

THE ROLE OF OMEGA-3 UNSATURATED FATTY ACIDS IN POSTPARTUM DEPRESSION: A SYSTEMATIC REVIEW AND NARRATIVE SYNTHESIS

Fatima Mougharbel
Masters of Science Program in
Interdisciplinary Health Sciences

Interdisciplinary School of Health Sciences
Faculty of Health Sciences
University of Ottawa
Ottawa, Ontario

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Supervisor: Raywat Deonandan, Ph.D.

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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 13–20% of women after birth and has an adverse effect on both the mother and the infant. Certain 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. Quality appraisal was performed using the tools produced by the effective public health practice project (EPHPP). 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. **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 association with PPD evaluations versus only few ones observed a beneficial effect of *n*-3 PUFAs supplementation on depressive symptoms. Significant heterogeneity was observed among included studies which can be explained by dissimilar study designs, differences in study duration, time period of measurement and number of participants, and in varied dosages and types of supplemental *n*-3 PUFAs. **Conclusions:** Overall, This systematic review and narrative synthesis failed to find a significant positive association between *n*-3 PUFAs intake and PPD. However further investigation of the specific molecular mechanisms underlying the function of *n*-3 PUFAs in the brain and the factors related to the pathophysiological nature of depression is warranted.

Keywords: Narrative synthesis, *n*-3 PUFAs, PPD, Systematic review.

Résumé

Contexte: La dépression post-partum est un problème de santé mentale complexe qui affecte les femmes en âge de procréer. Il s'agit d'une condition médicale sérieuse affectant près de 13 à 20% des femmes et portant des conséquences néfastes tant pour la mère que pour l'enfant. Des déficiences nutritives, durant ou après la grossesse, peuvent causer une dépression postnatale. Nous ne savons pas avec certitude si les acides gras de type oméga 3 sont efficaces pour le traitement et la prévention de la dépression postpartum. **Objectifs:** Évaluer les données probantes disponibles sur l'effet de l'acide gras polyinsaturé de type oméga-3 sur l'étiologie, la prévention et le traitement de la dépression postnatale. **Méthodes:** Une revue systématique analytique est réalisée pour synthétiser l'état des connaissances. Une recherche approfondie des bases de données électroniques répertorie les recherches quantitatives réalisées sur le sujet. L'appréciation de la qualité des études est réalisée en utilisant des outils élaborés par le Projet de pratique efficace en santé publique (PPESP). La synthèse narrative est éclairée par les quatre éléments formant la démarche proposée par Popay et al (2006). **Résultats :** Parmi les 181 articles initiaux, un total de 17 articles satisfont les critères établis. Sept de huit études expérimentales et quatre de neuf études observationnelles ne réussissent pas à établir un rôle préventif ou curatif de l'oméga 3 dans le cas de la dépression post-partum. L'hétérogénéité des résultats peut être expliquée par des modèles d'études qui diffèrent, notamment des divergences dans les durées d'étude, les périodes de mesure, les nombre de participants, ainsi que des variations dans les dosages et les types de suppléments d'acides gras polyinsaturés oméga-3. **Conclusions:** La majorité des études examinées n'imputent pas de liens entre l'apport en oméga 3 et la dépression post-partum. De futures recherches sont nécessaires pour une meilleure compréhension des processus sous-jacents.

Mots-clés: synthèse narrative. Acides gras polyinsaturés oméga-3, dépression postpartum, revue systématique

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ABBREVIATIONS

AA	Arachidonic Acid
ALA	Alpha Linolenic Acid
BDI	Beck Depression Inventory
CGI	Clinical Global Impression
CIDI	Composite International Diagnostic Interview
DHA	Docosahexaenoic Acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPA	Eicosapentaenoic Acid
EPDS	Edinburgh Postnatal Depression Scale
FFQ	Food Frequency Questionnaire
HAM-D	Hamilton Rating Scale for Depression
HRSD	Hamilton Rating Scale for Depression
ICD-10	The International Statistical Classification of Diseases and Related Health Problems, 10th Version
N-3PUFA	Omega-3 Polyunsaturated Fatty Acids
N-6PUFA	Omega-6 Polyunsaturated Fatty Acids
NIMH	National Institute of Mental Health
MMD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MADRS	Montgomery–Asberg Depression Rating Scale
PPD	Postpartum Depression
RCT	Randomized Controlled Trial
SCID	Structured Clinical Interview for DSM Disorders
TCAs	Tricyclic Antidepressants
WHO	World Health Organization

CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 Introduction

Depression is a major cause of disability for all ages and both genders (World Health Organization [WHO], 2008a). At least 350 million people (WHO, 2014) worldwide suffer from depression which presents with depressed mood, loss of pleasure, decreased energy and concentration, feelings of guilt or low self-esteem, disturbed sleep or appetite. At its worst, depression can lead to suicide. Worldwide, approximately 800,000 people die by suicide every year (WHO, 2014).

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. Postpartum depression (PPD) can affect up to 15% of new mothers (Stewart, Robertson, Dennis, Grace, & Wallington, 2003) during the first year after delivery, it is associated with diminished maternal somatic health as well as health and developmental problems in their offspring (Stewart et al., 2003). Recent reports stress the need for research concerning the causes and consequences of mental health disorders and for the application of this knowledge to policies and programs (Hoagwood & Olin, 2002). In this effort, researchers have begun to focus on the role of nutrition in depression. Particularly, research has indicated that essential fatty acids (FAs) such as omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) may play an important role in the etiology of PPD (Golding et al., 2009; Rees et al., 2005; Rees et al., 2009; Sontrop et al., 2008).

Interestingly, evidence suggests that *n*-3 PUFAs decrease by 50% during gestation and is not fully replenished up to 26 weeks postpartum (Al et al., 1995; Al et al., 1997; Huang et al., 2013; Holman, et al., 1991; Otto et al., 1997; Van den Ham et al., 2001).

The objective of this systematic review was to review and summarize the evidence from the peer-reviewed literature on the relationship between *n*-3 PUFAs and PPD affecting women and their offspring. After a detailed summary of current knowledge on the diagnosis and screening for PPD, the role of *n*-3 fatty acids in the structure and function of the human brain, evidence from observational and intervention studies that link *n*-3 PUFAs with PPD was reviewed and synthesized following the widely used narrative synthesis guideline by Popay et al. (2006).

1.2 Background

1.2.1 Definitional and conceptual issues

According to the World Health Organization, depression is expected to be the second leading cause of disease burden in the world (WHO, 2001) by 2020, and the first leading cause of burden by 2030 (Figure 1) (Mathers, Fat, & Boerma, 2008).

2004 Disease or injury	As % of total DALYs	Rank	Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1	1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2	2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3	3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4	4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5	5	3.8	COPD
Cerebrovascular disease	3.1	6	6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7	7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8	8	2.7	Refractive errors
Road traffic accidents	2.7	9	9	2.5	HIV/AIDS
Neonatal infections and other ^a	2.7	10	10	2.3	Diabetes mellitus
COPD	2.0	13	11	1.9	Neonatal infections and other ^a
Refractive errors	1.8	14	12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15	15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19	18	1.6	Diarrhoeal diseases

Figure 1. Ten leading causes of the world's burden of disease, measured in DALYs, for 2004 and projected for 2030. Source: Mathers, Fat, & Boerma, J. T. (2008)

Depression is associated with a high economic burden (National institute of mental health [NIMH], 2011). The global cost of mental illness is estimated to be nearly \$2.5 trillion (T) in 2010, with a projected increase to over \$6T by 2030 (National institute of mental health [NIMH], 2011). Women in particular are at greater risk of mental health disorders during the reproductive years (WHO, 2008b). The burden of depression is 50% higher for females than males (Marcus, Yasamy, Van Ommeren, Chisholm, & Saxena,

2012; WHO, 2008a). In fact, depression is the leading cause of disease burden for women, as measured in DALYs, in high-, low-, and middle-income countries (Figure 2) (WHO, 2008a).

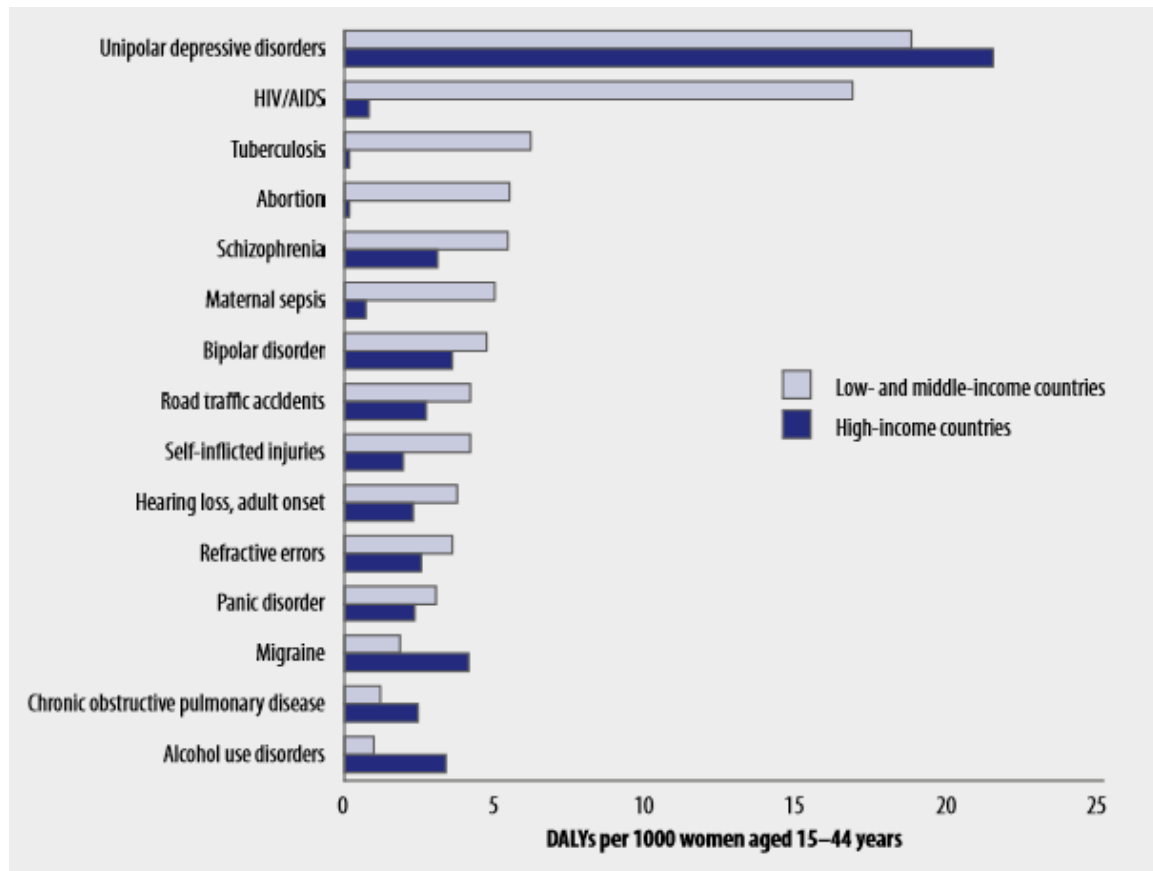


Figure 2. Leading causes of disease burden for women aged 15–44 years, high-income countries, and low- and middle income countries, 2004. Source: Mathers, Fat, & Boerma, J. T. (2008).

The WHO has indicated that addressing maternal mental health is important to achieving the fifth Millennium Development Goal in order ‘to improve maternal health’ (WHO 2008b).

Depression among mothers is of particular concern, as maternal mental health influences not only the mother but also her offspring. PPD refers to a major depressive episode with onset within 4 weeks after delivery and affects 10-15 % of women. PPD negatively

impacts the woman, her family, and several aspects of child development (Stewart, Robertson, Dennis, Grace, & Wallington, 2003).

1.2.2 Postpartum Affective Disorders

There are three common forms of postpartum complication: 1. "the blues" or, "baby blues" or, "maternity blues", 2. "postpartum depression" and 3. "puerperal postpartum psychosis". Each of these types differs in its prevalence, symptoms and management (Stewart, Robertson, Dennis, Grace, & Wallington, 2003). This review will focus on the PPD.

The prevalence, onset, and duration of the three different types of postpartum disorders are presented in Table 1 (Adapted from Nonacs & Cohen, 1998).

Table 1. Postpartum Affective Disorders: Summary of Onset, Duration & Treatment

Disorder	Prevalence	Onset	Duration	Treatment
Postpartum Blues	30 – 75%	Day 3 or 4	Hours to days	No treatment required other than reassurance
Postpartum Depression	10 – 15%	Within 12 months	Weeks-months	Treatment usually required
Postpartum Psychosis	0.1 – 0.2 %	Within two weeks	Weeks-months	Hospitalization usually required

Source: Nonacs, R. & Cohen, L. S. (1998)

1.2.2.1 Postpartum blues

Postpartum blues is the most common perceived puerperal mood disorder, with a 30-75% estimated prevalence range (O'Hara, Neunaber, & Zekoski, 1984). The symptoms usually start on day 3 or 4 postpartum, and persist for hours up to several days (Kennerly & Gath, 1989; Pitt, 1973). Symptoms of postpartum blues include mood lability, irritability, tearfulness, generalized anxiety, and sleep and appetite disturbance (Kennerly

& Gath, 1989; Pitt, 1973). Postnatal blues are time-limited and mild and do not need therapy other than reassurance. Often, the symptoms are reduced within days (Kennerly & Gath, 1989; Pitt, 1973).

1.2.2.2 Postpartum depression (PPD)

Postpartum depression is defined as the most common complication of childbearing and as such represents a considerable public health problem affecting women and their families. An individual is diagnosed with PPD if they are found to have at least four specific symptoms of major depression, including a change in the appetite, sleep disturbance, psychomotor agitation or retardation, fatigue, low energy, feeling of guilt, feelings of worthlessness, anxiety, poor concentration, irritability and suicidal ideation (APA, 2000; Robinson & Stewart, 2001). As a result, PPD can affect the mother, her marital relationship, and her children, which make it a serious issue to diagnose, treat and prevent (Robinson & Stewart, 2001). It occurs among 10-15% of postpartum women (Hantsoo et al., 2013; O'Hara & Swain, 1996; Robertson, Celasun, & Stewart, 2003; Warner, Appleby, Whitton, & Faragher, 1996). Furthermore, some prevalence estimates suggest that up to 41% of women who have previously experienced PPD may experience PPD in a subsequent pregnancy (American Psychological Association [APA], 2007).

An episode of PPD lasts at least two weeks must begin within the first 4 weeks after delivery (Robinson & Stewart, 2001). However, study suggests that depressive episodes are significantly more common in women in the first three months after delivery (Munk-Olsen, Laursen, Pedersen, Mors, & Mortensen 2006). As a result, many experts

believe that women remain at an increased risk for PPD for up to one year after delivery (Kendell, Wainwright, Hailey, & Shannon, 1976).

1.2.2.3 Puerperal or postpartum psychosis

Puerperal or postpartum psychosis is an episode of severe depressive symptoms. It is characterized by the occurrence of psychotic symptoms specified as postpartum psychotic affective illness or puerperal psychosis. It is different from PPD in terms of etiology, symptoms and treatment.

