The effect of maternal omega-3 polyunsaturated fatty acid supplementation on perinatal depression:

A Systematic review and Meta-analysis

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Table of Contents

TABLES AND FIGURES ..... **iii**

ABSTRACT ..... **iv**

DECLARATION ..... **v**

ACKNOWLEDGMENTS ..... **vi**

CHAPETER 1

Introduction **1**

1.1 Perinatal Depression: Definition 1

1.1.1 Etiology and Epidemiology 1

1.2 Perinatal Depression: Outcomes and Treatment Strategies 2

1.3 Caveats Associated with Pharmacological Treatment 4

1.4 Omega-3 long Chain Polyunsaturated Fatty Acids (LCPUFAs) 5

1.5 Omega-3 and Perinatal Depression 6

1.6 Current Study 7

1.6.1 Problem Statement 7

1.6.2 Aims 8

CHAPTER 2

Method **10**

2.1 Literature Search 10

2.2 Study Eligibility 10

2.3 Data Extraction and Organization 12

2.4 Data Preparation 14

2.5 Risk of Bias Assessment 14

2.6 Synthesis and Analysis of Effect Size 15

2.7 Moderator Analysis 16

CHAPTER 3

Results 17

3.1 Study Characteristics 17

3.2 Sample Characteristics 20

3.3 Risk of Bias Assessment 21

3.4 Effect of Omega-3 Supplementation for Maternal Mental Health 23

3.4.1 Perinatal Depression 23

3.4.2 Antenatal versus Postnatal Depression 23

3.5 Moderator Analysis 24

CHAPTER 4

Discussion 29

4.1 Key Findings 29

4.1.1 Intervention Period 30

4.1.2 Diagnosis and Psychometric Measures of Depression 31

4.1.3 Intervention Dose and Formulation 31

4.1.4 Other Potential Sources of Heterogeneity 32

4.2 Clinical Implications and Future Research 34

4.3 Limitations 35

4.4 Conclusion 36

References 38

Appendices 53

Appendix A: Logic grids per data base informing overall search strategy 53

Appendix B: Study characteristic summary table 63

TABLES AND FIGURES

Chapter 2: Method

Figure 1: PRISMA flowchart for study selection process

Chapter 3: Results

Figure 2: Risk of Bias assessment table

Table 1: Summary of risk of bias assessment for each included study

Table 2: Effect of omega-3 supplementation for perinatal depression

Table 3: Effect of omega-3 supplementation for antenatal depression

Table 4: Effect of omega-3 supplementation for postnatal depression

Table 5: Impact of psychometric measures on omega-3 supplement effect

Table 6. The effect of baseline mental health status on treatment outcome

ABSTRACT

Background: Treatment, particularly pharmacological interventions, remains challenging for perinatal depression – given the effects may be detrimental to the health of the infant. Abnormal levels of omega-3 polyunsaturated fatty acids (PUFAs) are reported to be associated with perinatal depression. During the perinatal period, omega-3 PUFAs decreases profoundly as a result of preferential transfer to the fetus; and may precipitate the onset of depression. While omega-3 PUFAs supplementation has shown benefits for major depression, it remains unclear whether the effects are similar for perinatal depression. *Aims*: To investigate the efficacy of maternal omega-3 supplementation for the treatment of antenatal and postpartum depression. *Methods*: Ten studies, comprising of 754 participants were identified from a comprehensive search of six electronic databases: Cochrane, Embase, PsycINFO, PubMed, Scopus, and Web of Science. Human randomized controlled trials that supplemented maternal diet with omega-3 PUFAs during pregnancy or postpartum, and assessed depression were included. Meta-analytic techniques were used to examine the effect of omega-3 PUFAs on depressive symptoms. Trial quality and methodological heterogeneity were also assessed. *Results*: Meta-analysis demonstrated no significant benefits of omega-3 supplementation compared to placebo, with a pooled effect size (Hedge's *g*) of -0.16 (95%CI [-0.42, 0.10], $p = .22$). Most trials had methodological limitations. *Conclusions*: The current findings does not conclusively support that omega-3 supplementation may be an effective treatment for perinatal depression. Future high-quality, large-scale research of comparable methodology, are necessary to assess the efficacy of omega-3 supplementation as a therapeutic agent for perinatal depression.

DECLARATION

This thesis contains no material which has been accepted for the award of any other degree of diploma in any University, and, to the best of my knowledge, this thesis contains no material previously published except where due reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library search and through we search engines, unless permission has been granted by the School to restrict access for a period of time.

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CHAPTER 1

Introduction

1.1 Perinatal Depression: Definition

Maternal perinatal depression, a form of depression, is experienced during pregnancy and/or after the birth of the infant. According to the DSM-V, perinatal depression is defined as 'the onset of depressive symptoms during pregnancy or within a month following delivery' (American Psychiatric Association, 2013). Perinatal depression differs from Major Depression, in that it must not be diagnosed prior to pregnancy. Perinatal depression is more serious than 'baby blues', which 80% of new mothers will experience (Degner, 2017). Perinatal depressive symptoms consists of mothers feeling profound sadness, lasting for more then a few weeks and may also involve symptoms such as anxiety; and interferes with their daily activities and living (Degner, 2017).

1.1.1 Etiology and Epidemiology Perinatal depression is one of the most common complications during pregnancy. According to a report published by the Australian Institution of Health and Welfare (2010), 1 in 10 mothers are diagnosed with perinatal depression with 1 in 10 mothers will experience depression during pregnancy, while 1 in 7 are affected.

It is estimated that the prevalence of perinatal depression is 12% in general population. However, estimates higher in individuals from certain groups including those with a prior history of (Major Depressive Disorder (MDD) and in those with a history of Postpartum Depression (PPD; Gaynes et al., 2005) In addition, an increased prevalence has also been noted in low-income women, and is more prevalent in ethnic minority groups, such as Hispanic women, African American and Aboriginal Australians (Zayas, Cunningham, McKee, & Jankowski, 2002). Moreover, the perinatal period has been documented to be a

time of high risk for psychiatric hospitalization, particularly women with comorbid disorders (e.g. bipolar) and those with past histories of MDD (Munk-Olsen, 2006). Most importantly, The onset of perinatal depression can significantly elevate the risk for maternal suicide. It has been reported that maternal suicides account for approximately 20% of all postpartum deaths and as a result, maternal suicide is one of the leading causes of maternal mortality in the perinatal period. (Lindahl Pearson, Colpe, 2005).

While the etiology of perinatal depression remains to be fully elucidate, there is consensus it is a heterogeneous disorder involving complex interactions between biological and environmental factors with childbirth and/or pregnancy as the triggering event (Martez-Brody, 2011). Research has shown that hormonal changes during pregnancy can lead to depressive symptoms during the perinatal period. In particular, pregnancy may lead to the abnormal function of the hypothalamic-pituitary- adrenal axis (HPA; Martez-Brody, 2011). The HPA controls hormone secretion, which is involved in regulating emotion. However, Sapolsky (2005) has shown that other hormones and systems, such as the hippocampal expression of brain-derived neurotrophic factor, may also be affected in perinatal depression. Therefore while research suggests hormonal changes during pregnancy and postpartum contribute to the onset of depression, this proposition does not comprehensively explain the incidence of the disorder.

1.2 Perinatal Depression: Outcomes and Treatment strategies

If left untreated perinatal depression can lead to adverse outcomes for the mother, her child, and family (Feldman, 2009; Logsdon, Wisner, & Pinto-Foltz, 2006). Depression during pregnancy has been linked to poor childbirth outcomes such as preterm delivery and low birth weight (Smith et al., 2011; Al, Van Houwelingen, & Hornstra, 1997; Al et al., 1995). Further, antenatal depression has been associated with premature delivery and mothers were

less likely to initiate breastfeeding (Eastwood et al., 2017); and antenatal depression can potentially increase the risk for developing postpartum depression (Robertson, Grace, Wallington, & Stewart, 2004). During the postpartum period, depression can have detrimental effects on maternal sensitivity (Campbell et al., 2004). In particular, a lack of maternal sensitivity is less likely to have children with secure attachment. Therefore the onset of maternal depression can lead to an emotional and physical disconnect by the mother toward the child (i.e., decreased sensitivity or rejecting care; Campbell et al., 2004). Consequently, depressed mothers are more likely to be intrusive and harsh with their infants (Campbell et al., 2004) and to exhibit other impaired parenting behaviors, such as lower rates of infant safety practices, such as not childproofing the household (Marmorstein, Malone, & Iacono, 2004). Postpartum depression can also lead to decreased healthy child development behaviors such as reading, singing, and playing games with their child (Paulson, Dauber, & Leiferman, 2006).

Moreover, research indicates that children exposed to perinatal (either during pregnancy or postpartum) depression have higher cortisol levels than infants of mothers who were not depressed. (Ashman et al., 2006; Halligan, Herbert, Goodyer, & Murray, 2004; Birch, Garfield, Hoffman, Uauy, & Birch, 2000). Importantly, this finding has also extends into adolescence whereby abnormal fetal cortisol levels are maintained throughout childhood. However, maternal treatment of depression during pregnancy appears to help normalize infant cortisol levels (Brenna et al., 2008).

Perinatal depression can also significantly impact the relationship of the family, as well as mother and child. In particular, a discord in the relationship between mother and partner has been identified as an important factor influencing both the development and outcome of PPD (Beck, 2001).

1.3 Caveats Associated with Pharmacological Treatment

Although it has become generally accepted knowledge that pregnancy is not protective with regard to onset of depression (Cohen et al., 2004), how best to treat depression during pregnancy and lactation remains strongly debated (Flores & Hendrick, 2002). Nonetheless, despite the ongoing controversies surrounding treatment, psychotropic use during pregnancy has become relatively common with a fourfold increase in use over the past decade. (Bakker, 2008). Moreover, recent reports have documented that up to 13% of all pregnant women are prescribed an antidepressant during pregnancy (Cooper, Willy, Pont, & Ray, 2007). In particular, the selective serotonin reuptake inhibitors (SSRIs) are the first-line, most frequently used antidepressants among pregnant women (Andrade, 2009; Cooper et al., 2007). The choice of whether to prescribe a medication during pregnancy is a difficult one, and prescribing must take into account the potential risks and benefits to the unborn infant and the mother. To date, the literature on the safety of antidepressants during pregnancy has yielded conflicting results and may mean that practical clinical recommendations are misinformed.

There are significant risks associated with exposure to untreated depression during pregnancy that are associated with serious adverse consequences for the developing neonate. Adverse outcomes associated with perinatal depression include premature birth, low birth weight, and future behavioral disturbances (Li, Liu, & Odouli, 2009; Grace Evindar, & Stewart, 2003). Studies have indicated that terminating antidepressant treatment in pregnancy leads to relapse of symptoms in approximately 60-70% of women (Cohen, 2004). The rate of relapse is further exacerbated for women with past histories of perinatal depression. Relapse then exposes the developing infant to the effects of untreated depression, which as stated above, can have potentially detrimental consequences for the mother, child, and family. Untreated depression during pregnancy is also one of the strongest risk factors for the

development of PPD. However, treating maternal depression with psychotropics can also have detrimental effects on the developing fetus. It has been documented that antidepressant use during pregnancy has been associated with risks to exposed infants including persistent pulmonary hypertension of the newborn (PPHN) and a neonatal withdrawal/toxicity syndrome (Hernández-Díaz et al., 2007; Moses-Kolko et al., 2005). Therefore given the caveats associated with pharmacological treatment, it is imperative to determine a treatment strategy that is safe for mother and infant.

1.4 Omega-3 Long Chain Polyunsaturated Fatty Acids (LCPUFAs)

Omega-3 describes a family of LCPUFA that is synthesized from the essential fatty acid alpha-linolenic acid, which is then converted to eicsopentaenoic acid (EPA) and docosahexaenoic acid (DHA) by enzymatic substrates (Levant, 2016). Biologically important PUFAs, such as DHA, can be synthesized from essential fatty acids or consumed directly from dietary sources including, fatty fish or plants. However humans are relatively poor at synthesizing LCPUFAs from the essential fatty acids (Brenna, 2002; Gerster, 1998). Further genetic polymorphisms may render certain individuals particularly poor at synthesizing or utilizing LC PUFA (Simopoulos, 2010; Ross 2007). Therefore, to ensure omega-3 LCPUFAs status remains at optimal levels, humans must consume adequate amounts of these essential fatty acids through diet (Levant, 2016).

