS and BDI-II at baseline, CIDI immediately after lipid extraction test	Household income, current breastfeeding	Prenatal fish consumption was not predictive of PPD, and postnatal n-3 status was not associated with PPD	Single FFQ and blood sample collected on fish consumption and PUFA status Majority of participants ate non oily fish, which was not separated from oily fish consumption
COHORT STUDIES									
Da Rocha (2012) Prospective cohort Brazil	Evaluate the link between an unbalanced dietary intake ratio between the n-6 and the n-3 fatty acids above 9 in the first trimester of pregnancy and the prevalence of PPD.	n = 106	Pregnant women	2005-2007	Food Frequency Questionnaire (FFQ) to assess the dietary intake in the first trimester	EPDS was applied in the fifth wave of follow-up, at least 30 days following delivery	Age, schooling, time elapsed since delivery and lipid consumption	Higher risk of postpartum depression in women with n-6:n-3 intake ratio greater than 9:1 during first trimester	Lack of dietary data in reasonable number of women for the 2nd and 3rd trimesters High loss to follow-up The study could not exclude women with pre-existing pregnancy depression

Table A2.*Continued (Observational studies)*

Study Design and Site	Objectives	Sample Size	Population	Duration of the Study	N-3 PUFA Assessment	Depression Assessment	Adjustment of Potential Confounders	Main findings	Limitation
COHORT STUDIES									
Markhus (2013) Prospective cohort Norway	To assess the link between seafood consumption, mental health, and infant development	n= 128	Pregnant women in their 24th week of gestation	20 months 2009-2011	Blood samples at the 28th gestation week, FFQ	EPDS at 3 months postpartum	No adjustment of the potential confounders	A low omega-3 index in late pregnancy was associated with higher depression score 3 months postpartum	Was not possible to control for the effect of confounders The selective drop-out effect or missing data
Miyake (2005) Prospective cohort Japan	Investigate the relationship of consumption of high-fat foods and specific types of fatty acids with the risk of PPD	n= 865	Pregnant women	November 2001-March 2003	Self-administered diet history questionnaire during pregnancy	EPDS between 2–9 months postpartum	Age, gestation weeks, parity, family structure, occupation, education, smoking, BMI, pregnancy medical status, changes in diet in the previous month, baby weight.	No evidence association between fatty acid intake and risk of postpartum depression	Wide range (2 to 9 months) for postnatal screening Single self-administered semi-quantitative dietary questionnaire
Otto (2003) Prospective cohort The Netherlands	Examine if DHA content of plasma phospholipids, and breastfeeding is related to an increased risk of postpartum depression	n = 112	Pregnant women	Delivery to 32 weeks postpartum	Blood samples at 36 weeks gestation, delivery, 32 weeks postpartum	EPDS at 32 weeks postpartum	Parity, educational level, breastfeeding, smoking and alcohol use	DHA was lower in the "possibly depressed" group (EPDS>10) compared with the not likely depressed (EPDS<10)	The covariates which were associated with depression were not considered by the authors in the analyses

Table A2. *Continued (Observational studies)*

Study Design and Site	Objectives	Sample Size	Population	Duration of the Study	N-3 PUFA Assessment	Depression Assessment	Adjustment of Potential Confounders	Main findings	Limitation
COHORT STUDIES									
Parker (2014) Prospective cohort Australia	Assess whether an unbalanced levels of n-3 and n-6 fatty acids in late pregnancy are related to perinatal depression	n = 1232	Pregnant women between 34 and 37 weeks >18 years of age		Diet questionnaire Blood sample at 30 weeks of pregnancy	EPDS, DSMIV and/ or Antidepressant at baseline. EPDS at 3 months postpartum	Age, education, income, marital status, parity, neuroticism scores, history of mood disorder, coffee, smoking and alcohol intake, pregnancy stress levels	PUFA status in late pregnancy is slightly linked with the risk of PPD based on EPDS but no association was found based on DSM criteria	Impossibility of drawing a cause and effect conclusion because of the observational design of this study.
Strom (2009) Prospective cohort Denmark	Explore the association between intake of fish and n-3 PUFAs during pregnancy and postpartum	n=54202	Pregnant women, Mid-pregnancy to 1 year postpartum	1996-2002	FFQ at 25 weeks' gestation	PPD admission (admission to psychiatric hospital or psychiatric) PPD prescription (a woman who filled a prescription for an antidepressant)	Age, parity, pre-pregnancy BMI, total energy intake, pregnancy smoking and alohol intake ,occupation, education, homeownership, marital status, social support and history of depression	There was no association between fish intake and risk of PPD admission group. Risk of PPD prescription was found to be higher for women with a lower fish intake.	The proportion of women classified as cases of PPD admission was relatively low in this study

RCT = Randomized controlled trial; MDD = Major depressive disorder; EPA = Eicosapentaenoic acid ; EPDS = Edinburgh Postnatal Depression Scale; DHA = Docosahexaenoic acid ; HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impression; PPD = Postpartum depression; MADRS = Montgomery-Asberg Depression Rating Scale; AA = Arachidonic acid; SCID = Structured Clinical Interview For DSM Disorders; CIDI = Composite International Diagnostic Interview; PUFA = Polyunsaturated fatty acids; FFQ = Food frequency questionnaire; BMI = Body Mass Index; DSM = Diagnostic and Statistical Manual of Mental Disorders ; MINI = Mini International Neuropsychiatric Interview; n-3 = Omega-3,