Puerperal or postpartum psychosis is the most severe and uncommon form of postnatal disorders and affects approximately one to two women per 1000 (Kendell, Chalmers, & Platz, 1987). Unlike PPD, postpartum psychosis presents itself much earlier, often within the first 2-3 days postpartum, and the majority of episodes begin developing within the first 2 weeks after delivery. Symptoms of postpartum psychosis include depressed mood, disorganized behaviour, mood swings, delusions and hallucinations (Brockington et al., 1981). Many studies have indicated that the majority of women with postpartum psychosis meet criteria for bipolar disorder (Brockington et al., 1981; Kendell, Chalmers, & Platz, 1987; Meltzer & Kumar, 1985; Okano et al., 1998; Schopf, Bryois, Jonquiere, & Le, 1984).

Puerperal psychosis necessitates hospitalization for treatment (Nonacs & Cohen, 1998). Even though women fully recover they remain at risk of developing further puerperal and non-puerperal episodes of bipolar affective disorder (Schopf et al., 1984).

1.2.3 Postpartum depression: Diagnostic issues

1.2.3.1 *Diagnosis*

To date, PPD is still classified as a mood disorder and is not considered as a separate disease. Two main systems are used by clinicians for diagnosis: The American Psychiatric Association's Diagnostic & Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (WHO & DIMDI, 2007) and the 10th edition of the International Classification of Diseases, (ICD-10) (APA, 2000). Both systems contain standard diagnostic criteria for common mental disorders, and are used globally to diagnose patients for clinical and research purposes (Robertson et al., 2003).

According to DSM-IV, symptoms must occur within the first 4 weeks after delivery in order to be identified as an affective or short psychotic episode that occurred during the postpartum period (APA, 1994). Similarly, in the ICD-10, the episode must be diagnosed through diagnostic category with the specifier to determine the association with the postpartum period (WHO, 1993).

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the DSM-V, was approved by the Board of Trustees of the American Psychiatric Association on December 1, 2012 (APA, 2012). Criteria for a Major Depressive Disorder in the DSM-V are not greatly changed from DSM-IV. Remarkable changes include; dropping the "bereavement exclusion", addition of several new depressive disorders, including Disruptive Mood Dysregulation Disorder, Premenstrual Dysphoric Disorder, and Persistent Depressive Disorder. The Disruptive Mood Dysregulation Disorder is used for children up to age 18 years (APA, 2013). The chapter on Depressive Disorders also

includes specifiers for mixed symptoms and for anxiety, along with guidance to physicians for suicidality guidance on suicide risk assessment. The term Dysthymia now falls under the category of Persistent Depressive Disorder (APA, 2013). The symptoms required to meet DSM-V criteria for a major depressive episode are shown in Figure 3.

Though widely used, it is important to note that the validity and reliability of the DSM-IV diagnosis have been criticized. The DSM-IV lacks validity because it has no relation to an agreed scientific model of mental disorder. As a result, decisions made using this diagnostic tool are somewhat arbitrary. The decreased reliability in this tool is due to the number of diagnosis that can be made based on similar symptom criteria (McLaren, 2007). In a research setting, it is ideal to use structured clinical interviews and/or a rating scale in order to increase the reliability of the DSM-IV (C. E. Dickmann, J. R. Dickmann, & Broocks, 2008).

In contrast to the DSM-IV, the validity of the ICD-10 diagnosis is high for severe and moderate types of depression, but decreases for mild depression (Bock, Bukh, Vinberg, Gether, & Kessing, 2009). Like the DSM-IV, in a research setting the usage of structured clinical interviews increases the reliability in diagnosis with the ICD-10. On the other hand, a short consultation decreases its reliability (Dickmann et al., 2008).

Criteria for Major Depressive Episode

- A. Five (or more) of the following symptoms have been present during the same 2 week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)
Note: In children and adolescents, can be irritable mood.
 - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
 - Significant weight loss when not dieting or weight gains (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
Note: In children, consider failure to make expected weight gains.
 - Insomnia or hypersomnia nearly every day.
 - Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
 - Fatigue or loss of energy nearly every day.
 - Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
 - Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
 - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- C. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism)

Figure 3.DSM-V Criteria for Major Depressive Disorder. Source: Mitchell et al., 2013

1.2.3.2 Assessment of Depression: Clinical & Self Report Measures

PPD assessment measures include standardized interviews, clinician-rated scales, and self-report questionnaires. Semi-structured clinical interviews based on diagnostic research criteria allow the derivation of psychopathological symptoms in order to generate diagnoses. Use of standardized interviews raises the reliability of diagnoses between researchers, and allows them to determine and assess the severity of symptoms

(Robertson et al., 2003). Below is a summary of the most common interviews and questionnaires used to assess depressive symptoms in PPD (Robertson et al., 2003).

i. Standardized interview

Several standardized interviews are used to diagnose PPD. This instrument requires the use of rigorous criteria to establish a trustworthy diagnosis. The main use of this tool is for research purpose to help clinicians and/or researchers, who are familiar with the DSM or ICD systems of diagnosis, to determine whether the participant's responses meet the diagnostic criteria. Unfortunately, this method is time-consuming, expensive, and not advised for general clinical practice (Robertson et al., 2003).

One example of a standardized interview is the Structured Clinical Interview for DSM-IV-R (SCID) which integrates DSM-IV diagnoses and has different versions for use within psychiatric populations (Spitzer, Williams, Gibbon, & First, 1992). It contains six self-contained modules and needs 45 to 60 minutes to be complete (Robertson et al., 2003). Despite the availability of convenient software for administration and scoring, clinical judgment is still necessary for the interview.

ii. Clinical rated scales

In order to diagnose depressive symptoms and monitor treatment response, various clinician-rated scales are available (Robertson et al., 2003). These scales are used to make clinical judgments consistent and provide rankings of duration and severity of depressive episodes. These scales are not employed for population-based screening (Robertson et al., 2003). The Hamilton Rating Scale for Depression (HRSD) and the

Montgomery-Asberg Depression Rating Scale are the most common scales reported in PPD literature (Robertson et al., 2003).

Hamilton Rating Scale for Depression (HAM-D or HRSD)

HRSD is one of the earliest scales developed to assess the severity of depression among patients (Hamilton, 1960). It has become the gold standards for depression clinical research and has been considered as the most popular depression severity screening in the history of major depressive disorders clinical trials and research (Cusin, Yang, Yeung, & Fava, 2010). There are several versions of HRSD available. The original version of HRSD contains 17 depressive symptoms. In contrast, the other versions list up to 31 items. In both versions, responses are rated on either a 3 or 5-point scale with a total score ranging from 0 to 50; a cut-off score of 15 and above is suggestive of major depression (Cusin et al., 2010).

The HRSD is administered weekly with an average interview duration of 12 minutes, though psychomotor retardation may extend the time (Cusin et al., 2010; Robertson et al., 2003). A recent literature review of 70 studies about the psychometric properties of the HRSD indicated that the majority of HRSD items have adequate reliability (Bagby, Ryder, Schuller, & Marshall, 2004). Inter-rater reliability has been reported to be very high for HRSD total scores (0.80–0.98) (Moberg et al., 2002). Test–retest reliability for the HRSD using the Structured Interview Guide has been reported to be as high as 0.81 and internal consistency of different versions of HRSD ranged from 0.48 to 0.92 (Hamilton, 2000).

Many published reviews have demonstrated that the majority of HRSD items are valid (Bagby et al., 2004; Cusin et al., 2010; Hamilton, 2000; Robertson et al., 2003) with a range from 0.65 to 0.90 (Hamilton, 2000).

Montgomery-Asberg Depression Rating Scale (MADRS).

The MADRS was developed as an observer rating scale and includes 10 items. It was designed to be sensitive to the effects of antidepressant medications such as tricyclic antidepressants (TCAs). Each item is rated in severity from 0 to 6 with a total score ranging from 0 to 60. Total scores between 7 and 18 on the MADRS indicate mild depression, while scores greater than 30 indicate severe depression although some studies have used a cut-off level of 11 (Montgomery, & Asberg, 1979). MADRS is commonly used in clinical studies and practice, administered weekly (Cusin et al., 2010).

In terms of validity, a high correlation of MADRS has been shown with the HRSD (Montgomery, & Asberg, 2000). A reliability test demonstrated an inter-rater reliability range from 0.89 to 0.97 for the MADRS (Cusin et al., 2010) as well as a very high internal consistency (Galinowski, & Lebert, 1995).

iii. Self-reported questionnaires

There are various types of self-report scales for the assessment of depressive symptomatology and the measurement of treatment response. Below, the Beck Depression Inventory (BDI) and the Edinburgh Postnatal Depression Scale (EPDS) will be briefly described. These measures are quite effective in detecting the frequency or severity of the depressive symptoms. However, high scores should be followed by an in-

depth assessment since self-reported questionnaires alone cannot be used to obtain a diagnosis (Robertson et al., 2003).

Beck Depression Inventory (BDI)

Currently, the gold standard of self-rating scales is the Beck Depression Inventory (BDI) and it is one of the most commonly used general self-report questionnaires (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Beck, Steer, & Garbin, 1988).

A study done by Milgrom, Ericksen, Negri, and Gemmill (2005) stated that BDI performed better in terms of diagnostic efficiency than the EPDS as a single diagnostic tool.

BDI includes 21 items concerning different symptom domains, such as cognitive symptoms, behaviors, somatic complaints, and interpersonal domains to measure the presence and severity of depressive symptoms (Beck, Rush, & Shaw, 1979; Kendall, Hollon, & Beck, 1987). In the scale, symptoms are scored from 0 to 3 to describe levels of increasing severity. Some researchers have preferred a cut-off score of 12 or 13 for screening and 20 or 21 for clinical research, though many studies have also used a cut-off score of 15/16. Additionally, other researchers recommended the usage of a different range of scores, where 0 to 9 signifies no symptomatology, 10 to 20 represents mild depression, 21 to 30 indicates moderate depression, and over 30 represents severe depression (Beck, Rush, & Shaw, 1979; Kendall, Hollon, & Beck, 1987).

Recently, BDI has been revised to correspond more closely to the diagnostic criteria of DSM-IV. Four new items: agitation, worthlessness, concentration difficulty, and loss of energy replaced the indicators of weight loss, body image change, work

difficulty, and somatic preoccupation which were eliminated. Additionally, the time frame for ratings has been extended from one to two weeks (Beck, Steer, Ball, & Ranieri, 1996; Steer, Clark, Beck, & Ranieri, 1999).

The BDI has high sensitivity and specificity and is valid and reliable in assessing the severity of depressive symptoms (Arnau, Meagher, Norris, & Bramson, 2001).

Edinburgh Postnatal Depression Scale (EPDS)

The Edinburgh Postnatal Depression Scale (EPDS) is the most well-known and evaluated instrument for PPD studies and for population-based screening (Lee et al., 2003). It is a 10-item self-report scale designed to screen for PPD in community samples by asking participants about their feelings over the previous seven days. Each item is scored on a 4-point scale (from 0 - 3), with a maximum score of 30 (Cox, Holden, & Sagovsky, 1987). To assess the results, different thresholds have been recommended for PPD symptomatology. Some researchers have suggested a cut-off score of 12 or 13 for major depression symptoms (Murray & Carothers, 1990), while other researchers have proposed a cut-off score of 9 or 10 to ensure they identify all possible cases of PPD (Cox, Murray, & Chapman, 1993; Murray & Carothers, 1990; Zelkowitz & Milet, 1995).

The strong validity and reliability of the original English version and its translation to multiple languages has been widely documented (Eberhard-Gran, Eskild, Tambs, Opjordsmoen, & Ove Samuelsen, 2001). The internal consistency of the EPDS has previously been found to be satisfactory (Cox et al., 1987).

Our findings confirm the results of Hannah and colleagues, who found that the EPDS completed at 5 days postpartum is a useful means of detecting women at risk for

postnatal depression. Our results suggest that implementing the EPDS earlier, at 2 to 3 days postpartum, is similarly effective in detecting women vulnerable to postnatal depression

1.2.4 Risk factors of PPD

Biological risk factors are believed to be associated with PPD. A biological theory of PPD proposed that rapid decline in the levels of reproductive hormones (progesterone and estrogen) that occur postpartum could be a possible risk factor for postpartum affective disorders (Wisner et al., 2002), but this hypothesis was countered by other research studies (Harris, 1994; Hendrick, Altshuler, & Suri, 1998). Another study proposed a possible relationship between the various neurotransmitter systems, tryptophan levels, and/or cortisol levels and the symptoms of PPD (Llewellyn, Stowe, & Nemeroff, 1997). Additionally, Harris (1996) demonstrated a minor association between PPD and thyroid dysfunction. Recently, Shapiro, Fraser, & Séguin (2012) reviewed the serotonin transporter (5-HTT) genotype and *n*-3 PUFAs as two possible risk factors of PPD and they found positive associations between *n*-3 PUFAs, the 5-HTT genotype, and PPD.

Therefore we conclude that the role of biology may contribute to the onset of postnatal depression. Genes, neurotransmitters, hormones, thought to influence mood, comprise a deeply complex system. Women who develop PPD may be particularly at risk to the biological changes that occur with child delivery.

Furthermore, research also suggests that non-biological factors may play an important role in increasing the susceptibility of some women to PPD. The strongest

predictive factor is a mother's past history of psychiatric illness or depression (O'Hara & Swain, 1996). Moreover, physical, sexual and psychological violence during pregnancy by an intimate partner has been shown to be strongly associated with postnatal depression (Ludermir, Lewis, Valongueiro, de Araújo, & Araya, 2010). Moderate risk factors include experiencing stressful life events during pregnancy, lack of emotional and social support, depression or anxiety during pregnancy, neuroticism, nervousness, low self-esteem, pessimism and childcare stress (Beck, 2001; O'Hara & Swain, 1996). Additionally, other risk factors for PPD include low cognitive level and socioeconomic factors such as low income and unemployment, obstetric complications such as preeclampsia, delivery related complications, such as emergency caesarean, instrumental delivery, excessive bleeding intrapartum and premature labor (Beck, 2001; O'Hara & Swain, 1996). With regard to ethnicity, a recent study by Howell, Mora, Horowitz, & Leventhal (2005) found that African-American and Hispanic mothers were more likely to have symptoms of PPD than Caucasian mothers, even when other individual, demographic and situational factors associated with these symptoms are similar among the African-American, Hispanic, and Caucasian mothers. Yet, in view article on PPD, Beck and colleagues (2006) found that rates of confirmed PPD were comparable across countries.

In conclusion, PPD is a complex multifactorial disorder with biological, social and psychological parameters shaping each individual's risk. Additional research is warranted in this field, in order to better understand the association of these potential risk factors and PPD.

1.2.5 Consequences of PPD

PPD has a negative impact not only on maternal well-being, but also infant and child development, and family consistency (Fisher, Cabral de Mello, & Izutsu, 2009; Harpham, Huttly, De Silva, & Abramsky al., 2005). These negative impacts will be briefly described below.

Women with PPD are at higher risk for smoking (Whitaker, Orzol, & Kahn, 2007), alcohol or forbidden substance abuse (Ross & Dennis, 2009), and are more likely to experience emotional or sexual abuse than mothers without PPD (Lindahl, Pearson, & Colpe, 2005). Unfortunately, self-inflicted injury is the second leading cause of maternal mortality in high-income countries. Suicide remains an important cause of maternal deaths in moderate and low-income countries, according to the World Health Organization (WHO, 2009).