Each of these constituents of omega-3 LCPUFAs is a component of the phospholipids in cells membranes (Surette, 2008). Variation in the fatty acid composition of phospholipids results in variation of the cell membrane, and therefore can alter the physiochemical properties of the membrane (Surette, 2008). The greatest concentration of omega-3 within the human body is the brain, with DHA being the most abundant species (Salem Jr, Litman, Kim, Gawrisch, 2001). In the brain, these LCPUFAs are involved in the development and

maintenance of neurons. They are also involved in synaptic transmission and various intra-cellular metabolic functions (e.g. gene expression; Salem Jr, Litman, Kim, & Gawrisch, 2001). Therefore, any variation in LCPUFAs component in cell membranes, have the potential to affect neuronal function.

1.5 Omega-3 and Perinatal Depression

Recent studies have reported omega-3 LCPUFAs may have a contributory role to the pathogenesis of perinatal depression. As the source of nutrition for the developing infant, there is considerable demand on pregnant and nursing mothers to supply DHA to their offspring (Birch, Garfield, Hoffman Uauy, & Birch, 2000; Innis, 2004; Levant 2016). Most DHA accumulates during the third trimester of pregnancy and continues through to the first few years of an infant's life (McNamara, & Carlson, 2006). Low availability of DHA can result in increased incorporation of the omega-6 LCPUFAs (docosapentaenoic acid; DPA), therefore altering the fatty acid component of the phospholipids. According to Meltzer-Broody (2011) while the overall growth of the brain is not affected, the change in composition of phospholipids however is associated with suboptimal visual, attention and intellectual development in the infant.

Without an adequate diet, mothers can become depleted of nutrients. The majority of studies have demonstrated that maternal plasma DHA levels can decrease by half in some individuals after a single pregnancy. Further, in the case of preferential transfer by lactation, fatty acid stores were not fully replenished at 26 weeks postpartum (van den Ham, van Houwelingen, & Hornstra, 2001). Additional pregnancies resulted in further reduction of maternal DHA levels in plasma and breast milk (Al, van Houwelinge, & Hornstra, 2000).

Epidemiologic and clinical studies suggest that pregnancy-associated changes in n-3 LCPUFAs status may contribute to the development of postpartum depression (Colangelo,

He, Whooley, Daviglus, & Liu, 2009). A cross-national analysis indicated that higher fish consumption, which was reflected in higher concentrations of DHA in breast milk, correlated with a lower incidence of perinatal depression (Hibbeln, 2002). Studies have reported that plasma or serum DHA concentrations was significantly lower in women experiencing depressive symptoms during the perinatal period than those who were not (Otto, de Groot, & Hornstra, 2005). Similarly, women who later developed postpartum depression had lower serum DHA levels after delivery than those who did not develop depressive symptoms (De Vriese, Christophe, & Maes, 2003).

Treating perinatal depression with omega-3 supplementation has shown beneficial effects, albeit it is as widely documented as major depression (Nemets, 2002). Nevertheless, various randomized controlled trials (RCTs) have demonstrated that treatment with a preparation containing docosahexaenoic acid (DHA) and/or eicosapentanoic acid (EPA) has effectively reduced depressive symptomology (Freeman et al., 2008). However, other RCTs have demonstrated that supplementation failed to prevent or reduce the symptoms of depression during the perinatal period (Doornbos et al. 2009; Marangell, 2004).

1.6 Current Study

1.6.1 Problem Statement. In recent years, non-pharmacological methods have demonstrated sufficient effectiveness in treating and prevention major depression (Yang, Han, Qiao, Tian, Qi, & Qiu, 2015). In particular there is a growing body of research suggesting that omega-3 LCPUFAs may be associated with perinatal depression, and therefore omega-3 supplementation may prevent or ameliorate depressive symptoms. While animal studies have shown that omega-3 has beneficial effects for perinatal depression, the evidence for human studies remains unclear (Able et al., 2009; Borba et al., 2010). Given clinical trials can vary in outcomes and methodological rigor, to determine the clinical

effectiveness and usefulness of omega-3 supplementation - one solution is a meta-analysis. Meta-analyses are a subset of systematic review, which involves collating empirical evidence based on pre-specified eligibility criteria. Meta-analyses utilize a quantitative and formal study design to systematically review previous literature and assess the strength of evidence on the treatment outcome for a particular disease. Statistical outcomes across studies are then integrated and summarized to obtain a single standard estimate of the effect (Gopalakrishnan & Ganeshkumar, 2013). The pooled effect size provides a more precise estimate of effect and greater statistical power than any individual study. Consequently, meta-analyses are considered the 'gold standard' of evidence-based healthcare that can assist in informed decision-making for the incorporation of an intervention into clinical practice (Haidich, 2010). The findings of this review may therefore have implications for treatment options that may be available for pregnant and postpartum mothers.

1.6.2 Aims. The current review will seek to investigate the efficacy of omega-3 supplementation on maternal mental health. Broadly, the aim of this review is to provide evidence for the clinical application of omega-3 supplementation in preventing and treating depression during the perinatal period. Meta-analytic techniques will be utilized to investigate whether there are beneficial treatment effects of omega-3 supplementation compared to placebo. Further, the current review plans to provide an updated review (from Jans, Giltay, & Van der Does 2010; Wojcicki & Heyman, 2011) and to further expand on the investigation by analyzing the antenatal and postnatal period separately; given the onset of depressive symptomology and adverse outcomes differ.

The primary aims are to:

1. Investigate the efficacy of omega-3 supplementation for preventing depressive symptoms at any point during pregnancy or postpartum.

2. Assess whether omega-3 supplementation is effective at reducing symptoms of depression during the antenatal period
3. Assess whether omega-3 supplementation is effective at reducing symptoms of depression during the postnatal period
4. Explore and explain sources of study heterogeneity by conducting exploratory moderator (subgroup) analyses.

CHAPTER 2

Method

2.1 Literature Search

A comprehensive search of six electronic databases (Cochrane, Embase, PsycINFO, Pubmed, Scopus and Web of Science) was conducted from March to April 2018 to source relevant studies examining omega-3 supplementation for perinatal, antenatal, and/or postnatal depression. Search term logic grids were devised for each database and tailored to their specific indexing terms (for specific logic grids, see Appendix A). A research librarian was consulted prior to conducting this search to identify relevant search terms. Contact with the research librarian continued during this process to improve accuracy and refine search terms. Key terms selected were related to type of supplementation (e.g. 'fish oil', 'omega-3 fatty acids'), pregnancy period (e.g. 'antenatal', 'postpartum'), and mental health outcome (e.g. 'depressive disorder').

Although search terms were relatively restrictive, no restrictions were set on date of publication to ensure maximum coverage. Further, reference lists of eligible studies and systematic reviews/meta-analyses were manually screened to identify additional publications. Finally, automatic email alerts were set up for each database (on a weekly basis) to ensure that any new studies published, meeting the key terms, were also covered. Email alerts were active between March and September 2018.

2.2 Study Eligibility

Studies were included if they recruited (a) pregnant or postpartum women whom were (b) either depressed or non-depressed. For individuals that were depressed, studies had to include women that were (c) clinically depressed or presented with depressed mood/symptomology. Studies investigating maternal depression could include (d) antenatal,

postnatal or perinatal depression (e) occurring up to one year after birth. This time frame was selected because it's a critical period for developing depression (Eastwood, 2017). Studies had to administer an (f) oral supplementation with a (g) supplement preparation containing: EPA, DHA, or both. Studies also had to include (h) a measure of symptoms of depression that were either generic (BDI; and/or PND-specific measures (e.g. EPDS) Maternal depression could be (i) represented as a primary or secondary outcome in studies. Finally studies had to (j) report synthesizable data that could be converted into an effect size (mean difference).

Studies were excluded if they were (a) non-human trials due to discordance between human and animal studies - as animal models may not adequately mimic clinical disease and treatment outcomes (Perel et al., 2007). To ensure methodological rigor studies not published in (b) English, and/or (c) in a peer-reviewed journal were also excluded (Rasmussen, & Montgomery, 2018). This allowed for methodological details and results to be examined effectively. Further, studies were excluded if design methodologies comprised of non-synthesizable data, such as (d) observational research (cohort/case study), (e) non-observational research (e.g. reviews), and (f) comments/replies to previous publications. Publications such as (g) conference/meeting abstracts were also excluded due to lack of detail in research methods and results for critical appraisal. . Finally, studies that did not employ a design methodology for clinical trials, such as (h) not being blinded, placebo-controlled, and/or randomized, were also excluded.

The initial literature search yielded 1,841 articles, of which 942 duplicates were removed (see Figure 1). The remaining 899 publications were screened by perusing titles and abstracts based on previously defined inclusion and exclusion criteria, and a further 817 publications was removed. A set of 82 full-text articles was reviewed based on the eligibility criteria. A total of 11 studies were identified for inclusion. No additional studies were

identified by a search of reference lists of relevant review/meta-analysis. A search of reference lists of included articles and email alerts also yielded no further studies. Overall, 11 studies were included in this review.

In accordance with the Preferred Reporting Items for Systematic Reviews and Mata-Analysis (PRISMA) guidelines (Liberati et al., 2009), data was collated for each study with a purposefully designed data extraction form (The Cochrane Pregnancy and Childbirth Group).

Where possible, information was extracted from each included trial on:

a) Study characteristics: Type of study design; setting/country; participant eligibility criteria; sample size (included in analysis); intervention type (including type, dose, duration and frequency of the intervention); intervention period (e.g. pregnancy, postnatal); serum fatty acid status; diagnosis of depression and measures of depression used.
b) Sample demographic characteristics: Mean age and standard deviation (SD); gestational age at trial enrolment (weeks) and SD; mean DHA and/or EPA serum level and SD;

2.3 Data Extraction and Organization

To enable effective analysis of outcome measures, data was grouped according to pregnancy period – during pregnancy (weeks) and/or postnatal (days/months) - for each intervention group. The data were further grouped into subdomains of individual psychosocial measures of depression. Finally, where possible, intent-to-treat (ITT) data was sought in favor of per protocol (PP) data.