Depression adversely affects the ability of the mother to interact appropriately with her child (Logsdon, Wisner, & Pinto-Foltz, 2006). Depressed women have been found to have poorer responsiveness to infant cues (Murray, Fiori-Cowley, Hooper, & Cooper, 1996) and more negative, hostile or disengaged parenting behaviors (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Furthermore, intrusive thoughts of accidental or intentional harm to the baby are common in the early postpartum time (Fairbrother & Woody, 2008). PPD also has a negative impact on other parenting behaviours such as problematic sleep habits, lower preventative health care utilization and undesirable safety practices (Field, 2010).

The adverse impact of maternal depression on infant outcomes is also a concern. Maternal depression increases the risk for negative infant feeding outcomes, including lower rates of initiating or maintaining breastfeeding and lower levels of breastfeeding self-efficacy (Dennis & McQueen, 2009). It has also been associated with baby's malnutrition in low-income countries (Rahman, Patel, Maselko, & Kirkwood, 2008). These disruptions in maternal-infant interactions have been associated with lower cognitive functioning and adverse emotional development in children (Walker, Wachs, & Gardner, 2007; Field, 2010). Chronic depression in mothers puts children at higher risk for behavioural problems (Oberlander et al., 2007) and later psychopathology, including anxiety, disruptive, and affective disorders; conversely, remission of depression in mothers is associated with reduction or remission in the children's psychiatric diagnoses (Weissman et al., 2006). Infants of depressed mothers have been shown to have a statistically significant poorer growth than infants of non-depressed mothers at the third month postpartum (Adewuya, Ola, Aloba, Mapayi, & Okeniyi, 2008).

Finally, PPD has the potential to not only adversely impact the mother and the child, but the family can be affected as well. Child abuse/neglect (Buist, 1998) and marital stress can result in separation or divorce (Boyce 1994; Holden 1991). With proper prevention and treatment, it is possible that many of these possible issues may be avoided. As a result, further investigations to prevent these consequences are needed.

1.2.6 Omega-3 PUFA's, Brain and Depression

Omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) are essential fatty acids which exist everywhere in the body. The main *n*-3 PUFAs present in the human body are docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha linolenic acid

(ALA). These fatty acids are essential to the proper function of cells (Holman, 1998). Humans cannot synthesize *n*-3 PUFAs; therefore, the body's supply comes from food consumption (Niemoller, Stark, & Bazan, 2009; Schuchardt, Huss, Strauss-Grabo, & Hahn, 2009). While DHA and EPA are mostly found in animal sources, ALA is found in non-animal food sources (Taha, Burnham, & Auvin, 2010). Fortunately, one of the advantages of consumption of *n*-3 PUFAs is their safety (Taha et al., 2010).

DHA is the most abundant *n*-3 PUFAs in the brain (Bazan, 2007). This is suggested to be in part due to the phospholipids' layer of neurons containing mainly DHA fatty acids (Niemoller et al., 2009). While it has been reported that the phospholipids' layer of neuronal membranes hold a huge amount of DHA during the postnatal period (Bazan, Musto, & Knott, 2011), Yavin (2006) stated that DHA increases during different periods of fetal brain development, highlighting the importance of DHA in the development of the central nervous system (CNS). During the pre-natal and the postpartum developmental period, building of critical brain circuits depends on the supply of DHA (Bazan, et al., 2011).

Research has demonstrated that *n*-3 PUFAs in both types EPA and DHA are efficient in cardiovascular disease (CVD) prevention due to their anti-inflammatory and cardio-protective effects (Kotwal, Jun, Sullivan, Perkovic & Neal, 2012). Additionally, Grosso et al. (2014a) has proposed a significant therapeutic role for *n*-3 PUFAs as a part of the treatment for certain forms of mental diseases, including depressive disorders. In fact, depression may share certain pathophysiological mechanisms with CVD, specifically in augmenting the production of pro-inflammatory cytokines, endothelial

dysfunction, and elevations in plasma homocysteine levels (Do, Dowd, Ranjit & House, 2012; Kaplan Machado-Vieira & Mallinger, 2012; Severus, Littman & Stoll, 2001).

Consequently, *n*-3 PUFAs are essential for healthy brain structure and function, they prevent or decreasing the inflammatory status occurring during depression and may be critical for maintaining healthy mood and keeping mental distress at bay.

1.2.7 Conceptual Framework and Significance

The initial drive behind this research project was to explore findings that have emerging from quantitative studies about the role of the *n*-3 PUFAs in the prophylaxis and treatment of PPD. With this purpose in mind, it became obvious that the conceptual model provided by Place, Billings, Blake, Frongillo, & Mann, (2014), who described the knowledge frameworks widely used by physicians, nurses, social workers, and psychologists, was a suitable conceptual framework to explore, as we sought to understand the applicability of our findings to a larger societal and medical context.

Their framework, whose elements deemed relevant to this project are summarized in Figure 4, involves the flow of subjects from antecedents, causes, symptoms and consequences, from an inclusive socio-biological perspective.

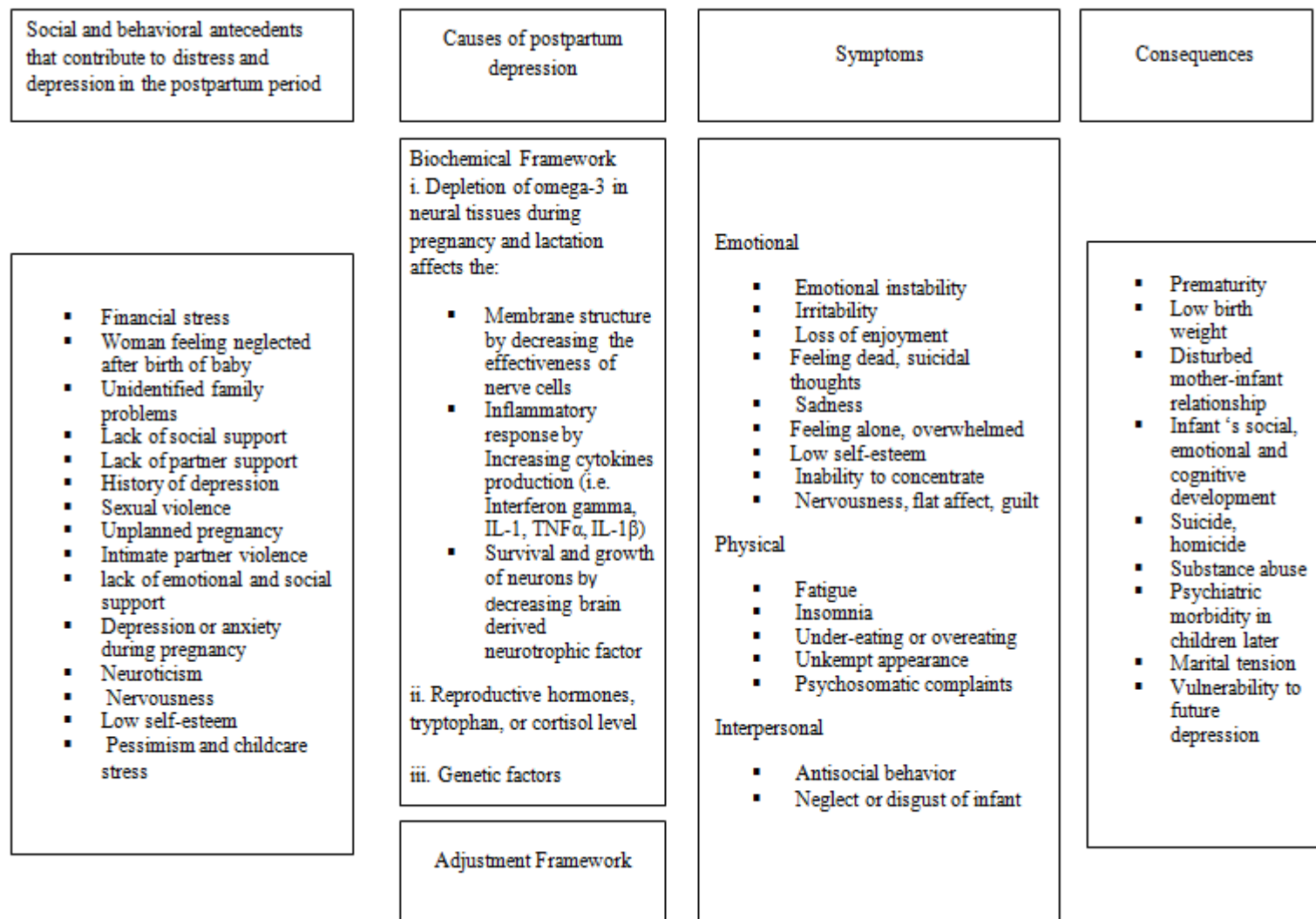


Figure 4. Conceptual Framework of PPD

With respect to the framework's biological causes and antecedents, we draw particular attention to the biological theory of depression proposed by many researchers Harris (1996); Llewellyn, Stowe, & Nemeroff (1997); Wisner et al., (2002), with particular emphasis on the inflammation theory that links *n*-3 PUFAs intake with the depressive disorder. As described previously, *n*-3 PUFAs block the action of cytokines (IL-1 β , -2 and -6, interferon-gamma, TNF α), which play a role in the inflammation response and cause feelings of depression (Maes & Smith, 1998; Suarez, Krishnan, & Lewis, 2003).

Pregnancy and lactation are challenging nutritional periods in the maternal experience, due to a higher demand of *n*-3 PUFAs from the fetus and the newborn, respectively, and a low DHA status may induce depressive symptoms (Otto, de Groot & Hornstra, 2003). It's important to note that PPD is correlated with symptoms of distress (Beck, 2001; Ludermir et al., 2010; O'Hara & Swain, 1996), and that researchers and health care providers believe that distress symptoms affect responsibilities associated with motherhood, as well as interpersonal interactions with the family and child (Fisher, Cabral de Mello, & Izutsu, 2009; Harpham, Huttly, De Silva, & Abramsky et al., 2005).

Furthermore, PPD has serious consequences for a woman and her family. Risks associated with untreated PPD, including poor maternal care and physiologic adverse effects to the fetus, may produce an outcome worse than the risks of treatment. It can be difficult to manage because of the potential adverse effects associated with various classes of antidepressants. These concerns are highlighted by recent data regarding a neonatal syndrome after in utero antidepressant exposure and data suggestive of teratogenicity with Paroxetine use. Also antidepressant medications may pose risks on the

baby during breastfeeding (Food and drug administration, 2005; Moses-Kolko et al., 2005).

Our framework might be useful for clinical policy development in nutritional approaches to maternal care, to the extent that it allows for the consideration of social, behavioural and biological determinants of health, not just proximal clinical causes and outcomes. The placing of diet in a larger context that informs not just biological health, but social health and cost effectiveness helps highlight the importance and power of using a simple nutritional intervention to achieve grander social outcomes, beginning with improved mental health and improved familiar interactions.

For the previous reasons, achieving an antidepressant effect through nutrition is therefore a promising public health idea. *N-3* PUFAs may be an option for the treatment or prevention of PPD because of their potential efficacy and favourable safety profile. This intervention would be relatively inexpensive, and women reluctant to take antidepressant medication might be more willing to enter treatment.

Currently, the American Psychiatric Association recommends a wide dosage range for *n-3* PUFA treatment of mood disorders (from 1–9 g EPA and DHA per day), with the EPA: DHA ratio undefined (freeman, 2008). Clarification of dosages for prevention or treatment of PPD might encourage more clinicians to treat pregnant and postpartum women with dietary modification or micronutrient supplements.

Any association of *n-3* PUFAs with PPD is also significant to governmental health and agriculture policy. It could be the basis for health education initiatives, including additional labeling of these nutrients in processed foods. Also, a demonstrated

link could support inclusion of more *n*-3 PUFAs rich foods in government benefit programs, such as the pregnant women nutritional support program in Canada.

We hope our findings provide a foundation for future studies of how researchers' conceptualizations of PPD- *n*-3 PUFAs linkage might affect detection and treatment practices, and might be useful in the development of new recommendations concerning *n*-3 PUFAs intake during pregnancy.

1.2.8 Literature Review and Rationale

1.2.8.1 Intervention for the prevention and treatment of PPD

Several studies and reviews have considered various strategies for the prevention and treatment of postnatal depression (Charbol et al., 2002; Dennis & Creedy, 2005; Dennis & Hodnett 2007; Dennis et Allen, 2008; Dennis et al., 2009; Hoffbrand, Howard, & Crawley, 2001; Howard, Hoffbrand, Henshaw, Boath, & Bradley, 2005; Stuart, O'Hara & Gorman, 2003; Wisner et al., 2004). However, to date it appears to be no effective strategy for the prevention or treatment of postnatal depression among these reviews.

One intervention that might be effective in preventing postnatal depression is telephone-based peer support among women at high risk (Dennis et al., 2009). Another study regarding intensive, professionally-based postpartum support for at-risk women appears promising (Dennis & Creedy, 2005). Alternative therapies including massage and acupuncture have failed to improve antenatal depression immediately after treatment or prevent postnatal depression (Dennis & Allen, 2008). One systematic review showed that some psychosocial and psychological interventions for treating PPD appear to be

effective in reducing postnatal depression however, the methodological quality of the included trials was not strong, and the long-term effectiveness is ambiguous (Dennis & Hodnett, 2007).

Antidepressants given postpartum cannot be recommended for prevention of postnatal depression as there is a lack of clear evidence (Howard et al., 2005). There is also little evidence for using antidepressants for the treatment of postnatal depression (Hoffbrand, et al., 2001), although this is obviously the current standard accepted practice among clinicians.

Another concern regarding the acceptability of antidepressants as a treatment for postnatal depression is their transfer from mother to infant through breastfeeding, although most antidepressants are believed to be safe with breastfeeding (Kendall-Tackett, Duffy, & Zollo, 2007). Nonetheless, a study by Fortinguerra, Clavenna and Bonati (2009) reported on the concentrations of different antidepressants that are excreted in breast milk and their associated toxicity profiles. Furthermore, taking antidepressants in the third trimester has been associated with adverse effects like transient neonatal withdrawal syndrome. This includes muscle weakness and respiratory difficulties (Oberlander et al., 2004). Using Paroxetine (antidepressant) during pregnancy might be associated with a higher risk of preterm birth, neonatal adaptation difficulties and congenital cardiac malformations (Udechuku, Nguyen, Hill, & Szego 2010). Therefore, though antidepressants may be considered unsafe, further investigations are required to strengthen this belief.

Studies proposed that dietary deficiencies in a pregnant or postnatal woman's diet may cause postnatal depression (Abou-Saleh, Ghubash, Karim, Krymski, & Anderson, 1999; Freeman, 2009; Harrison-Hohner et al., 2001; Miyake et al., 2006a; Wójcik et al., 2006). Hence, correcting these deficiencies with dietary supplements could prevent postnatal depression. The interventions considered were dietary supplements which include *n*-3 PUFAs, iron, calcium, vitamin B12 (cobalamin), riboflavin (B2), vitamin B6 (pyridoxine), folate and vitamin D (Abou-Saleh et al., 1999; Freeman, 2009; Harrison-Hohner et al., 2001; Miyake et al., 2006a; Wójcik et al., 2006).

1.2.8.2 Omega-3 polyunsaturated fatty acids (n-3 PUFA) and PPD

Omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) are fatty acids that contain 20 carbons chain and multiple double bonds. The Omega-6 polyunsaturated fatty acids (*n*-6 PUFA) including Arachidonic Acid (AA; 20:4n-6; which indicates the number of carbons: the number of double bonds, and the fatty acid family) and Docosapentaenoic Acid (*n*-6 DPA; 22:5n-6) are produced in the body from linoleic acid (LA). *n*-3 PUFAs including EPA; 20:5n-3 and DHA; 22:6n-3, are synthesized from ALA; 18:3n-3 (Levant, 2010; Parker et al., 2006).

N-3 PUFAs and *n*-6 PUFAs are known as essential fatty acids because humans cannot produce them and must get them from their diet (Kris-Etherton, Harris, & Appel, 2002). *N*-3 PUFAs are obtained from two dietary sources: seafood and certain nut (Kris-Etherton et al., 2002). Fish and fish oils contain (EPA, DHA), whereas canola, walnut, soybean, and flaxseed oils contain the (ALA) (Kris-Etherton et al., 2002).

A growing body of evidence suggests that *n*-3 polyunsaturated fatty acid (PUFA) status may contribute to the development of PPD (Al et al., 1995; Al, Van Houwelingen, & Hornstra 1997; Huang, Chuang, Li, Lin, & Glew 2013, Holman, Johnson, & Ogburn 1991; Otto et al., 1997; Van den Ham, van Houwelingen, & Hornstra 2001). The majority of studies reported that women have been found to be depleted by 50% in *n*-3 PUFAs during gestation and were not fully replenished at 26 weeks postpartum (Al et al., 1995; Al et al., 1997; Huang et al., 2013, Holman et al., 1991; Otto et al., 1997; Van den Ham et al., 2001). Therefore, mothers may be at a higher risk of suffering PPD when they become depleted of *n*-3 PUFAs (Hibbeln & Salem, 1995).

Many studies have determined that lower rates of fish consumption and low concentration of DHA in plasma or serum, have also been correlated with higher rates of postnatal depression (Golding et al., 2009; Otto, De Groot, & Hornstra, 2003; Rees, Austin, & Parker, 2005; Rees, Austin, Owen, & Parker, 2009; Sontrop, Avison, Evers, Speechley, & Campbell 2008).

1.2.8.3 Possible mechanisms of n-3 PUFAs ' effect on depression

We have limited knowledge of how *n*-3 PUFAs function in the brain. There are three major areas in which *n*-3 PUFAs seem to play a role.

1. *n*-3 PUFAs are essential components in neuronal membranes and play a critical role in how they function. They allow the nerve cells to be more receptive to neurotransmitters, enhancing their effectiveness (Bourre et al., 1991).

2. *n*-3 PUFAs also may chemically influence major depression. Certain chemicals in the brain, called cytokines such as including interleukin-1 beta (IL-1 β), -2 and -6,

interferon-gamma, and tumor necrosis factor alpha (TNF α), which play a role in the inflammation response, also cause feelings of depression (Maes et al., 2012; Maes & Smith, 1998; Suarez, Krishnan, & Lewis, 2003).

N-3 PUFAs block the action of these cytokines. They are many tricyclic and selective serotonin re-uptake inhibiting antidepressants (SSRI) also block these inflammatory cytokines (Maes et al., 2012; Maes & Smith, 1998; Suarez & al., 2003).

3. In addition, there is a chemical in the brain called brain derived neurotrophic factor. This chemical supports the survival and growth of neurons. Levels of brain derived neurotrophic factor are low in patients with severe depression. *N*-3 PUFAs enhance the function of brain derived neurotrophic factor, as do anti-depressant medication and exercise. Interestingly, diets high in saturated fat and sugar, as well as stress inhibit its production (Logan, 2003; Shimizu et al., 2003).

1.2.8.4 Aims of the present systematic review

Several experimental and observational studies evaluated the effectiveness of the *n*-3 PUFAs on PPD, but there is no current systematic review that has examined all quantitative designs (observational and experimental) that have been conducted to assess the efficacy *n*-3 PUFAs in the prevalence, prevention and treatment of the 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).

Many research studies indicated that traditional literature and narrative reviews tend to be more biased than a systematic review in terms of selection bias and publication bias. Narrative reviews set a broad research question, they lack a systematic search of the literature, and thus they often focus on a subset of studies in an area chosen based on availability or author selection. Also, in narrative and literature reviews, the approach to analyzing the collected information is often subjective and disorganized (Cook, Mulrow, & Haynes, 1997; Garg, Hackam, & Tonelli, 2008; Jørgensen, Hilden, & Gøtzsche, 2006; Uman, 2001). All these factors can affect the overall result of the study.

In a systematic review, research question is more specific and defined. Also, the approach of data collection is more comprehensive and explicit, and the rigorous critical evaluation (Cook, Mulrow, & Haynes, 1997). Therefore systematic reviews are more transparent than the narrative 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 clinical and observational efficacy of *n*-3 PUFAs in previous and more recent quantitative published studies in the last years and to discuss directions for future research in this area.

CHAPTER 2: RESEARCH QUESTIONS AND OBJECTIVES

2.1 Questions

The aim of this systematic review is to answer the following research questions:

Question1: What empirical research has been undertaken on the use of *n*-3 PUFAs either alone or in combination with other interventions in the PPD?

Question 2: What evidence is there that *n*-3 PUFAs utilization in the perinatal period has beneficial effects in the prevention and/or treatment of the PPD?

2.2 Objectives

The main objectives of this research are:

Objective 1: To create a conceptual map of the quantitative experimental and observational research that has been undertaken on *n*-3 PUFAs benefits for the prevention and treatment of postpartum depression to inform discussions on what future research might usefully address.

Objective 2: To synthesize the known evidence for the effects of *n*-3 PUFAs on the etiology, prevention, and treatment of postnatal depression up to 12 months postpartum for the benefit of researchers, health care providers, and users of the intervention.

CHAPTER 3: METHODS

This chapter describes the methods used in conducting the systematic review and narrative synthesis.

For the systematic review, we employed the methodology described by the Cochrane Collaboration and published in the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Collaboration, 2008). Though this was ostensibly a one-rater review, a second reviewer was made available in the event of uncertainties with respect to whether studies satisfied the inclusion criteria. The Narrative synthesis was conducted, guided by methods described by Popay et al. (2006).

Section 3.1 describes methods for identifying potentially relevant studies through searching and screening. This section also describes the data extraction procedure and quality assessment, as well as the purpose, process and quality assurance measures for each stage are described. Section 3.2 describes the methodology used to synthesize the studies identified as relevant to this project following the guideline for narrative synthesis as outlined by Popay et al. (2006).

3.1 Identifying and describing studies

In order to be considered relevant for answering the review question, ‘What evidence is there that *n*-3 PUFAs utilization in the perinatal period has beneficial effects in the prevention and/or treatment of PPD?, a set of inclusion/exclusion criteria were used to exclude all studies that fell outside of the objectives of this review. This section describes (i) the criteria; (ii) the methods for identifying potential studies; (iii) the

description of the screening/scanning of identified studies; (vi) the extraction of data; and (v) quality assurance.

3.1.1 Criteria for Considering Studies for This Review

Four criteria dictated whether a study would be included in the review. These criteria focused on the study designs, characteristics of participants, the type of intervention, and the outcomes.

3.1.1.1 Types of studies

The types of studies included in this review were: experimental and observational studies from 1990 covering randomized controlled trials (RCTs), cohort, case-control, and cross-sectional studies of *n*-3 PUFAs given to women in the antenatal or postnatal period, or both antenatal and postnatal period for the prevention of PPD. Studies were excluded if they were not reported in the English language; or if they were presented only as abstracts. Individual case report designs and trials involving animal subjects were also not eligible for inclusion.

We sought the opinion of an expert librarian in the Health Sciences department at the University of Ottawa (K. Fournier, personal communication, April 3, 2014) concerning grey literatures. After making a thorough search in the Open Grey – a multidisciplinary database of European grey literature – we didn't find any potentially relevant studies. Therefore we decided to search for only published research studies.

3.1.1.2 Types of participants

The types of participants deemed acceptable were: women who were pregnant or had given birth in the previous six weeks (new mothers). Trials could include women

with a history of depression and/or postnatal depression. Trials including women already taking *n*-3 PUFAs before trial commencement were also eligible.

3.1.1.3 Type of intervention

The types of intervention deemed acceptable were: *n*-3 PUFAs alone or in combination with another treatment.

3.1.1.4 Type of outcome measures

We included only studies reporting outcomes of PPD, as determined by any of the following scales:

1. An estimate of depression as measured by investigators or researchers using any of the following: screening instruments such as the EPDS (Cox, Holden, & Sagovsky 1987), HAM-D or BDI (Beck, Ward, Mendelson, Mock, & Erbaugh 1961; Hamilton, 1960), the MADRS (Montgomery & Asberg, 1979); or
2. Use of standard clinical measures of depression by a recognized diagnostic scales such as DSM IV-TR (APA, 2000) or the ICD10 (WHO, & DIMDI, 2006).

3.1.2 Search strategy

3.1.2.1 Electronic bibliographic databases

Ovid, CINAHL, Cochrane and Embase databases were thoroughly searched in collaboration with an expert librarian in the Health Sciences department at the University of Ottawa (K. Fournier, personal communication, April 3, 2014) for studies that met the inclusion criteria. The databases were searched on April, 2014 using combinations of

"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"

All records retrieved from the literature search will be stored and managed using Refworks, a multi-platform reference and citation manager.

3.1.2.2 Internet search

Using the global search engine, Google Scholar, to perform a search on published papers containing the same terms used in the databases search, as outlined in Section 3.1.2.1.

3.1.2.3 Reference lists

All reference lists of included studies were examined for additional relevant studies.

3.1.3 Data collection

3.1.3.1 Selection of studies

All abstracts were reviewed in relation to the inclusion/exclusion criteria. Unless the abstract clearly described one or more exclusion criteria, the full article was then examined to determine if it still met the inclusion criteria. Subsequently, we screened the references lists from retrieved articles and related reviews. We have presented a diagram (figure 5) detailing the selection process for this review as displayed in the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009).

3.1.3.2 Data extraction and management

A data extraction form was designed and employed to systematically extract data from all included studies. Data extracted included:

1. Authors and year of publication
2. Study design
3. Objective of the study
4. Sample size
5. Characteristics of the participants (Inclusion/Exclusion criteria),
6. Duration of the intervention/ study
7. Description of the intervention (experimental studies only)
8. n-3 PUFA measurement
9. Depression measurement
10. Adjustment of potential confounders (observational studies only)
11. Main findings
12. Limitation

All included studies are referred to by the first author's last name for conciseness.

3.1.4 Assessment of risk of bias in included studies (Quality assessment)

The Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project (EPHPP) was used to assess methodological quality (EPHPP; Thomas, Ciliska, Dobbins, & Micucci, 2004).

The EPHPP is a reliable and valid tool for the use in detecting bias within intervention studies, and is also considered suitable to be used in systematic reviews of the effectiveness of interventions (National Collaborating Centre for Methods and Tools, 2008). 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).

Studies were rated as strong if they: 1) included participants likely to represent the target population, 2) used a randomized controlled trial (RCT) or controlled clinical trial (CCT) design, 3) controlled for confounders, 4) blinded participants to the research question, and blinded outcomes assessors to participant status, 5) reported reliability and validity of the measures used, or used outcomes measures with known reliability and validity, and 6) reported a drop-out or withdrawal rate of 20% or less.

Scoring of the data collection methods was related to the validity and reliability of the methods were rated in relation to the validity and reliability of the tools used to diagnose and assess PPD in the included studies (see 1.2.3 Postpartum depression: Diagnostic issues).

3.2 Methods of analysis

To synthesize our findings, we employed the Narrative synthesis. It is defined as: "An approach to the systematic review and synthesis of findings from multiple studies that relies primarily on the use of words and text to summarize and explain the findings of the synthesis" (Popay et al., 2006, p.5). The key to this approach is not only to review what worked, but also to investigate why and how an intervention might have worked. This approach is particularly applicable to the present systematic review, due mostly to the extreme heterogeneity of found studies. Our chosen approach, a stepwise narrative methodology, has been used previously in a wide range of study reviews (Arai et al., 2007; Cabello et al., 2012; Galbraith & Brown, 2011; Dennison, Moss-Morris, & Chalder, 2009; Leamy, Bird, Le Boutillier, Williams, & Slade, 2011; McDermott et al., 2013; Schrank et al., 2013)

Narrative synthesis consists of four main elements: 1) developing a theory of how the intervention works, why and for whom; 2) developing a preliminary synthesis of findings of included studies; 3) exploring relationships in the data; and 4) assessing the robustness of the synthesis. Although represented sequentially, it is not necessary to proceed with the synthesis in a linear form. Instead we can follow an iterative approach. Within each element there are a variety of tools and techniques which may be used depending on the nature of the research evidence. Each of the tools and techniques of each element were assessed as to whether they would be relevant for the synthesis (see Table 2).

Classic narrative reviews may provide more flexibility to accommodate various study designs. Various forms of narrative synthesis are widely used in systematic

literature reviews. However, such reviews can be seen as less trustworthy if review methods, such as eligibility criteria or quality assessment of studies, are not made clearly (McDermott, Crellin, Ridder, & Orrell, 2013). Narrative synthesis has been criticized because of the lack of agreement on its elements and condition in order to establish trustworthiness (Pope, Mays, & Popay, 2007). Thus, in absence of traditional meta-analysis and classic narrative reviews, there is a need to evaluate evidence from *n*-3 PUFAs and PPD studies in a more transparent, systematic manner.

Popay et al. (2006) devised a guide "to make the process of narrative synthesis more systematic and to minimize bias". Narrative methods have long been recognized as useful for investigating heterogeneity across primary studies because it "is sometimes viewed as a 'second best' approach for the synthesis of findings from multiple studies about the effects of interventions only to be used when statistical meta-analysis or another specialist form of synthesis (such as meta-ethnography for qualitative studies) is not feasible" (Popay et al., 2006, p. 5).

As recommended by the Cochrane Centre, "Meta-analysis should only be considered when a group of studies is sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary" (Cochrane Collaboration, 2008, 9.5.1). In this review, a meta-analysis was not undertaken due to the clear 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. Furthermore, the Cochrane Handbook warns against combining "apples with oranges" as this will cause real differences to be obscured

(Cochrane Collaboration, 2008, para. 9.5.1). For this reason, a narrative synthesis approach was undertaken in lieu of a meta-analysis.

We confirmed our choices by contacting an experienced professor in systematic reviews (J. Jutai, personal communication, June 23, 2014); a methodologist (B. Hutton, personal communication, July 8, 2014); and a clinical expert (D. Moher, July 24, 2014) and they all agreed that the heterogeneity is a major obstacle limiting the applicability of traditional meta-analysis, giving weight to our eventual choice of a narrative synthesis approach.