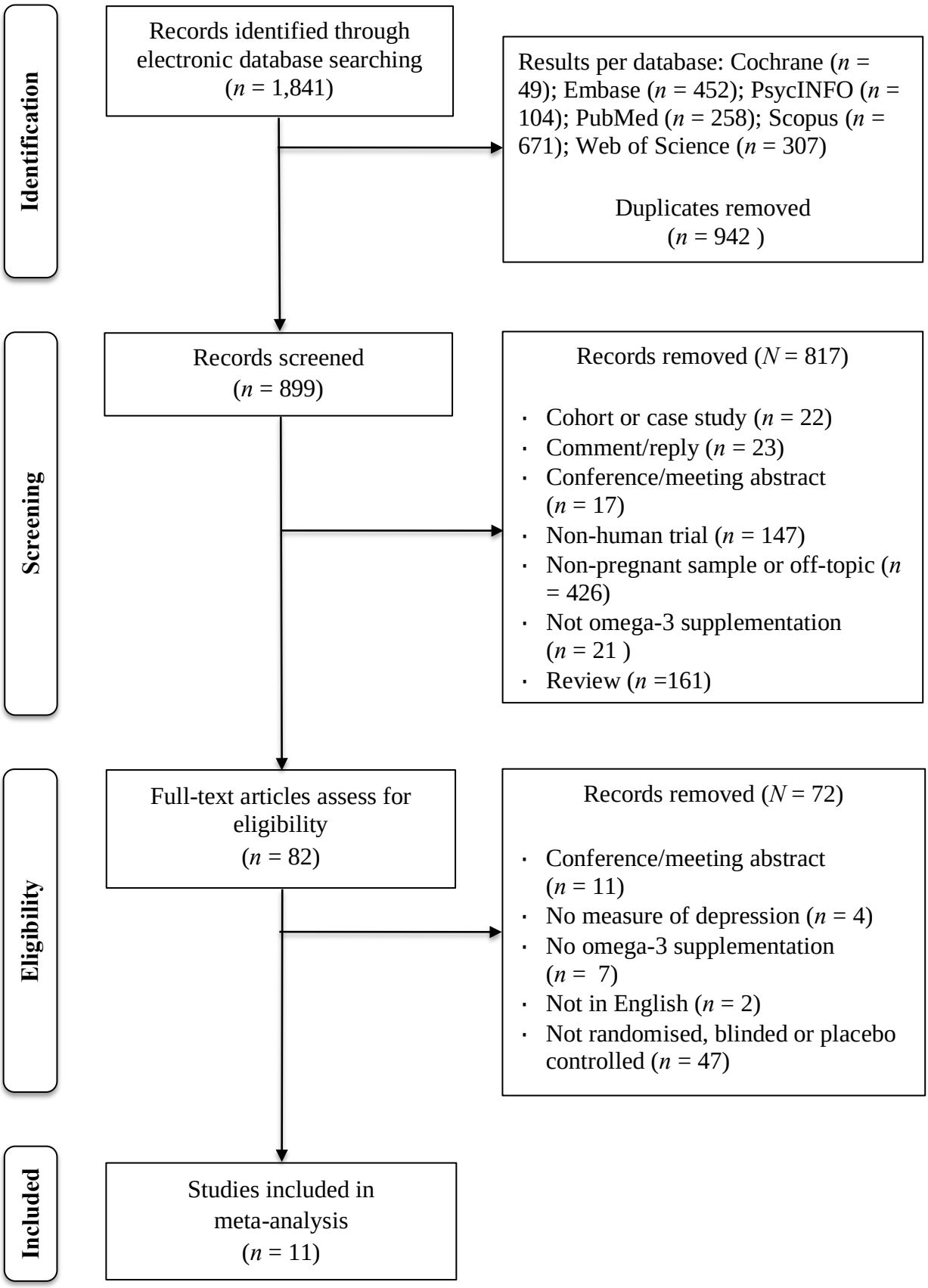


Figure 1. PRISMA flow diagram for study selection process

This allowed for the pragmatic evaluation of the intervention, and thus providing more accurate estimates of the treatment effect in practical clinical scenarios (Gupta, 2011). However, data was recorded for both ITT and PP trials.

2.4 Data Preparation

Prior to data analysis, three studies required data recalculation. First, Mozukerwich, 2013 included 3 intervention groups (DHA-rich vs. EPA-rich supplementation vs. control). The mean and SD of the active groups was therefore pooled to provide an overall averaged score and SD of one active group. The scores of this study then reflected two distinct intervention groups: active and control. Second, two studies (Doornboos et al., 2009; Vaz et al., 2017) only reported median values and ranges. These statistics were converted to estimated means and SD using an electronic calculator (Retrieved from http://www.comp/hkbu.edu.hk/~xwan/median2mean.html [accessed 8th August 2018]); based on the methods recommended by Hozo, Djulbegovic and Hozo (2005).

2.5 Risk of Bias Assessment

The extent to which the estimated treatment effect approximates the true effect largely depends on the validity of the included studies. Clinical trials inevitably vary in terms of methodological rigor, and may affect the cumulative evidence of the meta-analysis. As per the PRSIMA guidelines, a meta-analysis should therefore assess the risk of bias of included studies. The research author, in consultation with a second researcher, independently conducted these assessments according to The Cochrane Collaboration's tool for assessing risk of bias (Higgins & Green, 2011). The Collaboration's recommended tool for assessing risk of bias is a two part domain-based evaluation, in which bias was critically assessed for five domains: selection, performance, attrition, reporting and other biases not covered by the

other domains. For the current review, 'other biases' referred to conflicts of interest and funding for included studies. Each domain in the tool addressed specific subdomains (items; e.g. random sequence generation (selection bias) in a 'Risk of bias' table. Within in each subdomain, methodological characteristics and details of reporting were described to support a judgment about the risk of bias. Each subdomain was then assigned a judgment of 'Low risk', 'High risk', or 'Unclear risk' of bias (Higgins & Green, 2011). A risk of bias summary was provided; and the percentage for judgments for each risk of bias item, across all included studies, was also calculated.

2.6 Synthesis and Analysis of Effect Size

All statistical analyses were conducted using Review Manager 5.3 (RevMan) software. The clinical outcome of interest was the standardized mean difference in the change from baseline to endpoint scores on a depression rating scale, in patients taking omega-3 LCPUFAs supplements vs. patients taking placebo. Random effects model was used to allow for variation in effect sizes.

Standardized mean differences were measured for each individual study. As a requirement of meta-analyses, only one effect size was measured per study. Firstly, perinatal depression was investigated, then antenatal and postnatal depression were measured separately.

Three measures of statistical heterogeneity were used to assess variability between trials. Cochran's *Q*, tau (τ) and I^2. Cochran's *Q* shows whether there is a presence of heterogeneity between through null significance testing (Higgins Thompson, Deeks, & Altman, 2003). Tau represents an absolute value, which estimates the true variance between studies (Higgins Thompson, Deeks, & Altman, 2003). I^2 describes the percentage of variability that is due to heterogeneity, as visualized by the extent of overlap between confidence intervals (CIs), rather than chance. I^2 is represented as 0 (low heterogeneity) –

100% (high heterogeneity). If heterogeneity was >50%, possible sources of heterogeneity were explored (Borenstein, Higgins, Hedges, & Rothstein, 2017).

2.7 Moderator Analysis

Further, where data was available, possible sources of heterogeneity were explored. Various psychometric measures of depression were analyzed. For this review, some studies had utilized participants with major depression, whereas others had included healthy women whom presented with symptoms of depression (via self-report measures). The diagnosis of depression may therefore affect the treatment outcome; given research has favored omega-3 supplementation for clinical depression. The baseline mental health status (clinical depression versus depressed symptomology) of mothers was also explored.

Subgroup analyses on were planned for the following but not possible due to lack of data available. Research has shown that EPA may be better as an antidepressant than DHA (or vice versa), so differential effects between the type of supplementation was considered. The dosage of the supplementation has also shown differential effects, whereby evidence for optimal dosage for a treatment effect is not clear. Therefore differential effects of omega-3 supplement dosage (high >1000mg vs. low <1000mg dose) would have been explored.

CHAPTER 3

Results

3.1 Study Characteristics

Ten independent studies included in this review, comprising of a pooled sample size 754 participants, provided data for this meta-analysis. One study Makrides et al. (2010) was not included in any of the meta-analyses as data for effect size calculation could not be obtained. The publication dates of the studies were relatively recent, ranging from 2003 to 2017. All included studies were randomized controlled trials, and all except for Doornboos et al. (2008), included blinding in the study design.

A third of studies conducted trials among North American populations ($N_{studies}$ = 4; Freeman et al., 2008; Judge et al., 2014; Llorente et al., 2003; Mozurkewich et al., 2013), with the remaining populations spread around South America ($N_{studies}$ = 1; Vaz, Farias, Adegboye, Nardi, & Kac, 2017), Europe ($N_{studies}$ = 1; Doornbos et al., 2009), Asia ($N_{studies}$ =1; Su, Chiu, Huang, Huang, & Pariante, 2008) and the Middle East ($N_{studies}$ = 2; Farshbaf-Khalili, Mohammad-Alizadeh, Farshbaf-Khalili, Mohammadi, & Ostadrahimi, 2010; Kaviani, Saniee, Azima, Sharif, & Sayadi, 2014). The majority of study sample sizes were relatively small (n <100 participants; $N_{studies}$ = 7; Freeman et al., 2008; Judge, Beck, Durham, McKelvey, & Lammi-Keefe, 2014; Kaviani et al., 2014; Llorenete et al., 2003; Rees, Austin, & Parker, 2008; Su et al., 2008; Vaz et al., 2017). The three largest studies (Doornbos et al., 2009; Farshbaf-Khalili et al., 2017; Mozurkewich et al., 2013), of similar sample size (n = 100-150 participants), contributed to approximately a third of the entire sample. The majority of studies included samples that were derived from multi-center trials, however Doornbos et al. (2009) and Llorente et al. (2003) did not state sources of recruitment or describe the sample.

The intervention type was consistent across studies, with the majority utilizing oral omega-3 supplementation consisting of both DHA and EPA. Only Farshbaf-Khalili et al. (2017) had added alpha-linolenic acid (ALA) to the supplement mixture. The dose of active capsules varied considerably between studies, from approximately 220mg to 2000mg of omega-3. Five studies (Doornbos et al., 2009; Farshbaf-Khalili et al. 2017; Freeman et al. 2008; Kaviani et al. 2014; Llorente et al. 2003) required participants to consume one capsule per day from enrolment until the end of trial period. However, Judge et al. (2014) reported capsules were consumed only during weekdays. Both Mozurkewich et al. (2013) and Su et al. (2008) required participants to consume multiple doses of omega-3 supplements per day. All trials comparison treatments consisted of non-omega-3 PUFAs such as corn, paraffin or soybean oil, and generally matched the active treatment.

The intervention duration generally depended on the intervention period, with the majority of studies supplementing from pregnancy to postpartum. More than half of included studies reported data for the antenatal and postnatal period ($N_{studies}$ = 7; Doornbos et al., 2009; Farshbaf-Khalili et al. 2017; Freeman et al. 2008; Judge et al., 2014; Mozurkewich et al., 2013; Su et al., 2008; Vaz et al., 2017). Kaviani et al. (2014) only investigated mothers during the antennal period, while Llorente et al. (2003) explored treatment effects on postnatal women. The majority of studies enrolled participants and commenced supplementation at approximately the second trimester of gestation ($N_{studies}$ = 8). Only Rees et al. (2008) commenced supplementation at the third trimester of gestation, while Vaz et al. (2017) commenced during first trimester of gestation. The postnatal duration ranged from 6 weeks to 6 months.

Even though perinatal depression was the outcome of interest, half of included studies included participants with a healthy maternal baseline mood status (Doornbos et al., 2009; Farshbaf-Khalili et al., 2017; Judge et al., 2014; Llorente et al., 2003). At enrolment, those

whom presented with depressive symptomology (after screening) then continued with the intervention. Participants with a diagnosis of major depression were included in three studies (Freeman et al. 2009; Rees et al. 2008; Su et al., 2008), and those at risk of major depression were included in two studies (Mozurkewich et al., 2013; Vaz et al., 2017). A less common diagnosis was mothers with mild depression ($N_{studies}$ = 1; Kaviani et al., 2014).

Perinatal depression was a primary outcome for most studies ($N_{studies}$ = 10), with various screening tools being the most widely used psychometric test. Half of the studies had included more than one measure of depression within the trial (Freeman et al., 2008; Judge et al., 2014; Llorente et al., 2003; Mozurkewich et al. 2013; Rees et al., 2008; Su et al., 2008). Depression during the antenatal and postnatal period was commonly measured with the Edinburgh Postnatal Depression Scale (EPDS; Cox & Holden, 2003), indicating that this is the most widely used screening tool for perinatal depression ($N_{studies}$ = 7; Doornbos et al., 2009; Farshbaf-Khalili et al., 2017; Freeman et al., 2008; Judge et al., 2014; Llorente et al., 2003; Rees et al., 2008; Su et al., 2008). Even though some studies ($N_{studies}$ = 5; Doornbos et al., 2009; Farshbaf-Khalili et al., 2017; Kaviani et al., 2014; Su et al., 2008; Vaz et al. 2017) had been conducted in non-English speaking countries, only three studies (Doornbos et al., 2009; Su et al., 2008; Vaz et al., 2017) had explicitly stated the appropriate version of the EPDS (according to national language). The next most widely used screening tool was the Beck's Depression Inventory (BDI; Beck, Steer, & Brown, G. K., 1996) often utilized for general depression ($N_{studies}$ = 4; Kaviani et al., 2014; Llorente et al., 2003; Mozurkewich et al., 2013; Su et al. 2009), followed by the clinician rated Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960; $N_{studies}$ = 3; Freeman et al., 2008; Rees et al., 2008; Su et al., 2008). Only one study (Judge et al., 2014) had utilized the more recently developed Postpartum Depression Screening Scale (PDSS; Beck & Gable, 2000).