Table 2. Tools of likely use for elements 2 through 4 of the narrative synthesis

Name of tool/technique	Comments in relation to current synthesis	Should this technique be applied here?
Element 2. Developing a preliminary synthesis of findings of included studies		
Tabulating	This table will include the elements described previously to be included in the data extraction form.	Yes
Textual descriptions of studies	Since we will provide the findings of the data extraction form in this section, we will determine which aspects of each study will be taken from the reports later.	Yes but not in this stage
Grouping and clustering	We will organize the studies by their research design type	Yes
Transforming data into a common rubric	Since different outcome were presented, it is difficult to provide a common rubric for all studies	No
Vote counting as a descriptive tool	it is not possible to convert data to odds ratios/relative, risks/mean differences because not all studies provided the data of interest	No
Translating data	Inappropriate given predominantly quantitative studies	No

Table 2.*Continued*

Name of tool/technique	Comments in relation to current synthesis	Should this technique be applied here?
Element 3. Exploring relationships within and between studies		
Qualitative case description	This part is similar to the ‘textual descriptions’ previously. We revised the studies and extracted detailed data from them while highlighting the moderators.	yes
Graphs, frequency distributions, funnel plots, forest plots and L’Abbe plots, idea webbing	Not appropriate given the heterogeneity between studies. Concerning idea webbing: the nature and settings of each study make it impossible to provide a spider diagrams in order develop a visual picture of relationships across study results	No
Moderator variables and sub-group analyses	We explained how effects are likely to related to variations in intervention, population and settings.	Yes
Translation : reciprocal and refutational	Insufficient qualitative evidence in this review	No
Investigator conceptual triangulation and methodological triangulation	This approach would be more suitable to an analysis of implementation studies, in which more qualitative information exists and same for methodological triangulation which is more applicable to qualitative studies	No
Element 4. Tools and techniques for assessing robustness of the synthesis		
Best evidence synthesis	Inclusion/Exclusion criteria	Yes
Use of validity assessment	EPPI-centre approach was adopted using the quality assessment data presented in the summary tables.	Yes
Checking the Synthesis product with authors of primary studies	Not possible given the time available for this study	No
Reflecting critically on the synthesis process	Highlighting the limitation of the review	Yes

3.2.1 Element 1: Developing a theoretical model of how the interventions work, why, and for whom

The purpose of this section 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). To accomplish this purpose, we presented an extensive description of our theory in the early stage (see Chapter 1) by verifying how *n*-3 PUFAs work, why, and for whom.

3.2.2 Element 2: Developing a preliminary synthesis of findings of included studies

The primary goal of the preliminary synthesis is to provide an initial description and mapping of the results observed in all of the included studies. This will help to identify contextual and methodological factors that have influenced the published results.

Subsequent examination of the preliminary synthesis is useful to better understand and explain the role of *n*-3 PUFAs in the prevention and treatment of PPD. Popay et al. (2006) suggested in his guidelines that "how a reviewer approaches the preliminary synthesis . . . will depend in part on whether the evidence to be synthesized is quantitative, qualitative or both" (Popay et al., 2006). Accordingly, the data in our study is quantitative. With this in mind, we assessed each of the tools and techniques presented in table 2 as suggested by Popay et al. (2006)'s guideline and we selected four tools described in the guidance to develop our preliminary synthesis.

3.2.2.1 Tabulating the data

As suggested by Popay et al. (2006), data was extracted from the primary studies in tabular form in order to build up an initial description and to identify patterns across included studies. Data regarding the study design, objectives, sample size, characteristics of the participants, duration of the intervention/ study, characteristics of the intervention, n-3 PUFA measurement, depression measurement, confounders, findings and limitations were collected for each research study included in this project (see Table 3).

3.2.2.2 Textual description

Producing a descriptive paragraph on each included study is a useful tool for reviewers to become familiar with the included studies and to begin to compare and contrast findings across studies. It is important to develop narrative descriptions in a systematic way, including the same information for all studies and in the same order (Popay et al., 2006). However, after constructing the data extraction tables, textual descriptions seemed to be an unnecessary duplication of work since it would not add extra information at this point. As a result, this step was delayed until a later stage of the synthesis process (i.e., 3.2.3 *Exploring Relationships within and between Studies*).

3.2.2.3 Groupings and clusters

Grouping the included studies is an important way to analyze the data and look for patterns within and across the groups. As mentioned by Popay et al. (2006), studies can be clustered according to one or a combination of the intervention's type, characteristics of participants, the study design, and/or the nature of the findings.

In this review, the most obvious differences between the studies were: the study design and the role of the intervention (prevention or treatment of PPD). Consequently, we decided to cluster our studies according to: the study designs and the role of the n-3 fatty acids.

3.2.3.4 Common rubric and vote counting as a descriptive tool

The purpose of this part is to transform the results of included studies which might be presented in different numerical and/or statistical forms to a common numerical/statistical rubric if feasible. This helps to build a significant summary of study results and adequately assess the role and the effect of the intervention of interest (Popay et al., 2006). Tabulation of statistically significant and non-significant findings in reviews that assessed the effects of an intervention is considered an uncomplicated approach to vote-counting. (Popay et al., 2006)

In this particular review, the common rubric method was not possible due to the lack of desired data in some papers. As a result, we were unable to calculate the measures of interest and construct a common statistical rubric. Instead, we created tables in which the available statistical data on the effect of n-3 PUFAs on PPD of experimental and observational studies was included. For the vote counting, we used a (+) sign where the effect of the intervention was positive, and a (-) where the effect of the intervention was null.

3.2.3 Element 3: exploring relationships within and between studies

At this stage of the synthesis, the reviewer goes beyond identifying, listing, tabulating and counting results in order to explore the relationships within and between

the 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.

After assessing the relationships between study characteristics, we identified how these relationships may or may not align with the evidence reported in other research. Extra attention was paid to the heterogeneity of sample size, population, intervention characteristics, and depression measurement encompassed in the literature through the application of narrative methods, which is a convenient way to synthesize such findings. In this way, we were able to acknowledge the effects of different variables on the outcome and facilitate the understanding of differences between reported outcomes and the study designs with relation to *n*-3 PUFAs and PPD. The two main tools and techniques for exploring relationships within and between studies were conducted in the order described below:

1. Qualitative case reports/textual descriptions
2. Examination of moderator variables and subgroup analyses

3.2.3.1 Qualitative case reports/textual descriptions

During this stage of the synthesis, we provided a textual description of included studies by describing each study in more depth than in the tables. Qualitative case reports allow the reviewer to understand in detail the aspects of individual studies that may not have appeared pertinent at the beginning of the synthesis, but have become of interest during the subsequent stages of describing and exploring the study data. These summaries

were structured with the aim to provide information regarding the settings, objectives, participants, intervention, comparison, outcomes, and limitation along with any other factors of interest.

The analysis of relationships within and between studies described previously is helpful 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)

3.3.3.2 Examination of moderator variables and subgroup analyses

Examination of moderator variables and subgroup analyses is important because it highlights the variables that might moderate the main effects being examined in the review (Cooper & Hedges, 1994). In order to accomplish this, the reviewer must analyze either the characteristics that vary between studies (study quality, design, and/or setting) or the characteristics of the sample (outcomes and/or participants) (Popay et al., 2006). As a result, to help investigate whether or not there were any such moderators of effect, we created tables for both experimental and observational studies (Tables 8 and 9) in which we showed the overlap in interventions, depression scales, period of the study, objective of the study, the mental health status of the participants between the included studies.

3.2.4 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).

3.2.4.1 Strength of evidence (EPPI approach)

In order to determine the quality and relevance of each study, the Evidence for Policy and Practice Information and Coordinating Centre (EPPI) used a structure called "Weight of Evidence" to explain each component of the critical appraisal judgments (EPPI, 2010). In this method, the decision is categorized as a "weight", in order to judge each study as either "high", "medium" or "low" according to the quality and relevance of the study (EPPI, 2010).

Four criteria are used to appraise each study: (1) the study's methodological soundness, (2) the appropriateness of the study design to answering the review question, (3) the study relevance, and (4) an assessment of the overall weight of evidence which the study provides (Gough, 2007). The first three criteria contribute to the assessment of (4) study 'weight'. These are described by EPPI review authors as (1) trustworthiness, (2) appropriateness, (3) relevance, and (4) overall weight. The total study's "weight" is attained through the consideration of the following three dimensions, labeled A, B and C (EPPI, 2010; Gough, 2007).

A. Appraising the quality of the execution of design

Appraising the quality of the execution of design is meant to tell us how well the researchers have done each study (EPPI, 2010; Gough, 2007). A checklist is used to appraise the quality of each study against pre-established criteria. In our review, we used the EPHPP quality assessment tool to judge the methodological soundness of each study (see Section 4.1.3).

B. Appropriateness of research design for review questions

The appropriateness of the research design for our review questions and objectives is a consideration of the suitability of the various study designs for answering the question posed in the present review (EPPI, 2010; Gough, 2007). To accomplish this, we scored the data based on Kendall (2003), who stated that it is commonly known that the randomized controlled trials are considered as the most rigorous methods to explore the cause-effect relationship between an intervention and an outcome. Therefore, randomized controlled trials were given more weight than non-controlled experimental trials and the observational designs.

C. Appraising relevance of the focus of study to the review question

This step considers the degree to which each study's specific focus is relevant to the intent and focus of the present review (EPPI, 2010; Gough 2007). In this review, we gave higher weight to studies that were more relevant to the review questions and objectives by assessing the sample population of the study, context of the study, intervention studied, outcome measurement and ethical concerns.

D. Overall Weight of Evidence provided by study to answering the review question

Many strategies could be used to give an overall weight of evidence. The first option would be arithmetically combining the three aforementioned dimensions while considering each one as equally important and having equal weight. Another way of scoring would be to weigh the dimensions differently, either by considering the focus of the study the most critical. Thus, the overall score would be the same score of the topic focus. It is also possible to prioritize the quality of execution so that only studies scoring high on this dimension could get a high score overall (EPPI, 2010).

In we found that each of three dimensions is important because of variation amongst the included studies. This means that it is necessary to develop a way to assess the studies on each dimension and then combine the three dimensions in order to obtain an overall judgment. Thus, we give each dimension a score and averaging the scores.

3.2.4.2 Reflecting Critically on the Synthesis Process

As per the recommendations of Popay et al. (2006), we included an executive summary of the synthesis in order to reflect on the 1) methodology of the synthesis – especially focusing on the limitations and their possible impact on the results, 2) evidence used, in terms of quality, reliability, and validity 3) assumptions made, 4) discrepancies and uncertainties identified, and 5) areas where the evidence is weak or non-existent, with identification of possible areas for future research.

CHAPTER 4: RESULTS

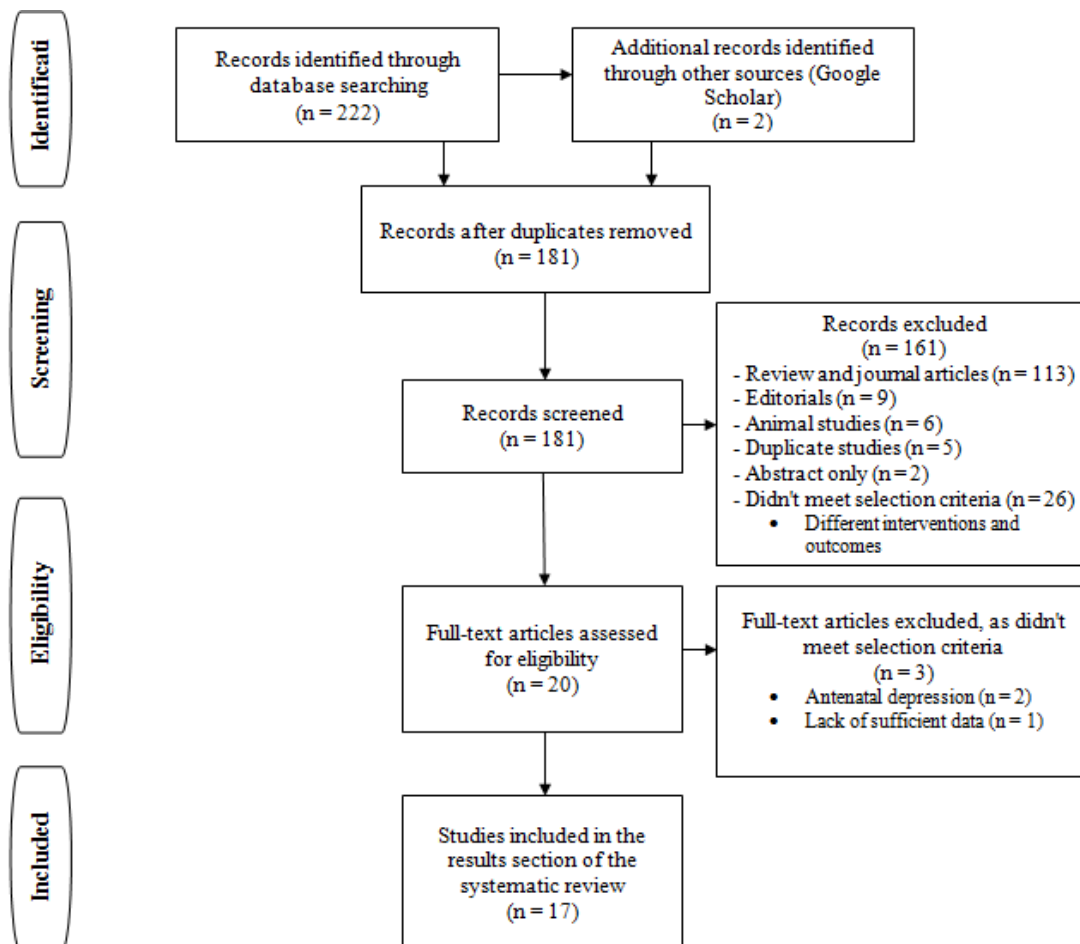
4.1 Results of the search

A search of the databases listed above was completed on April 3, 2014. The MeSH terms and keywords were combined to generate a list of 222 potential articles; 72 were retrieved from Medline, 51 from Embase, 48 from Cochrane and 51 from CINAHL. A search in Google scholar with the same research terms yielded two new eligible research studies. After duplicates were removed, 181 remained. The abstracts of these articles were reviewed and, of them, 17 articles were selected to be included in the review as they met the criteria listed above. No additional included studies were found from the reference lists of already included studies. Figure 5 displays a diagram detailing the selection process for this review.

4.1.1 Included studies

A total of 17 studies met the inclusion criteria: eight experimental studies and nine observational studies. Of the eight experimental studies included in this review, 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; Martinez, Zboyan, & Puryear, 2004). The nine observational studies include an 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., 2006b; Otto, De Groot, & Hornstra, 2003; Parker et al., 2014; Strøm, Mortensen, Halldorsson, Thorsdottir, & Olsen, 2009).

Figure 5. Prisma 2009 Flow Diagram



4.1.2 Data Extraction of Study Features

Studies were grouped by study designs and the objective of the intervention (*n*-3 PUFAs in the prevention or treatment of PPD).

The study features extracted from each publication were the name of the authors, year of publication, country, study design, objective of the study, sample size, characteristics of the participants (Inclusion/Exclusion criteria), duration of the intervention, description of the intervention (experimental studies only), PUFAs measurement, depression measurement, adjustment of potential confounders (observational studies only), main findings, and the limitation. The characteristics of eligible studies regarding the effects of *n*-3 PUFAs on PPD are described in the Table 3.