Changes in depressive symptoms were measured at various time points during trials conducted in the perinatal period. Most studies had measured symptoms at various time points, while utilizing the same participants. Doornbos et al. (2009) had measured treatment changes at 36 weeks pregnancy and 6 weeks postpartum. Farshbaf-Khalili et al. (2017), measured depression at two time points during pregnancy, with postpartum scores recorded 30-45 days after birth. Similarly, Mozurkewich et al. (2013) had measured depression during the second and third trimester of gestation, and at 6-8 weeks postpartum. Vaz et al. (2017) measured depression at the third trimester of gestation and one month postpartum. Judge et al. (2014) analyzed treatment changes at the third trimester of gestation and from 2 weeks to 6 months during the postpartum period. Unlike the previous trials mentioned, Rees et al. (2008) conducted a 6-week trial, which compared pre- and post-treatment effects for pregnant and postpartum women simultaneously. While Freeman et al. (2008) reported data for an 8-week trial on postpartum and pregnant women, separately. On the other hand, Kaviani et al. (2014) and Su et al. (2008) compared pre and post-treatment effects during pregnancy (for 6-8 weeks). While Llorente et al. (2003), measured changes in depressive symptoms from 3 weeks up to 18 months postpartum.

Full details of data extraction results are provided in Appendix B.

3.2 Sample Characteristics

Key demographic details were not reported by all included studies ($N_{studies}$ = 4; Doornbos et al., 2009; Judge et al., 2014; Vaz, 2017). The mean age of participants was 28.9 (*SD* = 6.5) years for the fish oil group and 30.3 (*SD* = 5.9) years for the control group. The average gestational age at enrolment was 25.4 (*SD* = 3.3) weeks with the average postnatal period being 10.8 (*SD* = 5.2) weeks. Only seven studies had reported baseline DHA and EPA serum levels, and those that did report showed low levels at baseline of approximately 3%

with and average increase of 4.6% (*SD* = 1.2) post-treatment. Both primiparous and/or multiparous were included in studies, however only some studies had described this characteristic.

3.3 Risk of Bias Assessment

A summary of the risk of bias associated with each included trial is presented in Table 1. Most trials had adequately reported independent processes of random sequence generation and selection bias was therefore low ($N_{studies}$ = 8). However, concealment of treatment allocation lacked sufficient detail, and judgment for risk of bias was therefore unclear ($N_{studies}$ = 5; Doornbos et al., 2009; Judge et al., 2014; Kaviani et al., 2014; Su et al., 2008; Vaz et al., 2017). The majority of studies had adequately blinded participants and assessors of outcomes to minimize bias. Almost all trials had low attrition bias as participant withdrawals and follow-ups were acknowledged and missing data was imputed using ITT analysis. One trial (Doorboos et al., 2009) reported a high-dropout rate with the main reasons for attrition being: lack of motivation to participate and pregnancy complications. The sample size across groups were relatively balanced; but given the relatively small and underpowered sample of the trial this may have given rise to clinically relevant bias, and therefore increased the risk of attrition bias. Furthermore, publication bias was not present in the majority of trials ($N_{studies}$ =9). Only one study (Llorente et al., 2003) failed to report supporting evidence for an observed effect. For example, a significant effect was found but the corresponding statistic was not reported. This trial was therefore judged to be ‘high risk’. Finally, the observed effect of most studies was not influenced by source of funding or conflicts of interest (e.g. companies which supplied the fish oil capsules; $N_{studies}$ = 9).

Table 1. Summary of risk of bias assessment for each included study.

Lead Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Free from incomplete outcome data	Free of selective reporting	Free from other biases[a]
Doornbos (2009)	+	?	?	?	-	+	?
Farshbaf-Khalili (2009)	+	+	+	+	+	+	+
Freeman (2008)	?	?	?	+	+	+	+
Judge (2014)	+	+	+	+	+	+	+
Kaviani (2014)	+	?	?	?	+	+	+
Llorente (2003)	+	+	+	+	+	-	+
Mozurkewich (2013)	+	+	+	+	+	+	+
Rees (2008)	+	+	+	+	+	+	+
Su (2008)	?	?	?	?	+	+	+
Vaz (2017)	+	?	+	+	+	+	+

Notes. [a]other biases included conflict of interests and sources of funding.

3.4 Effect of Omega-3 Supplementation for Maternal Mental Health

3.4.1 Perinatal Depression. Findings are summarized and presented in Table 2. All included RCTs reported the effect of omega-3 supplementation on pre- and post-treatment depression changes during the perinatal period. A random effects meta-analysis conducted on treatment groups resulted in a standardized mean pooled effect size of -0.16 (95% CI [-0.42, 0.10], p = .22). The observed effect therefore showed no benefits of omega-3 supplementation for reducing depressed symptomology when compared to placebo. However, significant (moderate) heterogeneity was detected across studies (I^2 = 65%, χ^2 = 25.52, df = 9, p < .05).

3.4.2 Antenatal versus Postnatal Depression. Similar results were found when analyzing the effect of omega-3 supplementation for antenatal and postnatal depression (see Tables 3 and 4). For both cases, the observed effect was not significant with a mean pooled effect size of: antenatal -0.13 (95% CI [-0.40, 0.14], p = .35) and postnatal -0.04 (95% CI [-0.20, 0.13], p = .67). Heterogeneity was present and significant for antenatal depression (I^2 = 65%, χ^2 = 25.80, df = 9, p < 0.05). However, homogeneity was detected across studies for postnatal depression.

Table 2. Effect of omega-3 supplementation for perinatal depression

	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Doornbos	4.4243	3.2938	68	4.4659	3.4922	32	11.3%	-0.01 [-0.43, 0.41]
Farshbar-Khalili	9.6	5.3	75	10.9	5.1	75	12.9%	-0.25 [-0.57, 0.07]
Freeman, P.	10.96	5.92	28	8.09	4.96	28	9.6%	0.52 [-0.01, 1.05]
Judge, M.P.	45.55	13.5	20	48.42	17.18	22	8.5%	-0.18 [-0.79, 0.43]
Kaviani, M.	9.17	5.3	40	14.7	6.46	40	10.6%	-0.93 [-1.39, -0.46]
Llorente, A.M.	5.8	7.1	44	4.8	5.9	45	11.4%	0.15 [-0.26, 0.57]
Mozurkewich, E. L.	6.1558	4.9942	77	5.9	6.1	41	12.0%	0.05 [-0.33, 0.43]
Rees, A.	8.5	5.5	13	9	5.2	13	6.6%	-0.09 [-0.86, 0.68]
Su, K.P.	8.5	5.5	17	14.3	6.3	16	7.1%	-0.96 [-1.68, -0.23]
Vaz, J.S	6.8561	5.4322	32	7.4279	4.687	28	9.9%	-0.11 [-0.62, 0.40]
Total (95% CI)			**414**			**340**	**100.0%**	**-0.16 [-0.42, 0.10]**

Heterogeneity: Tau² = 0.11; Chi² = 25.54, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 1.22 (P = 0.22)

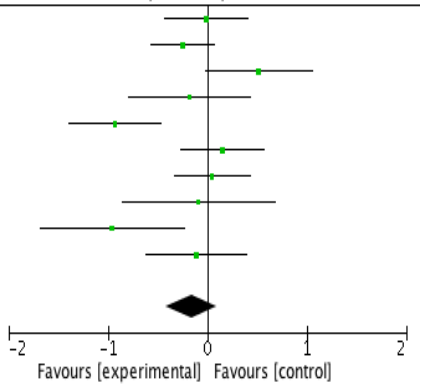


Table 3. Effect of omega-3 supplementation for antenatal depression

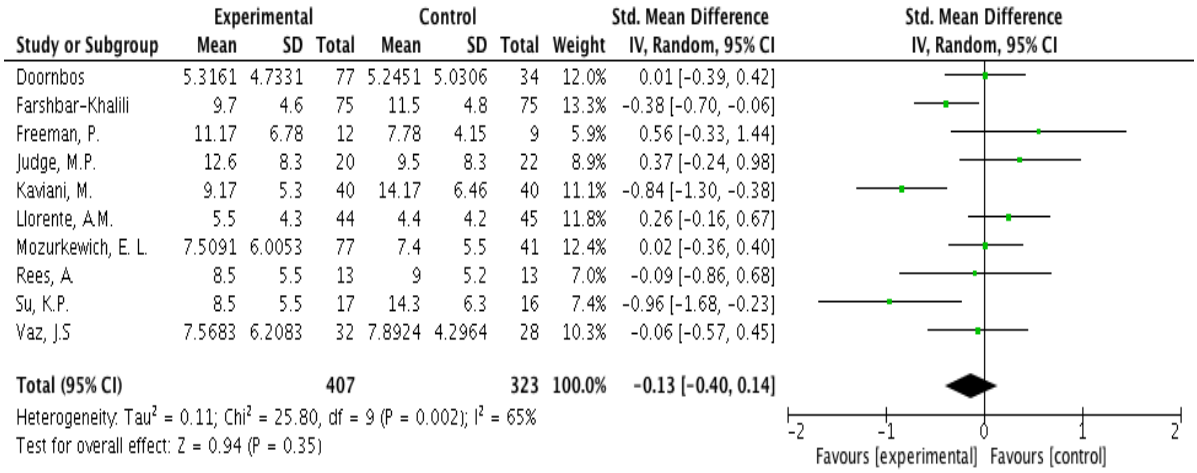
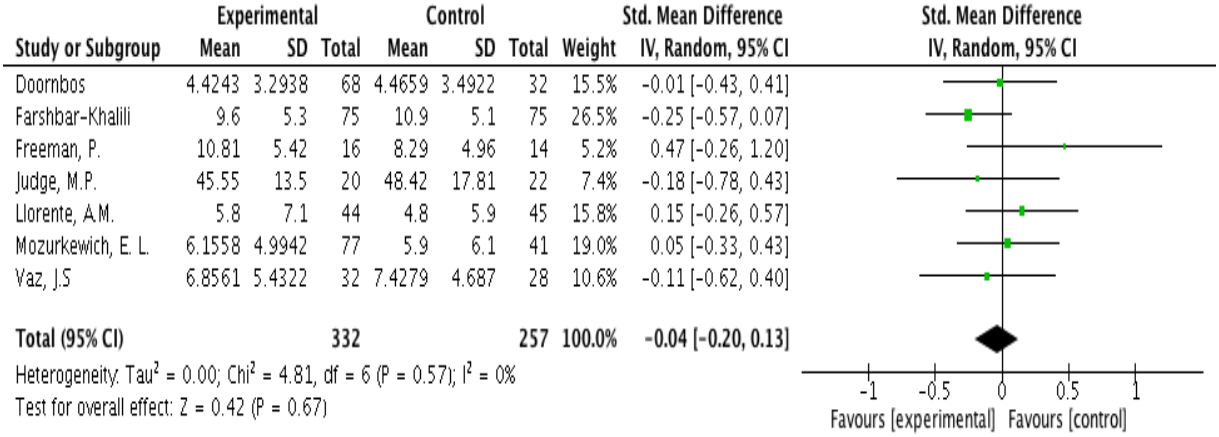


Table 4. Effect of omega-3 supplementation for postnatal depression



3.5 Moderator Analysis

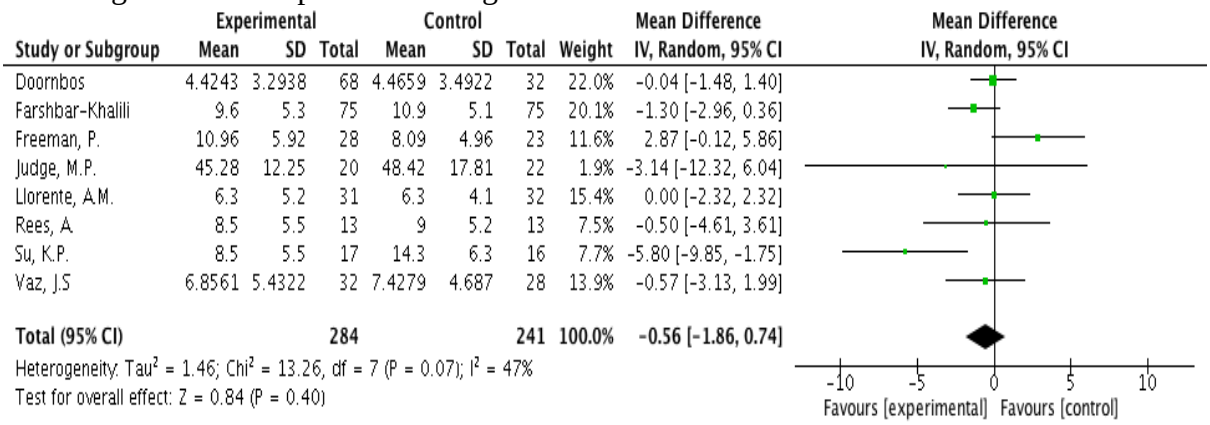
Subgroup analysis was performed to explore possible sources of heterogeneity. First, the different psychometric measures of depression across studies were explored. (Findings are summarized in Table 5). For the perinatal depression, both the BDI ($N_{studies}$ = 4) and EPDS ($N_{studies}$ =8) were not significant, -0.56 (95% CI [-1.86, 0.74], p = .40) and -2.64 (95% CI [-6.52, 1.24], p = .18) respectively. Heterogeneity within these subgroups was also moderate to high, thus demonstrating that there may be other sources of heterogeneity. Heterogeneity was similar for the HAM-D but the pooled effect was significant, 4.83 (95%

CI [-0.65, 9.01], p = .02). However the observed effect had favored controlled conditions, therefore omega-3 supplementation in fact did not reduce depressive symptoms. For antenatal depression, the observed effect was not significant for both the EPDS and BDI but, as found in perinatal depression, a significant effect was found for the HAM-D. When analyzing postnatal depression the observed effect again showed that omega-3 supplementation did not ameliorate depressive symptoms. Overall, the psychometric measures were not a source of heterogeneity.

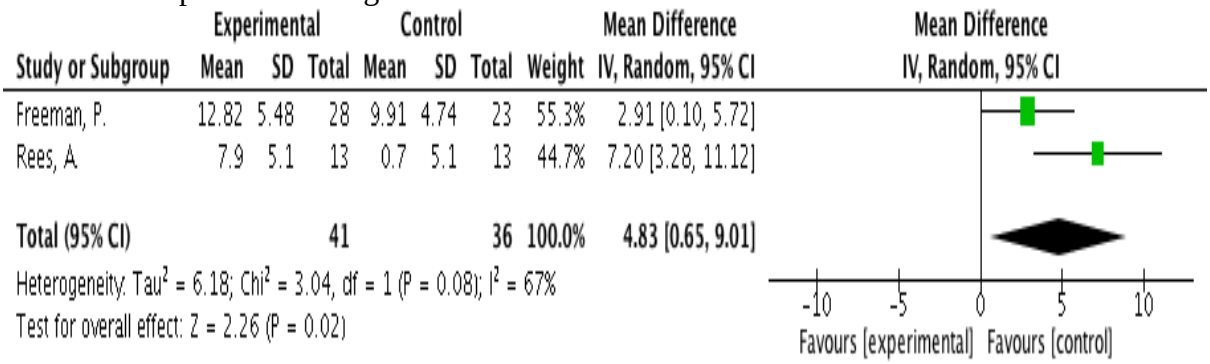
Table 5. Impacts of psychometric measures of depression on omega-3 supplement effect

Perinatal depression:

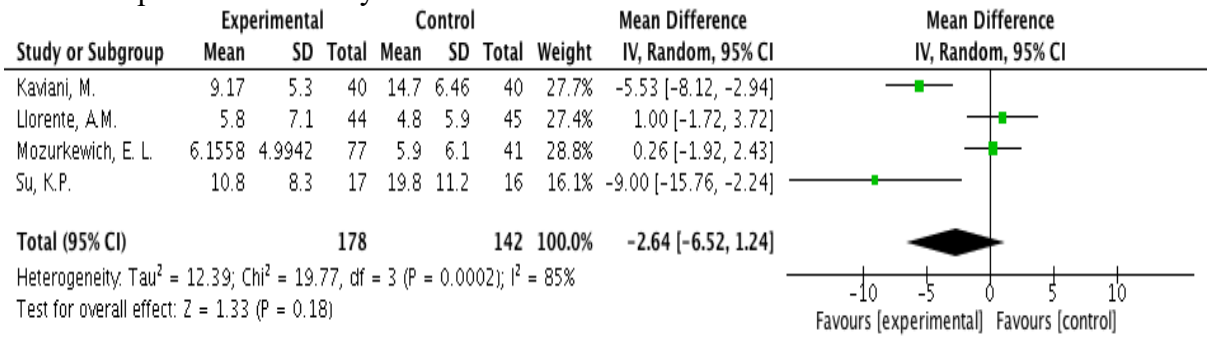
Edinburg Postnatal Depression Rating Scale



Hamilton Depression Rating Scale

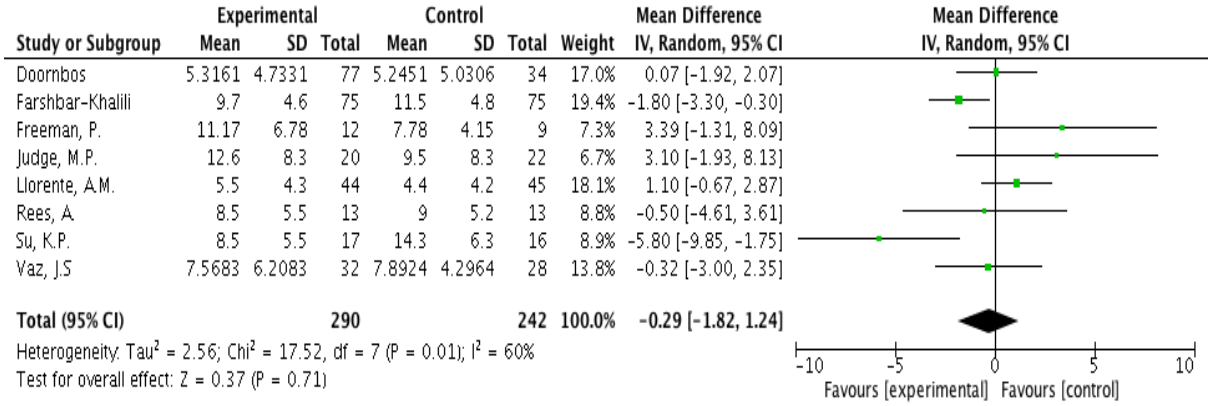


Beck's Depression inventory

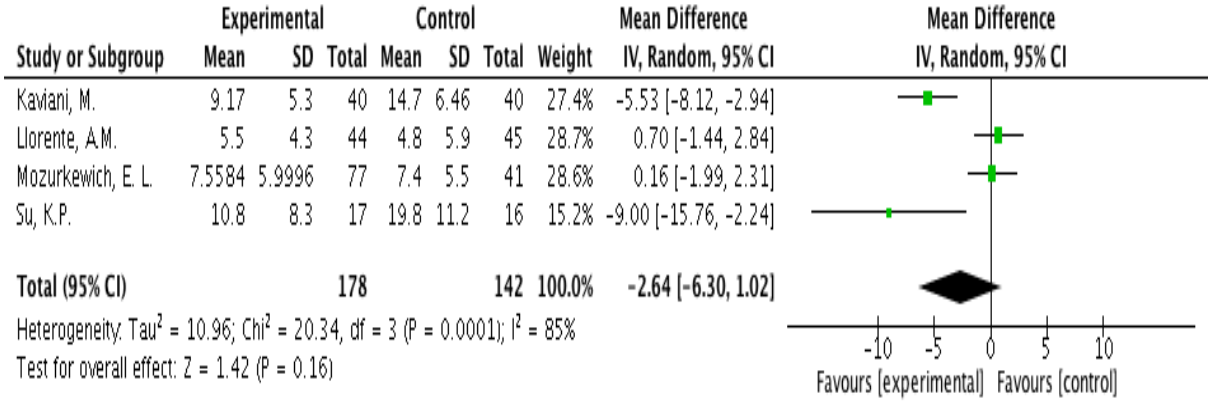


Antenatal depression:

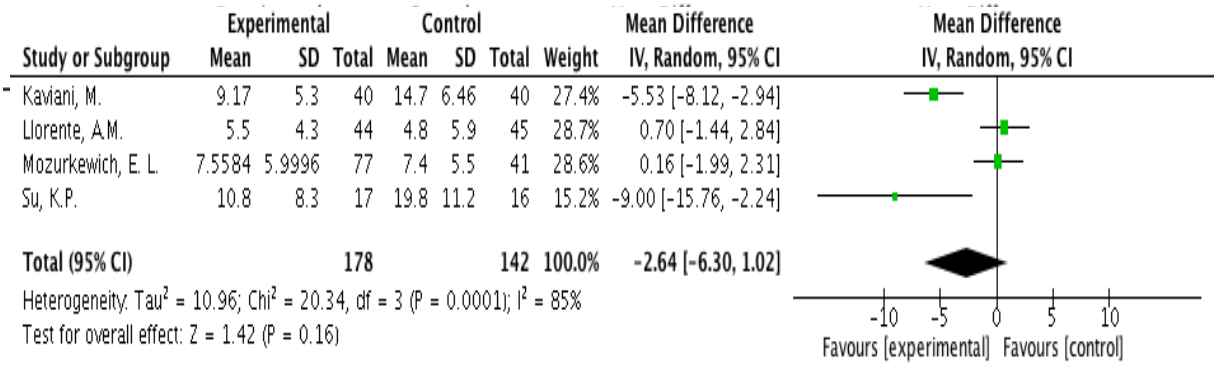
Edinburg Postnatal Depression Rating Scale