Table 3. 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 arms were given psychotherapy	Placebo (corn oil)	–	EPDS, HAM-D, CGI biweekly for 8 weeks	No significant 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 - Supportive psychotherapy - The 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 as indicated by EPDS, HAM-D and MADRS.	- Small sample size - The large placebo response and/or spontaneous remissions which may have masked any n-3 beneficial effect
RANDOMIZED CONTROLLED 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 3. 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 between groups in depression scores at 4 months (BDI score)	- Small sample size - Short 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 concentration of DHA in cord blood was measured using 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 3. 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. - The 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; prior 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 3.*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	- To 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 3.*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	To 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 3.*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	To 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 to 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 post partum depression	- Wide range (2 to 9 months) for postnatal Screening - Single self-administered semi-quantitative dietary questionnaire
Otto (2003) Prospective cohort The Netherlands	To 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 3.*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	To 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	To 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 of 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 alcohol 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 , n-6 = Omega-6.

4.1.3 Methodological quality assessment

Table 4 presents the rating scores for each included paper. Overall, methodological quality ratings indicated four strong, nine moderate, and three weak studies. Three of all studies assessed by the Quality Assessment Tool for Quantitative Studies (EPHPP) were given a weak global rating (Hibbeln, 2002; Marangell et al., 2004; Markhus et al., 2013; Otto et al., 2003). The study design and lack of controlling confounders were the reasons of the weak rating for Hibbeln (2002) paper. Concerning Marangell et al. (2004) research study, the open label pilot trial was the reason of its weak rating. For Markhus et al., (2013) the lack of controlling confounders and the high dropout percentage were the reasons of its weak rating.

The most common reason for a study not receiving a ‘strong’ rating was due to a low responder rate from eligible participants and high withdrawal/dropout, which led to otherwise "strong" articles being rated as "moderate" (Browne et al., 2006; da Rocha & Kac, 2012; Doornbos et al., 2006; Freeman et al., 2006; Freeman et al., 2008; Miyake et al., 2006b ; Rees et al., 2008; Strøm et al., 2009). Lack of controlling confounders was the reason for not receiving a rating of ‘strong’ for De Vriese et al. (2003).

Table 4. Methodological quality ratings of n-3 PUFAs for PPD

Author, yr [ref]	Selection bias			Study design		Confounders			Blinding			Data collection			Withdrawals + dropouts			Global rating	Risk of bias
	Q1	Q2	Rating	Design	Rating	Q1	Q2	Rating	Q1	Q2	Rating	Q1	Q2	Rating	Q1	Q2	Rating		
Freeman 2006	4	5	3	1	1	1	1	1	2	2	1	1	1	1	1	2	2	Moderate	Moderate
Freeman 2008	4	5	3	1	1	2	-	1	3	2	2	1	1	1	1	1	1	Moderate	Moderate
Rees 2008	2	3	3	1	1	1	1	1	2	2	1	1	1	1	1	1	1	Moderate	Moderate
Llorent 2003	1	5	1	1	1	2	-	1	2	2	1	1	1	1	1	2	2	Strong	Low
Marangell 2004	2	5	2	7	3	2	-	1	1	1	3	1	1	1	1	1	1	weak	High
Doornbos 2009	4	5	3	1	1	2	-	1	2	2	1	1	1	1	1	2	2	Moderate	Moderate
Makrides 2010	1	2	2	1	1	2	-	1	2	2	1	1	1	1	1	1	1	Strong	Low
Mozurkewich 2013	1	1	1	1	1	1	1	1	2	2	1	1	1	1	1	1	1	Strong	Low
Hibbeln 2002	4	5	3	7	3	3	-	3	-	-	-	1	1	1	-	-	-	weak	High
De Vriese 2003	2	5	2	3	2	3	4	3	3	1	2	1	1	1	2	-	1	Moderate	Moderate
Otto 2003	2	5	2	3	2	2	-	1	1	1	2	1	1	1	2	-	1	Strong	weak
Strom 2009	2	2	2	3	2	1	1	1	3	3	2	3	3	2	1	3	3	Moderate	Moderate
Da Rocha 2012	2	5	2	3	2	1	1	1	3	3	2	1	1	1	1	3	3	Moderate	Moderate
Markhus 2013	2	5	2	3	2	1	3	3	3	3	2	1	1	1	1	3	3	weak	High
Parker 2014	2	5	2	3	2	1	1	1	3	3	2	1	1	1	1	2	2	Strong	weak
Miyake 2005	1	3	3	3	2	1	1	1	3	1	2	1	1	1	1	1	1	Moderate	Moderate
Browne 2009	2	3	3	4	2	1	1	1	3	3	2	1	1	1	1	1	1	Moderate	Moderate

4.2 Data Analysis

4.2.1 Overall Results in Context with Expectations Arising from the Literature

The most relevant features of the 17 studies included in this systematic review and narrative-synthesis are displayed in Table 5. Considerable differences among studies were found for all characteristics examined.

Table 5. Relevant features of the 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 ratio	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

Overall, methodological quality ratings indicated four strong (Llorent 2003, Makrides 2010, Mozurkewich 2013; Otto 2003), nine moderate (Da Rocha et Kac, 2012; De vriese, 2003; Doornbos et al., 2009; Freeman et al., 2006; Freeman et al., 2008; Rees et al., 2008; Strom et al., 2009; Miyake et al., 2005; Browne et al., 2009), and three weak studies (Hibbeln, 2002; Marangell et al., 2004; Markhus et al., 2013).

Six experimental trials studied both EPA and DHA (Browne et al., 2006; De Vriese et al., 2003; Freeman et al., 2006; Freeman et al., 2008;; Makrides et al., 2010; Marangell et al., 2004; Mozurkewich et al., 2013; Rees et al., 2008), two studies examined pure DHA (Llorent et al., 2003; Otto et al., 2003; Strom et al., 2009), one DHA+AA (Doornbos et al., 2009), one study observed EPA, DHA and ALA (De vriese, 2003), two study examined the omega-6/omega-3 ratio (Da Rocha et Kac, 2012, Parker et al., 2014) and two studies examined the total fatty acids (Miyake et al., 2005, Markhus et al., 2013). The dose of EPA+DHA ranged between 0.2 g and 6 g in all of the clinical trials mentioned above.

Most of the observational trials used the EPDS (Browne et al., 2006; da Rocha & Kac, 2012; Markhus et al., 2013; Miyake et al., 2006b; Otto et al., 2003; Strøm et al., 2009), while one used the HAM-D (Hibbeln, 2002), and two trials used the DSM (De vriese et al., 2003; Parker et al., 2014).

Four experimental trials used EPDS and HAM-D (Freeman et al., 2006; Freeman et al., 2008; Marangell et al., 2004; Rees et al., 2008) and two used the BDI (Llorent et al., 2003; Mozurkewich et al., 2013).

Six experimental trials used the intervention of interest during pregnancy and postpartum (Doornbos et al., 2009; Freeman et al., 2008; Makrides et al., 2010; Marangell et al., 2004; Mozurkewich et al., 2013; Rees et al., 2008) and two trials started postpartum (Freeman et al., 2006; Llorent et al., 2003).

In twelve studies, participants were healthy women (Browne et al., 2006; da Rocha & Kac, 2012; De Vriese et al., 2003; Doornbos et al., 2009; Hibbeln, 2002; Llorent et al., 2003; Makrides et al., 2010; Markhus et al., 2013; Miyake et al., 2006b; Otto et al., 2003;

Parker et al., 2014; Strøm et al., 2009), whereas in three studies, women were depressed (Freeman et al., 2006; Freeman et al., 2008; Rees et al., 2008), and had a history of depression in two other studies (Marangell et al., 2004; Mozurkewich et al., 2013).

Four studies used both the FFQ and a blood test to assess the fatty acids (Browne et al., 2006; Doornbos et al., 2009; Markhus et al., 2013; Parker et al., 2014), four used only a blood test (De Vriese et al., 2003; Llorent et al., 2003; Mozurkewich et al., 2013; Rees et al., 2008), four used only the FFQ (Rocha & Kac, 2012; Marangell et al., 2004; Miyake et al., 2006b; Strøm et al., 2009), one assessed fatty acid status in breast milk (Hibbeln, 2002), and one assessed fatty acid status in cord blood (Makrides et al., 2010).

In a randomized, non-placebo controlled dose ranging trial for PPD, women who had recently delivered and had a history of PPD were randomized to EPA/DHA fatty acids combination (ratio 1.5:1, respectively) with varying doses of 0.5 g day⁻¹ (n = 6), 1.4 g day⁻¹ (n = 3) or 2.8 g day⁻¹ (n = 7) of *n*-3 PUFAs for 8 weeks. The pre-treatment EPDS and HAM-D mean scores were 18.1 and 19.1, respectively. Post-treatment mean scores were 9.3 and 10.0. Thus, the percent decreases on the EPDS and HAM-D were 51.5% and 48.8%, respectively. Freeman et al (2006) demonstrated a significant improvement in all groups after an 8-week supplementation; however, this study was limited by its small sample size (n=16) and lack of placebo group.

Rees et al. (2008) conducted a double-blind placebo controlled trial among women with depression (n = 26) in Australia and found that the consumption of fish oil supplements (6 g/day) for a period of six weeks did not result in any benefit compared to the placebo that contained monounsaturated fatty acids (85%), and a small amount of

saturated fat (7%) and PUFAs (8%). This suggests that fish oil supplementation is ineffective for PPD.

Similarly, no differences were reported in the study by Freeman et al. (2008) where 51 participants consumed *n*-3 supplements at levels of 1.9 g/day (EPA:DHA ratio = 1.4:1) or a placebo for 8 weeks and were assessed with the EPDS and HAM-D bi-weekly. This research study also provided supportive psychotherapy to participants in both treatment groups. Although depression scores were significantly lower in both groups ($P < 0.0001$), no differences were reported when results were compared between the intervention and placebo groups. The ability to detect an effect of *n*-3 PUFAs may have been limited by sample size, study length and/or dose. Interestingly, the authors also acknowledged that the benefits of supportive psychotherapy may have limited the ability to detect an effect of *n*-3 PUFAs.

In a placebo-controlled randomized trial (RCT) with 138 breast-feeding women, Llorent et al. (2003) investigated the combination of *n*-3 PUFAs and supportive psychotherapy for the treatment of PPD. Llorent et al. (2003) also failed to detect any benefits of providing 200 mg/day of DHA for 4 months when using either self-rating [EPDS and BDI] or diagnostic measures of depression. They also found that 65% of the participants had at least one outcome measure. However, DHA levels increased by 8% in the DHA group after 4 months (3.40 ± 0.97 mg/dL) compared with a 31% decline in the placebo group (2.27 ± 0.87 mg/dL) in this study.

These findings were aligned with the results observed in an open-label study by Marangell et al. (2004). In this study, euthymic pregnant women with a past history of

postnatal depression were recruited, and supplemented from the mid-third trimester with 3 g day fish oil (1.4 EPA:DHA). Four out of seven women developed depression at 12 weeks post-partum. It is important to note that only seven participants were included in this study, which may have resulted in a lack of association in this investigation Marangell et al. (2004).

In an RCT conducted in the Netherlands, Doornbos et al. (2009) observed 182 pregnant women who were randomly allocated to receive supplements containing either DHA only (220 mg), DHA + AA (220 mg each) or a placebo (soybean oil) from week 16 of pregnancy until 3 months postpartum. The assessment of fatty acid content in plasma samples was performed at 16 and 36 weeks of pregnancy, while depressive symptoms were measured in weeks 16 and 36 of pregnancy, 6 weeks postpartum using the EPDS and within 1 week postpartum using a blues questionnaire. Unfortunately, this study had a high dropout rate and only 119 women completed the study out of 182 initial participants. The intervention groups did not differ in mean EPDS scores or changes in EPDS scores. Furthermore, there was no correlation between red blood cell fatty acids and the fatty acids ratio with EPDS or blues scores.

In an Australian large RCT, Makrides et al. (2010) examined the effect on PPD after providing 800 mg of DHA supplementation from 21 weeks gestation until delivery in 2399 participants. In this study, the authors found no benefits for DHA-rich fish oil in the prevention of depressive symptoms using the EPDS at 6 weeks and 6 months postpartum compared with a placebo.

However, the results observed by Makrides et al. (2010) were in agreement with those of Mozurkewich et al. (2013), who failed to determine an inverse relationship between EPA and DHA fish oil supplementation and PPD. Makrides et al. (2006) provided EPA-rich fish oil (1060 mg EPA plus 274 mg DHA), DHA-rich fish oil (900 mg DHA plus 180 mg EPA), or soy oil placebo. Following assessment of depressive symptoms using the BDI and the Mini-International Neuropsychiatric Interview at baseline, 26-28 weeks, 34-36 weeks of pregnancy and at 6-8 weeks' postpartum, authors found no differences in depression scores between the EPA, DHA and control groups.

In an Ecological analysis, Hibbeln (2002) studied the existing data regarding 14,532 mothers for the prevalence of PPD. Data were measured using the EPDS and was compared with the published data on the DHA, EPA and AA content in mothers' milk and seafood consumption in 23 countries. Hibbeln (2002) reported that higher seafood consumption was inversely correlated with higher seafood intake associated with lower levels of depressive symptoms as measured with the EPDS. In the same report, Hibbeln (2002) stated that higher concentrations of DHA in mothers' milk predicted a lower prevalence of PPD using simple and logarithmic models. The associations were adjusted for known risk factors of PPD, but this data was not available for all countries. The author acknowledged that the correlation between *n*-3 PUFAs and PPD does not support causality.

In a cross-sectional study, De Vriese et al. (2003) and his colleagues highlighted that *n*-3 PUFA levels were significantly lower in women who developed PPD than in women who did not. De Vriese et al. (2003) observed this finding among 10 participants with PPD and 38 non-depressed controls. In this study, blood samples were taken shortly

after delivery, and PPD was diagnosed retrospectively according to the DSM criteria (American Psychiatric Association, 1994) 24 to 40 weeks after delivery. Authors confirmed that the failure to control for potential confounders was a limitation in this study.

Similarly, in a prospective study, Otto et al. (2003) found that depressed women with higher EPDS scores had a significantly lower ratio of DHA to *n*-6 PUFAs among the group. PPD was measured retrospectively using EPDS at 32 weeks after delivery. Improvement in DHA status according to this index was significantly greater for 88 non-depressed versus 24 participants who may be depressed after adjustment for parity, education level, breast feeding, smoking, and alcohol use (OR=0.88; P=0.03). Concentrations of EPA, ALA and total N-3 PUFAs were lower, and concentrations of LA, AA and total N-6 PUFAs were higher among the possibly depressed versus non-depressed participants in each instance.

In another prospective cohort study, Da Rocha and Kac (2012) followed a sample of women at gestational weeks 8–13, 19–21, 26–28; and 36–40. The dietary intake in the first trimester of pregnancy was assessed using a FFQ. The EPDS was applied at least 30 days following delivery for the assessment of PPD. Da Rocha and Kac (2012) stated that a higher risk of PPD in women with an *n*-6 to *n*-3 intake ratio greater than 9 to 1 was observed during the first trimester. Results remained statistically significant even when the analysis was adjusted for the effect of several confounding factors such as age; schooling; pre-pregnancy BMI; lipid consumption; and time elapsed since delivery. However, they did not include the history of depression as a covariate, nor did they screen for depression at the study onset.