Hamilton Depression Rating Scale

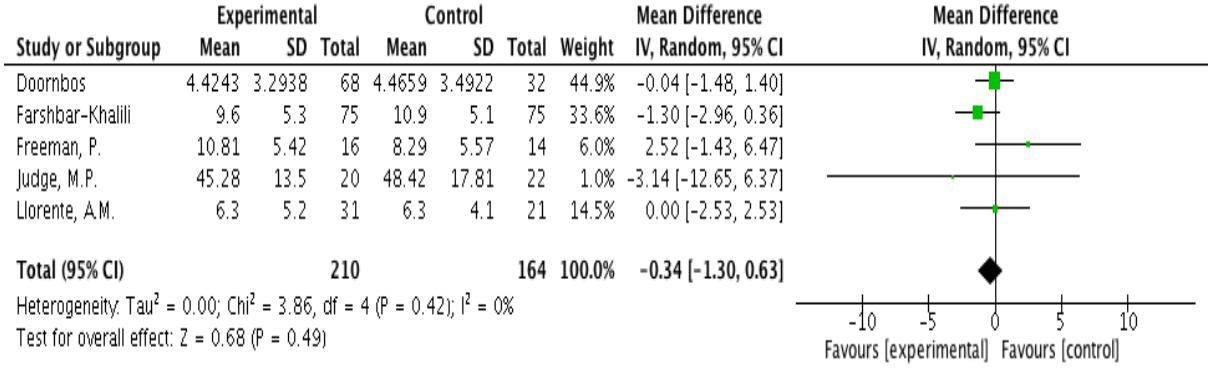


Beck's Depression Inventory

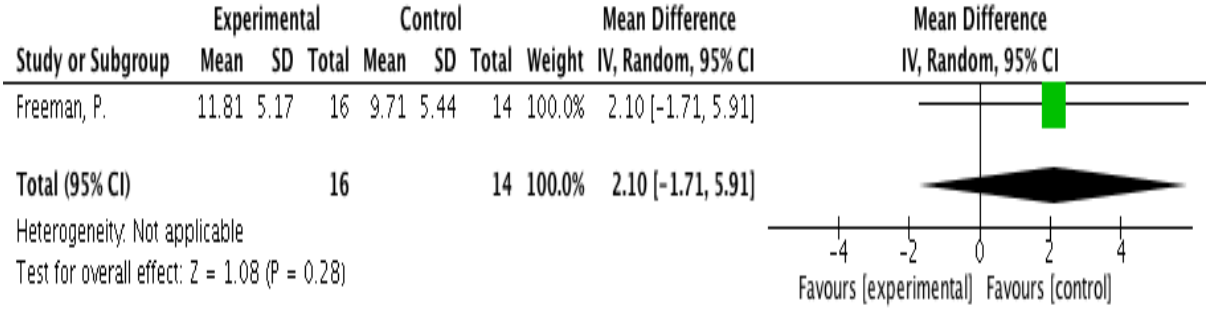


Postnatal depression

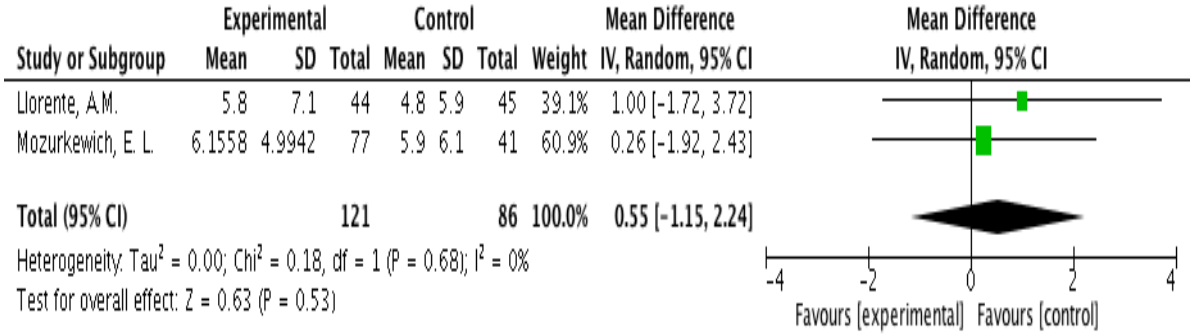
Edinburgh Postnatal Depression Rating Scale



Hamilton Depression Rating Scale



Beck's Depression Inventory

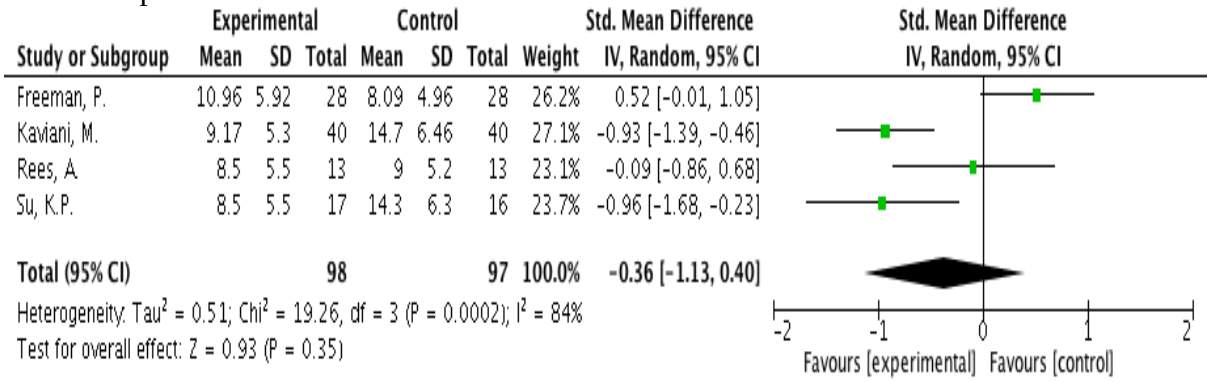


Second, the mental health status of mothers did not account for heterogeneity between studies (Table 6). The observed effect was neither significant for clinical depression -0.36 (95% CI [-1.13, 0.40], p = .35), nor was it for studies that included participants whom presented with depressive symptoms -0.09 (95% CI [-0.29, 0.12], p = .40). High heterogeneity was detected for studies including healthy participants, but homogeneity was

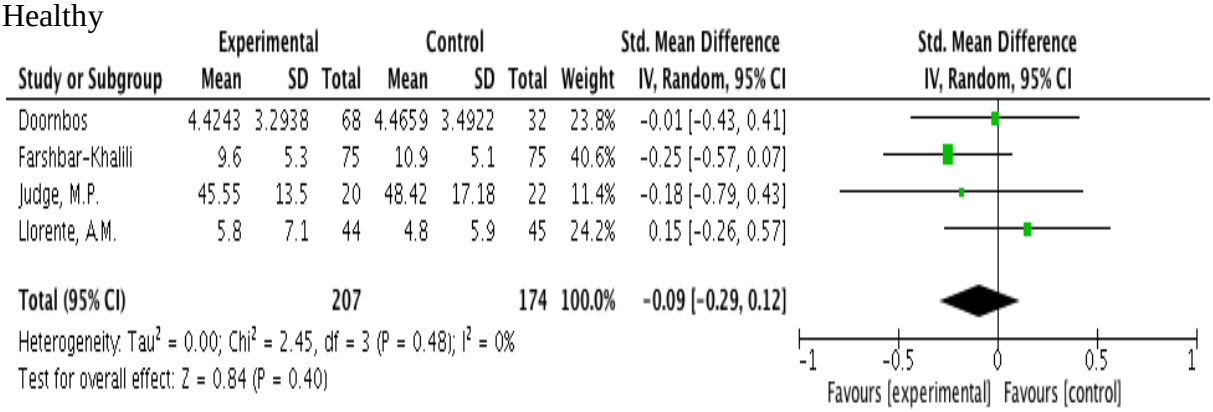
not present for the clinically diagnosed population. The results here suggest that the diagnosis of depression did not affect the treatment outcome.

Table 6. The effect of baseline mental health status on treatment outcome

Clinical depression



Healthy



CHAPTER 4

Discussion

4.1 Key Findings

Although a relatively new area of research for the maternal population, the current evidence adds nuance to the continuing debate on the effect of omega-3 supplementation on (perinatal) depression. Ten independent studies, comprising of 754 participants, were analyzed to provide a systematic assessment of the efficacy of omega-3 LCPUFAs supplementation for preventing and treating perinatal depression. The results of the current systematic review and meta-analysis did not show benefits for omega-3 LCPUFA supplementation for treating depressive symptoms during the perinatal period. Effect sizes across studies were consistently close to zero, along with a null effect found within the majority of individual studies. However, the heterogeneity and dispersion of effect estimates noted across studies suggested some imprecision in the result. Therefore, the evidence is not sufficiently robust and interpretation of results should be considered with caution. These findings, along with methodological limitations, clinical and research implications are evaluated and discussed below.

Evidence from the current meta-analysis is inline with the two previous reports (Jans et al., 2010; Wojcicki & Heyman, 2011) assessing the efficacy of omega-3 PUFAs for perinatal depression. But it should be noted that significant heterogeneity existed within these meta-analyses. Wojcicki and Heyman (2011) had included studies utilizing other empirical methods (e.g. longitudinal trials) and results may not be comparative to RCTs given estimates of average treatment effects are not as reliable. In evidence-based medicine, RCTs are considered the ‘gold standard’ for evaluating the efficacy an intervention on health outcomes (Faraoni & Schaefer, 2016).

4.1.1 Intervention Period. Omega-3 supplementation during the antenatal, postnatal period did not show benefits for reducing depression symptoms when compared to placebo. But despite no significant benefits being found for the time period of studies (antenatal, postnatal or combined antenatal/postnatal), the results of individual studies suggest that the intervention period has some effect on depression outcomes. Maternal omega-3 LCPUFAs depletion occurs most intensely during pregnancy, peaking between the third trimester and postpartum (lactation; Lefkowitz, Lim, Lin, & Salem 2005); therefore supplementation during this time may be more efficacious in treating antenatal depression while preventing postnatal depression (Strøm, Mortensen, Halldorsson, Thorsdottir, & Olsen, 2009). Trials by Kaviani et al. (2014), and Su et al. (2008) provided supplementation only during pregnancy and found an effect, while one study (Llorente et al., 2003) showed no benefit for supplementation during the postnatal period. Three studies (Farshbaf-Khalili et al., 2017; Judge et al., 2014; Su et al., 2008) combining the antenatal and postnatal periods, found consumption of omega-3 LCPUFAs capsules had reduced depressive symptoms during pregnancy and prevented the onset of postpartum depression. The results of these studies may therefore suggest that supplementation may not be viable at the beginning of the postnatal period because it may be too late to meet the metabolic demands and depletion associated with pregnancy.

However, the evidence provided does not adequately explain which time period is best for intervention. The majority of studies had not provided evidence for any differential effect during pregnancy and postpartum. More specifically, the RCTs that included perinatal depression had evaluated depression scores at baseline and postpartum, rather than comparing scores throughout specific time points during the perinatal period. Future research needs to focus specifically on antenatal and postnatal period, which may control for some heterogeneity and enable robust comparative evaluations.

4.1.2 Diagnosis and Psychometric Measures of Depression. Overall, the screening tools for perinatal did not influence the outcome. However it was noted studies that utilized the HAM-D (perinatal and antenatal) and BDI (antenatal) were significant. Only four studies (Freeman et al., 2008; Kaviani et al., 2014; Rees et al., 2008; Su et al.,2008) validated depression symptoms through the use of a diagnostic interview and these studies were able to assess for more severe depression with participants being diagnosed with clinical depression. Although the diagnoses made had no effect on treatment outcome, the results of individual studies may suggest that treatment is more effectively for clinically diagnosed depression. Each of these studies showed an effect, therefore possibly indicating that the severity of depression may play a role in response to omega-3 PUFA supplementation. Further this may also suggest that effects may be restricted to depressed populations, as omega-3 PUFA status in these populations are remarkably lower compared to healthy populations (Appleton, Rogers, & Ness, 2010). However, further research into the effects of omega-3 supplementation on clinically diagnosed perinatal depression is required.

4.1.3 Intervention Dose and Formulation. Data relating to the dosage could not be combined, but research suggests that the amount of supplementation is likely to contribute to the outcome effect (Freeman et al., 2006; Mischoulon et al., 2008). Studies providing 200-300mg/day of omega-3 PUFAs did not report a change in depression scores post-treatment (Doornbos et al., 2009; Judge et al., 2014; Llorente et al., 2003). While those providing more than 1000mg/day found an effect (Farshbaf-Khalili et al., 2017; Freeman et al., 2008; Kaviani et al., 2014; Mozurkewich et al., 2013; Su et al., 2008; Vaz et al., 2017), albeit the study by Rees et al. (2008), which used a high dose (2000mg), found no effect. These results are in line with research in major depression where high-dose (>1g/day omega-3 LCPUFA) supplementation is generally more effective as a therapeutic treatment (Colangelo , He, Whooley, Daviglus, & Liu, 2009; Su, Huang, Chiu, & Shen, 2003; Su et al., 2008). For the

maternal population this finding is perhaps intuitive, given high doses of omega-3 may maintain omega-3 PUFAs reserves while allowing adequate amounts to be transferred to the fetus**.** However to date, there has only been one dose-ranging trial for the maternal population (Freeman et al., 2006) and the optimal dosage for treating general depression still remains unclear (Lin & Su, 2007).

Further, the omega-3 LCPUFAs formulation varied considerably across studies. The majority of investigators utilized a combination of DHA and EPA, while one added ALA to DHA. To date, only one trial (Mozukerwich et al., 2013) had investigated the differential effect of omega-3 PUFA formulation: EPA-rich versus DHA-rich supplementation. The study did not find an effect. Therefore optimal formulation, including the ratio for DHA to EPA for the prevention and treatment of perinatal depression is unknown (Simopoulos, 2002). Research in major depression has demonstrated that EPA-rich omega-3 PUFAs solution is more effective at decreasing depressive symptomology than DHA-rich supplement (Martins, 2009). For example, previous literature showed that EPA had an effect on core depressive symptoms, such as guilt feelings, depressed mood, and worthlessness (Nemets, Stahl, & Belmaker, 2002). However, given the triggers and causes of perinatal depression may be slightly different this hypothesis may not apply to the maternal population. Further research is required to investigate the differential effects of EPA-rich and DHA-rich omega-3 LCPUFAs on perinatal depression.

4.1.4 Other Potential Sources of Heterogeneity. Omega-3 LCPUFAs serum levels were not recorded in all studies, thus the incorporation of the fatty acids into other tissue and red blood cells (RBCs) is not known. Further the rate of fish consumption was not recorded in all studies ($N_{studies}$ = 7; Doornbos et al., 2009;Farshbaf-Khalili et al., 2017; Judge et al., 2014; Llorente, et al., 2003; Makrides et al., 2010; Su et al., 2008; Vaz et al., 2017). As this was not reported it is difficult to recognize the baseline levels of participants; if

supplementation had increased serum levels; and thus contributed to the outcome effect. Previous research has demonstrated that the severity of depressive symptoms was inversely related to omega-3 PUFAs consumption (Golding, Steer, Emmett, Davis, & Hibbeln, 2009).

Omega-3 is an essential fatty acid that must be obtained through dietary intake. Generally, the blood level of a clinical study drug can be assumed to be zero for commencement of trial. However this assumption is not warranted for trials of food supplements such as omega-3 fatty acids, as the nutrient can be present in blood levels through consumption of fish, various vegetables or nuts/legumes (Meyer et al., 2003). Higher baseline blood levels of omega-3 may enable therapeutic levels to be easily reached within the duration of the trial (Peet, Murphy, Shay, & Horrobin, 1998). Further, it has been purported that individuals with high omega-3 levels at baseline incorporate these fatty acids into RBCs and other tissues more efficiently than do those with lower levels of omega-3. These individuals are therefore better able to utilize the omega-3provided by the supplements (De Vriese, Christophe, & Maes, 2003)

There is consensus between clinicians and researchers that multiple factors - which may be biological, psychosocial, or environmental in nature - are likely to interact in triggering and maintaining depression (Beck, 2001). This is no exception for perinatal depression. Low socioeconomic status, ethnicity (particularly African-American, Hispanics, and Aboriginal Australians) and genetic predisposition have been associated with depression (Dolbier et al., 2013; Hutto, Kim-Godwin, Pollard, & Kemppainen, 2011; Prandl, Rooney, & Bishop, 2012). Further, research has shown that those whom have completed high-level education and were married were less likely to develop depression (Bjelland et al., 2008; Leigh, & Milgrom, 2008). In the case of mothers, a lack of support network, sleep and appropriate nutrients (such as omega-3 supplementation) has been implicated in perinatal depression (Leigh & Milgrom, 2008). Some of the included studies had recorded these

factors, and given that the causes of depression is multifactorial, treatment with omega-3 supplementation may not have been adequate. More generally, the effect of omega-3 LCPUFAs intervention is likely to be modest because it is a single nutrient. During pregnancy and postpartum various biological changes occur (e.g. changes in hormone secretion; Maccari et al., 2003) and therefore to detect a modest effect, the sample sizes need to be large for omega-3 LCPUFA. In addition, large sample sizes can increase the probability that known genetic and environmental influences on perinatal depression are balanced between groups and thus do not confound trial outcomes.

4.2 Clinical Implications and Future Research

The evidence provided in the current review can help to guide future research investigating the efficacy of omega-3 supplementation for perinatal depression. As described above, there are various potential areas which could be further explored to elucidate some factors which may affect the treatment outcome. For example, the evidence for major depression suggests that omega-3 PUFA supplementation may be more effective as a treatment than a preventative intervention. This may also be reflected in perinatal depression, given the studies that included participants with clinical depression found some benefits (as compared to studies that found no effect in healthy populations). Further, if future research is to continue investigating preventative effects of omega-3 in healthy populations, larger samples are needed to detect an effect. The dosage, and intervention type (EPA, DHA and ALA) require further investigation as the optimal dose and length of supplementation remains unknown.

Researchers need to consider the formulation of the intervention, as recent research in major depression has demonstrated that EPA-rich supplementation may be more efficacious than DHA-rich supplementation (Martins, 2009). Fish consumption is correlated with depressive symptomology, thus comparing the effects of fish consumption per capita may be

viable (i.e. to investigate the effects of omega-3 supplementation for perinatal depression on high versus low fish consumption per population and/or per capita).

The intervention period (antenatal and postnatal) should also be further explored, as supplementation during the antenatal period could potentially affect the outcomes of the postnatal period. In other words, it could potentially prevent postpartum depression; or supplementing prior to (planned) pregnancies may prevent antenatal depression. Finally, given that omega-3 PUFAs are a single nutrient and perinatal depression is multifaceted, future research could potentially assess the efficacy of omega-3 supplementation as a monotherapy versus supplementation as an adjunct (e.g. to psychotherapy).

In terms of clinical implications, the individual studies show some promise for treatment with omega-3 supplementation. As highlighted in the introduction, there are various caveats and unknown long-term effects associated with pharmacological treatment. Further, given that omega-3 PUFAs are affected in perinatal depression it is viable to further investigate its effects. Specifically, the reported side effects were minimal for omega-3 supplementation. For example, side effects usually included reflux or unpleasant aftertaste (Farshbaf-Khalili et al., 2017). If omega-3 supplementation is found to be successful this will allow for more treatment options for mothers experiencing depression in the perinatal period. The treatment has the potential to be beneficial to mother and baby.

4.3 Limitations

Besides the methodological weaknesses that were identified in studies, some limitations were evident in this review; which further complicate the interpretation of the results of the current meta-analysis. First, despite the rigorous search strategy, not all relevant studies may have been included. Multiple databases and key search terms were employed to ensure maximal coverage, but the stringent eligibility criteria, particularly in including RCTs,

meant that fewer studies were included in the review. Further, longitudinal designs would contribute to understanding the long-term effects of omega-3 supplementation. Studies that were not published in English were also excluded. This again limited the number of included studies. Recent evidence suggests that fewer than fives studies meta-analyzed with a random effects model may be underpowered (Jackson & Turner, 2017). However, due to the methodological limitations and small sample size of individual studies, the systematic assessment may have also been underpowered to detect an effect.

Second, the moderator analyses may have been underpowered to detect true treatment effects of omega-3 supplementation. While moderator analyses allowed for identification and exploration of potential sources of heterogeneity, the lack of studies included in subgroup analyses meant that the results were not robust. According to Fu et al. (2011), the Cochrane Collaboration recommends a minimum of 10 studies for robust subgroup analysis.

Finally, in relation to the study characteristic, most studies measured a change in mood or depressive symptoms, but none had measured a change in clinical diagnosis. Further, in the studies with non-depressed participants, baseline depressive symptoms were already low. This, combined with a small sample size, has probably resulted in insufficient power to detect small-to-moderate treatment effects in most studies

4.4 Conclusion

Perinatal depression is a prevalent disorder and can have devastating consequences for the mother, child and family. Finding an effective treatment that is safe is therefore imperative. In particular, reports on omega-3 supplementation have shown some benefits in treating and preventing depression. However, the evidence reported in the current review may be insufficient evidence to support omega-3 LCPFA supplementation for treating or preventing perinatal depression. This review highlighted various methodological limitations

which meant results could not be viewed with a high degree of confidence. Despite a lack of supporting evidence, further studies are warranted as minimal side effects were reported and supplementation did not worsen depressive symptoms. Further large-scaled, well- powered studies with comparable methodology are necessary to assess whether omega-3 supplementation is an effective therapeutic agent for perinatal depression. More specifically, the evidence from these trials will be able to inform and provide safe evidence-based treatment for pregnant and postnatal women.

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Appendices

Appendix A

Logic grids per database informing overall search strategy

All searches were conducted throughout April 2018. Additional results were sourced by automatic email alerts created for each database.

PubMed

Fish oil	AND	*Depression*	AND	*Pregnancy period*
Fish oil*[tw]		Depressive		postpartum[tw]
OR		disorder[tw]		OR
Fish		OR		postpartum[mh:
oils[mh:noexp]		Depressive		noexp]
OR		disorder[mh:noe		OR
Fatty Acids,		xp]		postnatal[tiab]
Omega-3[tw]		OR		OR
OR		Depressi*[tiab]		post-natal[tiab]
fatty acids,		OR		OR
Omega-		maternal		post-
3[mh:noexp]		health[tw]		partum[tiab]
OR		OR		OR
fatty acids,		maternal		perinatal[tiab]
essential[tw]		health[mh]		OR
OR		OR		peri-natal[tiab]
Fatty acids,		mental		OR
essential[mh]		health[tw]		peripartum[tw]
OR		OR		OR
Docosahexaenoi		mental		peripartum[mh]
c Acid*[tw]		health[mh:noexp		OR
OR		]		peri-
Docosahexaenoi		OR		partum[tiab]
c Acid[mh]		Depression,		OR
OR		postpartum[mh]		prenatal[tiab]

Eicosapentaenoic Acid*[tw] OR Eicosapentaenoic Acid[mh] OR icosapentaenoic acid*[tiab] OR alpha-Linolenic Acid[tw] OR Alpha-linolenic acid[mh] OR Omega-3[tiab] OR Long chain polyunsaturated fatty acid*[tiab] OR n-3 fatty acid*[tiab] OR PUFA[tiab] OR DHA[tiab] OR EPA[tiab] OR ALA[tiab]	OR Depression, postpartum[tw]	OR pre-natal[tiab] OR antenatal[tiab] OR ante-natal[tiab] OR pregnancy[tw] OR pregnancy[mh:noexp] OR Puerperium[tiab] OR antepartum[tiab] OR intrapartum [tiab]

Note: Search conducted on 10th April 2018. No language or date filters were applied. Search results yielded 258 articles.

PsycINFO

Fish oil	AND	*Depression*	AND	*Pregnancy period*
fish oil$.mp		depression.sh		Pregnancy.sh
OR		OR		OR
fatty acid.sh		depression.mp		Pregnancy.mp
OR		OR		OR
fatty acid$.mp		depressive disorder$.mp		perinatal period.sh
OR		OR		OR
essential fatty acid$.mp		major depression.sh		Perinatal.mp
OR		OR		OR
Docosahexaenoic acid$. mp		major depression.mp		peri-natal.mp
OR		OR		OR
eicosapentaenoic acid$.mp		Mental health.sh		antepartum period.sh
OR		OR		OR
icosapentaenoic acid$.ti,ab		Mental health.mp		antepartum.mp
OR		OR		OR
Alpha-linolenic acid$.mp		maternal health.mp		Ante-partum.mp
OR		OR		OR
polyunsaturated fatty		Depressive.mp		intrapartum period.sh
acid$.mp		OR		OR
OR		Postpartum depression.sh		Intrapartum.mp
n-3 polyunsaturated fatty		OR		OR
acid$.mp		postpartum deression.mp		Intra-partum.mp
OR				OR
PUFA.mp				prenatal.mp
OR				OR
(long chain adj2 fatty				pre-natal.mp
acid$).ti,ab				OR
OR				Postnatal period.sh
omega-3.mp				OR
OR				Postnatal.mp
DHA.mp				OR
OR				post-natal.mp

ALA.mp		OR
OR		Post-partum.mp
EPA.mp		OR
		peripartum.mp
		OR
		peri-partum.mp
		OR
		postnatal.mp
		OR
		post-natal.mp
		OR
		puerperium.mp

Note: Search conducted on 10th April 2018. No language or date filters were applied. Search results yielded 104 articles.