The same conclusion was drawn in a published study for Markhus et al. (2013) who indicated a significant relationship between *n*-3 PUFAs and PPD among 72 women from 24 weeks of gestation. FFQ used to assess Fatty acids in pregnancy and a blood test in the 28th gestation week and depression measured using (EPDS) three months after delivery. In this study, it was found that 6.9% of the mothers of the study population (*n*=43) scored ≥ 10 on the EPDS (Markhus et al., 2013). During late pregnancy (week 28), *n*-3 PUFAs index among participants was inversely associated with levels of depressive symptoms postpartum in a simple non-linear regression. Authors stated that *n*-3 PUFAs status in pregnancy could be a possible biological risk factor for PPD.

In a large clinical trial, Miyake et al. (2006b) analyzed data from a large prospective cohort study of pregnant women (*n*=865) and their off spring in Japan. They found no significant associations between intakes of other fatty acids such as EPA or the *n*-6 fatty acids, or with the *n*-3: *n*-6 fatty acid ratio during pregnancy and risk of PPD based on a self-administered Japanese version of the EPDS between 2 and 9 months postpartum. Some of the strengths of this study include the large sample size, the high rate of follow-up (>85%), and careful control for confounding factors.

Miyake et al's (2006b) findings were supported by a recent cohort study of approximately 900 women in late pregnancy by Parker et al. (2014). After assessing depression through EPDS and DSM criteria and measuring of blood fatty acids content including total *n*-3 PUFAs, the ratio of *n*-6 to *n*-3 PUFAs, DHA *n*-3 PUFAs, and the combination of DHA and EPA *n*-3 PUFAs, the authors found an insignificant association between fatty acid intake during pregnancy and PPD when measuring depression using

the EPDS. In contrast, no association were found between fatty acids and PPD when using the DSM criteria.

A large, longitudinal study was done by Strom et al. (2009) who prospectively interviewed a large sample of pregnant women between 12 and 30 weeks of gestation and again when their offspring were between 8 and 18 months of age. In this study, authors found no association between fish intake and hospital admission for PPD, but a higher risk for antidepressant use among postpartum women who consumed low relative to high amounts of fish. Moreover, they found that those women who consumed less than 3 g fish/day were at higher risk for PPD-prescription than those who consumed greater than 30 g/day and those who ate the smallest amount of *n*-3 PUFAs tended more towards PPD prescriptions [odds ratio (OR)=1.6; 95% confidence interval (CI) = 1.26, 2.06] (Strøm et al., 2009). This study had a very large sample size (~50 000), but the rate of participation was low (35%). It should be noted that the primary outcomes included hospital admission for PPD and antidepressant prescription, but this study was not able to capture women with depression who did not seek treatment. Also, based on registry information, PPD admission and prescription during the first year postpartum, was only 0.3 and 1.6%, respectively.

Brown et al (2006) supported the previous null findings of Miyake et al. (2006 b) through a case-control study. Browne et al. (2006) assessed the link between fatty acids and PPD among 80 women (41 diagnosed with depression and 39 controls). Screening for depression was done using the EPDS and BDI diagnosis based on CIDI. This diagnosis tool assesses fatty acids intake using FFQ during pregnancy (Brown et al., 2006). Authors reported that fish consumption during pregnancy was not preventative of

PPD and that the blood status of the *n*-3 PUFAs after birth was not associated with postnatal depression (Brown et al., 2006).

4.2.2 Developing a preliminary synthesis

In the present review studying the role of *n*-3 PUFAs in PPD, the available data is mainly quantitative. Each tool and technique presented in this section was assessed as to whether they would be convenient for the synthesis (Table 2).

4.2.2.1 Tabulating the data

By observing the data available in Table 3, it is clear that the majority of experimental studies demonstrated no relationship between *n*-3 PUFAs and PPD. Critically; only one study (Freeman et al., 2006) reported an improvement in women's depression scores from baseline. Among the observational studies, nearly half also demonstrated no association the two variables of interest (Browne et al., 2006; Miyake et al., 2006b; Parker et al., 2014; Strøm et al., 2009).

4.2.2.2 Textual description

As detailed tables about the characteristics of the studies have already been provided, our textual description won't add over and above the information mentioned in the tables. In order to prevent an unnecessary duplication of details, the use of this technique was postponed until the next phase of the synthesis process (i.e., Section 4.2.3 *Exploring Relationships within and between Studies*).

4.2.2.3 Groupings and clusters

We examined the data extraction tables in order to determine the presence of clusters of characteristics, by which a systematic synthesis could be organized. There

were evident differences between the study designs and the objectives of the studies (treatment/ prevention of PPD). Therefore, the studies were grouped according to the study design and objectives of the trials.

4.2.2.4 Summary of data and vote counting on the efficacy of n-3 PUFAs on PPD

Instead of a common rubric, Tables 6 and 7 included the statistical outcomes on the effects of *n*-3 PUFAs on PPD of experimental and observational studies. For vote counting, we used a (+) sign where the effect of the intervention was positive and a (-) where the effect of the intervention was null. Table 6 describes the effectiveness of *n*-3 PUFAs on PPD. It includes the intervention type, daily dose, the depression scale; baseline and endpoint score for the intervention group (*n*-3 PUFAs group) and the control group. The data is presented in the form of mean and standard deviation (SD) in several studies (Freeman et al., 2006; Freeman et al., 2008, Llorent et al., 2003; Mozurkewich et al., 2013), as medians in the study by Doornbos et al.(2009), and as risk ratio and confidence intervals (OR; CI) in the study by Makrides et al. (2010). In a study about the role of *n*-3 PUFAs in the treatment of perinatal depression, Rees et al. (2008) did not provide any data or measures for the PPD scores, they just showed the total perinatal depression score. Additionally, Marangell et al. (2004) provided his data for the seven participants individually without mentioning the total PPD score for all participants. Therefore; Table 6 lacks the PPD measures for these two trials.

Table 7 presents the results about the efficacy of *n*-3 PUFAs on the PPD based on the depression scores data. For each study, the groups of interest, the depression scale, the type of intervention of interest, the form of the data, and the results are listed. This table clearly shows that the groups of interest were not identical in all the studies. Browne et

al., (2006); De Vriese et al. (2003); Otto et al., (2003) and Parker et al., (2014) compared the group of postpartum depressed women (Group 1) with a control group (Group 2). In contrast, Miyake et al., (2005) and Markhus et al., (2013) compared participants with low n-3 intake (Group 1) with those with high n-3 intake (Group 2). Strom et al. compared the lowest n-3 intake among women with "PPD admission"(admission to psychiatric hospital or psychiatric ward because of depression up to 1 year postpartum) and "PPD prescription" (woman who filled a prescription for an antidepressant) (Group 1) with the highest n-3 intake among women with "PPD admission" and "PPD prescription" (Group 2). Da Rocha & Kac (2012) compared the women with n-6/n-3 ratio intake lower than 9:1 (Group 1) with those with an-6/n-3 ratio intake greater than 9:1 (Group 2). Data is presented in the form of the mean and standard deviation in several studies (Browne et al., 2006; De Vriese et al., 2003; Otto et al., 2003; Parker et al., 2014), odds ratio in two studies (Miyake et & al., 2006b; Strøm et al., 2009), prevalence ratio in one study (Da Rocha & Kac, 2012), and the median in one study (Markhus et al., 2013). No data was available in the ecological study by (Hibbeln, 2002).

Table 6. Summary of Available Data of the Efficacy Studies of *n*-3 PUFAs in PPD in Clinical Trials

Study design	Intervention daily dose (g)	Depression Scale	Baseline depression score		Endpoint depression score (Postpartum)			Vote counting
			Omega-3 group	Placebo group	Omega-3 group	Placebo group		
Freeman 2008 RCT (n=51)	1.9 (EPA + DHA)	EPDS HAM-D (mean, SD)	16.81 ± 4.02 19.50 ± 3.58	15.86 ± 2.93 18.21 ± 2.36	10.81 ± 5.42 11.81 ± 5.17	8.29 ± 5.57 9.71 ± 5.44		-
Doornbos 2009 RCT (n=119)	0.22 DHA DHA + AA	EPDS median (25th,75th percentile)	-	-	4.00 (2.5; 7.0)	5.00 (2.0; 6.5)		-
Llorent 2003 RCT (n=89)	0.2 DHA	BDI (mean, SD)	7.1 ± 4.7	6.5 ± 4.2	5.8 ± 7.1	4.8 ± 5.9		-
Makrides 2010 (RCT) (n=2399)	0.8 DHA 0.1 EPA	EPDS > 12 % (95% CI)	9.61 (8.04-11.49)	10.88(9.19-12.87)	9.74(8.17-11.60)	11.50(9.78-13.51)		-
Mozurkewich 2013 (RCT) (n=118)	DHA-rich : (900 mg DHA and 180 mg EPA) EPA-rich : (1060 mg EPA and 274 DHA)	BDI (mean, SD)	EPA	DHA	Placebo	EPA	DHA	Placebo
			8.41 ± 5.65	7.79 ± 5.29	7.15 ± 5.21	6.6 ± 5.2	5.7 ± 4.8	5.9 ± 6.1
Freeman 2006 Open label (n=16)	0.5, 1.4 or 2.8 (EPA + DHA)	EPDS HRSD (mean)	18.1 19.1	- -	9.3 10.0	- -		+

RCT = Randomized controlled trial; EPA = Eicosapentaenoic acid; DHA = Docosahexaenoic acid; EPDS = Edinburgh Postnatal Depression Scale; HAM-D = Hamilton Rating Scale for Depression; AA = Arachidonic acid. SD = Standard Deviation; CI = Confidence Interval.

Table 7. Summary of Available Data Efficacy Studies of *n*-3 PUFAs in PPD in Observational Trials

Reference	N	Group 1	Group 2	Depression assessment	Intervention of interest	Data form	Outcome group1	Outcome group 2	Vote counting
De Vriese (2003) Cross-sectional study	48	PPD = 10	Control = 38	DSM-interview	Σ of n-3 in (PL) Σ of n-3 in (CE)	Mean (SD)	4.02 ± 0.56 1.19 ± 0.26	5.43 ± 1.46 1.58 ± 0.51	+
Browne (2009) Case-control study	67	PPD = 15	Control = 37	EPDS	Total of n-3	Mean (SD)	5.49 ± 1.63	5.77 ± 1.12	-
Da Rocha (2012) Cohort study	101	n-6/n-3 ratio intake $\leq$ 9:1	n-6/n-3 ratio intake $>$ 9:1	EPDS	n-6/n-3 ratio intake	Prevalence ratio (95% CI)	2.50 (1.21–5.14)	1.00	+
Otto (2003) Cohort study	112	PPD = 24	Control = 88	EPDS	DHA/n-6 DPA (baseline) DHA/n-6 DPA (endpoint)	Mean (SD)	10.97 ± 6.97 2.34 ± 5.56	9.52 ± 5.35 4.86 ± 5.41	+
Markhus (2013) Cohort study	43	Participants with lowest n-3 index = 28	Participants with highest n-3 index = 32	EPDS	n-3 index (EPA-DHA)	Median	5.0	2	+
Miyake (2005) Cohort study	121	Participants with lowest n-3 index = 28	Participants with highest n-3 index = 32	EPDS	n-3 PUFA	Crude OR (95% CI)	1.00	0.85 (0.49–1.47)	-
Parker (2014) Cohort study	773	PPD = 138	Control = 635	EPDS	Total of n-3	Mean (SD)	9.1 ± 1.3	9.4 ± 1.8	-
Strom (2009) Cohort study	112	lowest n-3 intake PPD admission = 13 PPD prescription = 116	Highest n-3 intake PPD admission = 26 PPD prescription = 134	Admission Prescription	n-3 PUFA	Adjusted OR (95% CI)	0.82 (0.42, 1.64) 1.46 (1.12, 1.90)	1.11 (1.12, 1.90) 1.03 (0.81, 1.32)	-

PPD = Postpartum depression; DSM = Diagnostic and Statistical Manual of Mental Disorders; EPDS = Edinburgh Postnatal Depression Scale; PL = Phospholipids; CE = Cholesteryl ester; n-3 = Omega-3; n-6 = Omega-6, DPA = Docosapentaenoic acid; EPA = Eicosapentaenoic acid; DHA = Docosahexaenoic acid. SD = Standard deviation; OR = Odds ration; CI = Confidence Interval

4.2.3 Exploring Relationships within and between Studies

4.2.3 Exploring Relationships within and between Studies

Two types of relationships of interest are described in this section: 1) the relationship between characteristics of individual studies and their reported findings and 2) the relationship between the findings of different studies. We used two main tools and techniques for exploring relationships within and between studies: 1) qualitative case reports and 2) the examination of moderator variables and subgroup analyses.

4.2.3.1 Qualitative case reports/textual descriptions

The textual description is included as Appendix A.

4.2.3.2 Examination of moderator variables and subgroup analyses and exploring the Influence of Heterogeneity

Tables 8 and 9 present the various components that make up the research for each study (objectives, number of participants, period of the intervention/study, mental health status, depression assessment, n-3 assessment and fatty acid type) and the overlap in the components between them in order to help the reviewer investigate whether there were any moderators of effects.

Unfortunately, the heterogeneity of the interventions, the diversity of research designs, and the limited explanations of the study findings and clinical implications were major issues that did not allow consolidation of evidence to develop a clear interpretation and conclusion.

However, the high variability regarding the time period of study and supplementation (prenatal, postnatal or combined prenatal/postnatal) was obvious within the reviewed studies.

Five RCTs found a no association after combining study subjects in the prenatal and the postnatal periods and providing both groups with the same supplementation (Doornbos et al., 2009; Freeman et al., 2008; Makrides et al., 2010; Marangell et al., 2004; Mozurkewich et al., 2013; Rees et al., 2008). Two studies supplemented the women only during the postpartum period, though only one observed an effect (Llorent et al., 2003; Freeman et al., 2006).

It is possible that supplementation that begins in the postpartum period may be too late to meet the metabolic demands and depletion of *n*-3 PUFAs associated with pregnancy. It is also likely that the amount of the supplementation may also play a role. Studies providing only 200–220 mg/day of DHA did not report any difference in depressive scores after treatment (Freeman et al., 2008; Doornbos et al., 2009; Llorent et al., 2003); whereas a study by Freeman et al. (2006) found an effect at higher levels of supplementation (3.4 g/day), but studies by Makrides et al., 2010; Marangell et al., 2004; Mozurkewich et al. 2013; Rees et al., 2008 did not observe an effect at lower levels (≥ 0.8 g/day).

All studies used different formulations of *n*-3 PUFAs. Some investigators did not provide EPA (Llorent et al., 2003), while one added AA in addition to DHA (Doornbos et al., 2009). Currently, the optimal ratio of DHA to EPA for the prevention and treatment of PPD is unknown. Typically, most fish, especially the oily fish type which are recommended for containing high concentration of *n*-3 PUFAs, have a 2:1 ratio for DHA:EPA, whilst commercial fish oils will often have a ratio of 2:3 or lower (Lavie, Milani, Mehra, Ventura, 2009). The only study that had a higher ratio of DHA to EPA did not find any effect (Makrides et al., 2010).