Embase

Fish oil	AND	*Depression*	AND	*Pregnancy period*
‘fish oil$’:de,ti,ab		'depressive symptom*’:ti,ab		Pregnancy:de,ti,ab
OR		OR		OR
'omega-3 fatty acid$':de,ti,ab		Depression:de,ti,ab		perinatal:de,ti,ab
OR		OR		OR
‘essential fatty acid$’:de,ti,ab		'major depression':de,ti,ab		peri-natal:de,ti,ab
OR		OR		OR
'polyunsaturated fatty		‘mental health’:de,ti,ab		Prenatal:ti,ab
acid$':de,ti,ab		OR		OR
OR		‘maternal health’:ti,ab		postnatal:ti,ab
(long chain near/2 fatty		OR		OR
acid$):ti,ab		‘postnatal		Puerperium:de,ti,ab
OR		depression’:de,ti,ab		OR
'docosahexaenoic				postpartum:ti,ab
acid$':de,ti,ab				OR
OR				post-partum:ti,ab

'icosapentaenioc acid$':de,ti,ab OR 'linolenic acid':de,ti,ab OR 'n-3 fatty acid$':ti,ab OR PUFA:ti,ab OR DHA:ti,ab OR EPA:ti,ab OR ALA:ti,ab	OR antenatal:ti,ab OR ante-natal:ti,ab OR Pre-natal:de,ti,ab OR post-natal:de,ti,ab OR antepartum:ti,ab OR Ante-partum:ti,ab OR peripartum:ti,ab OR peri-partum:ti,ab OR intrapartum:ti,ab OR post-partum:ti,ab

Note: Search conducted on 11th April 2018. No language or date filters were applied. Search results yielded 452 articles.

Scopus

Fish oil AND	*Depression* AND	*Pregnancy period*
TITLE-ABS-KEY("fish oil") OR TITLE-ABS-KEY("omega 3 fatty acid*") OR TITLE-ABS-KEY("essential	TITLE-ABS-KEY(depressive) OR TITLE-ABS-KEY(depression) OR	TITLE-ABS-KEY(pregnancy) OR TITLE-ABS-KEY(perinatal) OR TITLE-ABS-KEY(peri-

fatty acid*”)	TITLE-ABS-KEY(“maternal	natal)
OR	health”)	OR
TITLE-ABS-KEY(fatty	OR	TITLE-ABS-KEY(prenatal)
acid*)	TITLE-ABS-KEY({mental	OR
OR	health})	TITLE-ABS-KEY(pre-natal)
TITLE-ABS-	OR	OR
KEY(“docosahexaenoic	TITLE-ABS-KEY(“major	TITLE-ABS-KEY(post-
acid*”)	depression”)	natal)
OR	Or	OR
TITLE-ABS-	TITLE-ABS-	TITLE-ABS-KEY(postnatal)
KEY(“eicosapentaenoic	KEY(“postpartum	OR
acid*”) OR	depression”)	TITLE-ABS-KEY(antenatal)
TITLE-ABS-		OR
KEY({icosapentaenoic acid})		TITLE-ABS-KEY(ante-
OR		natal)
TITLE-ABS-KEY(“alpha-		OR
linolenic acid”)		TITLE-ABS-
OR		KEY(antepartum)
TITLE-ABS-		OR
KEY(“polyunsaturated fatty		TITLE-ABS-KEY(ante-
acid*”)		partum)
OR		OR
TITLE-ABS-KEY(“long		TITLE-ABS-
chain W/2 fatty acid*”)		KEY(peripartum)
OR		OR
TITLE-ABS-KEY ({PUFA})		TITLE-ABS-KEY(peri-
OR		partum)
TITLE-ABS-KEY({DHA})		OR
OR		TITLE-ABS-
TITLE-ABS-KEY({EPA})		KEY(intrapartum)
OR		OR
TITLE-ABS-KEY({ALA})		TITLE-ABS-
		KEY(postpartum)

		OR TITLE-ABS-KEY(post-partum) OR TITLE-ABS-KEY(Puerperium)

Note: Search conducted on 11th April 2018. No language or date filters were applied. Search results yielded 671 articles.

Web of Science

Fish oil AND	*Depression* AND	*Pregnancy period*
TS=("fish oil$") OR TS=("essential fatty acid$") OR TS=("omega-3 fatty acid$") OR TS=("docosahexaenoic acid$") OR TS=("eicosapentaenoic acid$") OR TS=(“icosapentaenoic acid”) OR TS=("alpha-Linolenic acid$") OR TS=("omega-3”) OR TS=(“fatty acid$”) OR TS=("polyunsaturated fatty acid$")	TS=(depressive) OR TS=(“major depressive disorder$”) OR TS=("major depression") OR TS=("mental health") OR TS=("maternal health") OR TS=(“postpartum depression”)	TS=(pregnancy) OR TS=(perinatal) OR TS=(peri-natal) OR TS=(prenatal) OR TS=(pre-natal) OR TS=(postnatal) OR TS=(post-natal) OR TS=(postpartum) OR TS=(post-partum) OR TS=(peurperium) OR TS=(antepartum) OR

OR	TS=(ante-partum)
TI=(EPA)	OR
OR	TS=(intrapartum)
TI=(DHA)	OR
OR	TS=(peripartum)
TI=(ALA)	OR
OR	TS=(peri-partum)
TI=(PUFA)	

Note: Search conducted on 12th April 2018. No language or date filters were applied. Search results yielded 307 articles.

Cochrane

	Fish oil
#1	[mh ^"fish oil*"]
#2	[mh ^"Fatty Acids, Omega-3"]
#3	[mh ^"Fatty Acids, Essential"]
#4	[mh^"Fatty Acids, Unsaturated"]
#5	[mh ^"docosahexaenoic acid*"]
#6	[mh^"alpha-Linolenic Acid*"]
#7	[mh ^"Eicosapentaenoic Acid*”]
#8	(icosapentaenoic acid*):ti,ab,kw
#9	(eicosapentaenoic acid*):ti,ab,kw
#10	(alpha-Linolenic acid*):ti,ab,kw
#11	(docosahexaenoic acid*):ti,ab,kw
#12	(omega-3):ti,ab,kw
#13	(fish oil*):ti,ab,kw
#14	(EPA):ti,ab,kw
#15	(DHA):ti,ab,kw
#16	(ALA):ti,ab,kw
#17	(polyunsaturated fatty acid*):ti,ab,kw
#18	(PUFA):ti,ab,kw

#19	(long chain near/2 fatty acid*):ti,ab,kw
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
	[redacted]
	Depression
#21	[mh^depression]
#22	[mh^“Depressive Disorder, Major”]
#23	[mh^“Depressive Disorder”]
#24	[mh^“Maternal Health”]
#25	[mh^“Mental Health”]
#26	[mh^“postpartum depression”]
#27	(depression):ti,ab,kw
#28	(depressive disorder, major):ti,ab,kw
#29	(Depressive disorder):ti,ab,kw
#30	(Maternal health):ti,ab,tw
#31	(mental health):ti,ab,tw
#32	(postpartum depression):ti,ab,kw
#33	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
	[redacted]
	Pregnancy period
#34	[mh^"postpartum period"]
#35	(perinatal):ti,ab,kw
#36	[mh^"pregnancy"]
#37	(postpartum) ti,ab,kw
#38	(post-partum) ti,ab,kw
#39	(peri-natal):ti,ab,kw
#40	(perinatal):ti,ab,kw
#41	(prenatal):ti,ab,kw
#42	(pre-natal):ti,ab,kw
#43	(antenatal):ti,ab,kw
#44	(ante-natal):ti,ab,kw
#45	(antepartum):ti,ab,kw

#46	(ante-partum):ti,ab,kw
#47	(peripartum):ti,ab,kw
#48	(peri-partum):ti,ab,kw
#49	(intrapartum):ti,ab,kw
#50	(puerperium):ti,ab,kw
#51	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50
#52	#20 AND #31 AND #51

Note: Search conducted on 13th April 2018. No language or date filters were applied. Search results were retrieved from the Cochrane central register of controlled trials (CENTRAL) database of the Cochrane Library. Search yielded 49 articles.

Appendix B

Study characteristic summary table

Lead author (year)	***N* included in analysis (FO/placebo)**	**Country/setting**	**Study design**	**Intervention type and dose**	**Intervention period**	**Intervention duration**	**Subjects baseline mood status**	**Mood measure and outcome effect**
Doornbos (2009)	119 (42/41/46) PP, completers only	The Netherlands	Randomised controlled trial	Form: x1 capsule/day 220mg DHA/ DHA+AA (220mg each)/ placebo	Pregnancy and postpartum	From 14-20 weeks until 3 months postpartum	Healthy	EPDS/Null
Farshbaf-Khalili (2017)	150 (75/75) ITT	Iran/ Governmental primary health care centers	Randomised, triple-blind, placebo controlled trial	Form: x1 capsule/day 120mg DHA + 180mg EPA + 400mg ALA/ placebo	Pregnancy and postpartum	From 20 weeks until 1 month postpartum	Healthy	EPDS/ significant effect (found at third trimester)
Freeman (2008)	51 (28/23) PP, completers only	USA/ Women's Mental health centers	Randomised, double-blind, placebo controlled trial	Form: x1 capsule/day 1100mgEPA +800mg DHA/placebo	Pregnancy (12-32 weeks) and/or postpartum (up to 6 months)	8 weeks	Major depression (diagnosed)	EPDS, HAM-D/null
Judge (2014)	42 (20/22) PP, completers only	USA/Hospitals	Randomized, double-blind, controlled trial	Form: x1 capsule/5 days weekly 300mg DHA/placebo	Pregnancy and postpartum	From 20 weeks until 6 months postpartum	Healthy	CES-D, PDSS/significant effect

Kaviani (2014)	80 (40/40) ITT	Iran/Shiraz Health Centers	Randomised, double-blind controlled trial	Form: x1 capsule/day 1000mg DHA/ placebo	Pregnancy (>20 weeks)	6 weeks	Mild depression (diagnosed)	BDI/ significant effect
Llorente (2003)	89 (44/45) PP, completers only	USA	Randomised, double-blind, controlled trial	Form: x1 capsule/day 200mg DHA/ placebo	Postpartum	4 months	Healthy	BDI; EPDS and SCID in subgroups/ null
Mozurkewich (2013)	118 (39/38/41) PP, completers only	USA/ University and Hospital Health systems	Randomised, double-blind, controlled trial	Form: x2 capsule/day 1060mg EPA+274mg DHA/ 900mg DHA+180mg EPA/ placebo	Pregnancy and postpartum	From 12-20 weeks until 6-8 weeks postpartum	At risk for major depression	BDI; MINI/null
Rees (2008)	26 (13/13) ITT	Australia/ Hospital	Randomised, double-blind, controlled trial	Form: 6g/day divided doses 6g FO (27.3% DHA+6.9% EPA+80mg vitamin E+3.3% omega-6)/ placebo	Pregnancy (20-48 weeks) and/or Postpartum (up to 6 months)	6 weeks	Major depression (diagnosed)	EPDS, HAM-D, MADRS/ null
Su (2008)	24 (13/11) PP, completers only; 33 (17/16) ITT	China/ Hospital	Randomized, double-blind, placebo controlled trial	Form: x5 capsule/day 2200mg EPA + 1200mg DHA/placebo	Pregnancy (16-32 weeks)	8 weeks	Major depression (diagnosed, onset in weeks 16-32))	HAM-D, EPDS, BDI/ significant effect

Vaz (2017)	32 (15/17) PP, completers only; 60 (32/28) ITT	Brazil/ Health Care Centre	Randomised, double-blind, placebo controlled trial	Form: x6 capsule/day 1080mg EPA +720mg DHA+0.2mg/g vitamin E/ placebo	Pregnancy (5-13 weeks) and postpartum (4-6 weeks)	16 weeks	At risk for major depression (and/or with previous history of depression)	EPDS/ null

FO-fish oil; PP- per protocol; ITT-intent-to-treat; DHA-docosahexaenoic acid; EPA-eicosapentaenoic acid; AA- alpha-linolenic acid; EPDS-Edinburgh Postnatal Depression Rating Scale; BDI-Beck's Depression Inventory; HAM-D-Hamilton Depression Rating Scale; MADRS-Montgomery and Asberg Depression Rating Scale; PDSS-Postpartum Depression Screening Scale.