Another reason for heterogeneity in the studies was that there were different measures of the predictors and outcomes. Concerning the predictors, some studies assessed fish intake and/or

n-3 PUFAs consumption. Nine (Browne et al., 2009; De Vriese et al., 2003; Doornbos et al., 2009; Llorent et al., 2003; Makrides et al., 2010, Markhus et al., 2013; Mozurkewich et al., 2013; Parker et al., 2014 and Rees et al., 2008) out of the 17 studies assessed blood fatty acid levels. Only four of them assessed in the postpartum period (Browne et al., 2009; De Vriese et al., 2003; Llorent et al., 2003; Otto et al., 2003).

Some of the RCTs and pilot trials that were reviewed, had a very small sample size ranging from 7-26 participants (Freeman et al., 2006; Rees et al., 2008; Marangell et al., 2004). The trials with the larger sample sizes, and hence more power to find an effect, also tended to supplement with smaller amounts of *n*-3 PUFAs (200–220 mg/day of DHA) and had null results (Doornbos et al., 2009 and Llorent et al., 2003). A large size study with 2399 participants by Makrides et al. (2010), randomized for a higher ratio of DHA to EPA found no effects of *n*-3 PUFAs on the PPD. The study by Freeman et al. (2008) contained only 59 subjects who were supplemented with higher levels of *n*-3 PUFAs (up to 2.7 g/ day) and was the only study that found a decreased risk for depression in the supplemented group.

In the observational studies, most of the studies that had very small sample sizes e.g. (48 by Devries et al., 2003; 106 by Da Rocha et al., 2012; 128 by Markhus et al., 2013 and 112 by Otto et al., 2003) had positive results which contrast the results that came from the high sample sizes studies e.g. (1232 by Parker et al., 2014 and 54202 by Strom et al., 2009) and (865 by Miyake et al., 2005). Although, the ecological study by Hibbeln (2002) with 14532 subjects find an effect of the *n*-3 PUFAs on the PPD and the small size case-control study with 80 participants by Browne et al., (2009) came up with no effect.

While most studies used the EPDS (Browne et al., 2006; da Rocha & Kac, 2012; Freeman et al., 2006; Freeman et al., 2008; Marangell et al., 2004; Markhus et al., 2013; Miyake, et al., 2006b; Otto et al., 2003; Rees et al., 2008; Strøm et al., 2009), different cut-off points have been used. For example, a score of 10 or higher on the EPDS was associated with symptoms of depression in research carried out by Otto et al. (2003) and Markhus et al. (2013) In contrast, Miyake et al. (2006b) used a threshold score of 8/9 to define depression in Japanese women.

In the observational studies, most of the studies had very small sample sizes ranging from 48-128 participants (48 by Devries et al., 2003; 106 by Da Rocha et al., 2012; 128 by Markhus et al., 2013 and 112 by Otto et al., 2003) and had positive results in comparison to the null results observed in studies with large sample sizes ranging from 865-54202 participants (1232 by Parker et al., 2014 and 54202 by Strom et al., 2009) and (865 by Miyake et al., 2005). However, the large ecological study by Hibbeln (2002) with 14532 subjects did observe an effect of the *n*-3 PUFAs on PPD, while the small case-control study with 80 participants by Browne et al. (2009) observed no effect.

While most studies used the EPDS (Browne et al.,2006; da Rocha & Kac, 2012; Freeman et al., 2006; Freeman et al., 2008; Marangell et al., 2004; Markhus et al., 2013; Miyake et al., 2006b; Otto et al., 2003; Rees et al., 2008; Strøm et al., 2009), different cut-off points have been used. For example, a score of 10 or higher on the EPDS was associated with symptoms of depression in research carried out by Otto et al. (2003) and Markhus et al. (2013) In contrast, Miyake et al. (2006b) used a threshold score of 8/9 to define depression in Japanese women.

Table 8. Omega-3 and PPD: Potential moderator variables (variables which can be expected to moderate the main effects being examined by the review) - experimental trials.

Reference	Subjects	Period of the study		Objectives				Mental health status			Depression assessment					n-3 assessment				Fatty acid type							Vote counting
		Pregnancy	Postpartum	Treatment of PPD	Prevention of PPD	n-3 and the prevalence risk of PPD	Relation between n-3 and PPD	Depressed	History of depression	Healthy	EPDS	HAMD	DSM	BDI	Other	Blood test	FFQ	Cord blood	Breast milk	ALA	EPA-DHA	AA	DHA	n-6	n-6/n-3 ratio	Total fatty acids	
Freeman (2008) RCT	51	√	√	√				√			√	√			√ ¹						√						-
Rees (2008) RCT	26	√	√	√				√			√	√			√ ²	√					√						-
Doornbos (2009) RCT	119	√	√		√					√	√					√	√				√	√					-
Llorent (2003) RCT	89		√		√					√			√			√						√					-
Makrides (2010) RCT	2399	√	√		√					√	√							√			√						-
Mozurkewich (2013) RCT	126	√	√		√				√				√	√ ³		√					√						-
Marangell (2004) Open label pilot trial	7	√	√		√				√		√	√					√				√						-
Freeman (2006) Open Label	16		√	√				√			√	√									√						+

PPD = Postpartum depression; EPDS = Edinburgh Postnatal Depression Scale; HAM-D = Hamilton Rating Scale for Depression; DSM = Diagnostic and Statistical Manual of Mental Disorders ; BDI = Beck Depression Inventory; n-3 = Omega-3; n-6 = Omega-6; ALA = alpha-linolenic acid; EPA = Eicosapentaenoic acid; DHA = Docosahexaenoic acid; AA = Arachidonic acid; FFQ = Food frequency questionnaire.¹CGI = Clinical Global Impression; ²MADRS = Montgomery-Asberg Depression Rating Scale; ³MINI = Mini International Neuropsychiatric Interview.

Table 9. Omega-3 and PPD: Potential moderator variables (variables which can be expected to moderate the main effects being examined by the review) - observational studies.

Reference	Subjects	Period of the study		Objectives				Mental health status			Depression assessment					n-3 assessment				Fatty acid type							Vote counting
		Pregnancy	Postpartum	Treatment of PPD	Prevention of PPD	n-3 and the prevalence risk of PPD	Relation between n-3 and PPD	Depressed	History of depression	Healthy	EPDS	HAMD	DSM	BDI	Other	Blood test	FFQ	Cord blood	Breast milk	ALA	EPA-DHA	AA	DHA	n-6	n-6/n-3 ratio	Total fatty acids	
Hibblen (2002) Ecological study	14532		√				√			√		√							√	√		√	√	√			+
De Vriese (2003) Cross-sectional	48	√	√				√			√			√			√				√	√						+
Browne (2009) Case-control	80	√	√				√			√	√					√	√			√							-
Da Rocha (2012) Cohort study	106	√	√			√				√	√						√							√			+
Markhus (2013) Cohort study	128	√	√				√			√	√					√	√								√		+
Miyake (2005) Cohort study	865	√	√			√				√	√						√								√		-
Otto (2003) Cohort study	112	√	√			√				√	√					√						√					+
Parker (2014) Cohort study	895	√	√				√			√	√		√			√	√							√			-
Strom (2009) Cohort study	54202	√	√				√			√				√ ¹		√						√					-

PPD = Postpartum depression; EPDS = Edinburgh Postnatal Depression Scale; HAM-D = Hamilton Rating Scale for Depression; DSM = Diagnostic and Statistical Manual of Mental Disorders; BDI = Beck Depression Inventory; n-3 = Omega-3; n-6 = Omega-6; ALA = alpha-linolenic acid ; EPA = Eicosapentaenoic acid; DHA = Docosahexaenoic acid; AA = Arachidonic acid; FFQ = Food frequency questionnaire. ¹PPD admission (admission to psychiatric hospital or psychiatric) PPD prescription (a woman who filled a prescription for an antidepressant)

4.2.4 Assessing the Robustness of the Synthesis Product

Table 10, below, presents the weighting of studies by quality, according to four EPPI criteria used to appraise each study. The first three criteria contribute to the assessment of study weight (EPPI, 2010): A) the study's methodological soundness, B) the appropriateness of the study design to answering the review question, C) the study relevance. The fourth criterion involves an assessment of the overall weight of evidence.

Almost all papers received the same overall rating (Dimension D) as the quality assessment scores (Dimension A). Only one paper differed in score (Markhus et al., 2013). This is because the high score this study has taken for the relevance of the focus of study to the review question (Dimension C) led to a medium overall score.

Finally, there was a graded relationship between the quality rating and the results that found no association between *n*-3 PUFAs and PPD. Among the weak studies, 50% were null; while among those with moderate quality, 50% were also null. However, among strong studies, all results found no association between *n*-3 PUFAs and PPD.

Table 10. Weighting of Studies by Quality, According to Four Criteria of the EPPI approach.

Study	Dimension A	Dimension B	Dimension C	Dimension D
Freeman (2008)	Medium	High	Medium	Medium
Rees (2008)	Medium	High	Medium	Medium
Doornbos (2009)	Medium	High	Medium	Medium
Llorent (2003)	High	High	High	High
Makrides (2010)	High	High	High	High
Mozurkewich (2013)	High	High	Moderate	High
Freeman (2006)	Medium	Low	High	Medium
Marangell (2004)	Low	Low	Medium	Low
Hibbeln (2002)	Low	Low	High	Low
De Vriese (2003)	Medium	Medium	High	Medium
Browne (2009)	Medium	Medium	High	Medium
Da Rocha (2012)	Medium	Medium	High	Medium
Markhus (2013)	Low	Medium	High	Medium
Miyake (2005)	Medium	Medium	High	Medium
Otto (2003)	Medium	Medium	High	Medium
Parker (2014)	High	Medium	High	High
Strom (2009)	Medium	Medium	High	Medium

Dimension A = The study's methodological soundness; Dimension B = The appropriateness of the study design to answering the review question; Dimension C = The study relevance; and Dimension D = An assessment of the overall weight of evidence which the study provides

CHAPTER 5: DISCUSSION

5.1 Pertinent Findings and limitations of the included studies

The aim of this systematic review and narrative synthesis was to examine the overall clinical and observational studies regarding the role of *n*-3 PUFAs in the treatment and prevention of PPD, with a secondary aim to provide some recommendation for future research.

Many limitations complicated the interpretation of the findings. First, the small sample size, as only 17 studies met the inclusion criteria. Second, clinical and methodological heterogeneity among included studies. 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.

Third, most studies measured depression using the EPDS, 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). Fourth, the analyses that have been previously conducted focused on the effects of *n*-3 PUFAs supplementation on depressive symptoms; however, information regarding the pathophysiological nature of depression occurring in patients was often lacking.

Fifth, none of the studies reviewed assessed brain or synaptic DHA content, while few assessed plasma DHA levels (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). 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). Another study stated that plasma levels of fatty acids are not a perfect measure of dietary intake and are also an imperfect predictor of fatty acid levels in brain tissue (Shapiro et al., 2012). 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 more 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; Martins, Bentsen & Puri, 2012). The findings regarding the different efficacy of EPA compared to DHA and EPA-DHA combinations were confirmed by Grosso et al., (2014b) meta-analysis when he grouped the 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 *n*-3 PUFAs is challenging for proper interpretation since DHA is a major structural constituent of neuronal membranes (Grosso et al., 2014b).

Although heterogeneity among included studies makes it difficult to synthesize the findings, however, on the basis of our findings the overall analysis of these studies

suggested on 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) came with promising results.

As we stated previously, research indicated that randomized controlled trials are considered as the most rigorous methods to explore the cause-effect relationship between an intervention and an outcome (Kendall, 2003). All randomized controlled trials included in this review (Doornbos et al., 2009; Freeman et al., 2008; Llorent et al., 2003; Makrides et al., 2010; Mozurkewich et al., 2013; Rees, Austin, & Parker, 2008) reported no association of supplementation with *n*-3 PUFAs and/or consumption of fish and a decreased risk for maternal PPD.

The lack of associations in the observational studies may be a result of different sample size, under-reporting of fatty acid intake, lack of control of potential variables. It was also clear that the cohort research studies and the cross-sectional study with positive findings suffered from small sample sizes (Da Rocha & Kac, 2012; De Vriese et al., 2003; Markhus et al. 2006b; Otto et al. 2003) (106, 48, 128 and 112 respectively), whereas large sample sizes were seen in those with null findings (Miyake et al., 2006b; Parker et al. 2014; Strom et al. 2009) (865, 895 and 94202 respectively). In other words, in terms of raw sample size, observations showing no associations were comparatively including large number of participants. The only paper that came out with positive findings, despite having a large sample size was that of Hibbeln (2002); *n*=14532. But this paper is weak in terms of its internal validity and quality. Also the author

acknowledged that his findings do not prove that higher *n*-3 PUFAs status can cause lower prevalence rates of PPD.

5.2 In Context with Literature

In our review, the overwhelming majority of the studies found that PUFA had no association with PPD evaluations versus only few ones observed a beneficial effect of *n*-3 PUFA supplementation on depressive symptoms. It was not surprising to discover that this structured systematic review and narrative synthesis provided a clear and more transparent conclusion compared to previous articles and literature reviews that assessed the efficacy of *n*-3 PUFAs on maternal mental health in terms of perinatal depression PPD and found mixed results (Borja-Hart & Marino, 2010; Freeman, 2006; Jans, Giltay, & Willem Van der Does, 2010; Levant, 2010; Ramakrishnan, 2011; Wojcicki & Heyman, 2011).

A review of literature was done by Freeman (2006) on the role of *n*-3 PUFAs on perinatal depression indicated, unsurprisingly, that there are inconsistent findings within this field. Another literature review by Borja-Hart and Marino (2010) found mixed results in seven studies of *n*-3 PUFAs for the prevention or treatment of perinatal depression.

A systematic review has been done by Wojcicki and Heyman (2011) on the possible link between *n*-3 PUFAs supplementation during the perinatal period and the risk of maternal perinatal depression. Out of ten articles, six found no association, two found mixed results, and two found a positive association between *n*-3 PUFAs and reduced incidence of maternal perinatal depression.

Lastly, a meta-analysis was conducted by Jans et al. (2010) to assess the efficacy of *n*-3 PUFAs supplementation for perinatal depression, but couldn't answer whether EPA and DHA administration is effective in the prevention or treatment of perinatal depression. In conclusion, although the present systematic review and narrative synthesis is in line with previous literature expectations in terms of high heterogeneity that makes a synthesis problematic, but it succeeded to reduce the ambiguity in results presented in the relevant literature and articles reviews. This review came with an evident conclusion that no association between *n*-3 PUFAs intake and PPD prevention and treatment.

5.4 Implication for Future Research and Recommendation for consumption of *n*-3 PUFAs

This systematic review and narrative synthesis failed to find a significant positive association between *n*-3 PUFAs intake and PPD. It is important in the future to better identify 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. Possible studies combined with imaging of the structural changes in the brain over years are warranted to help better understand the mechanism of *n*-3 PUFAs.

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). Also a sufficient intake of *n*-3 PUFAs throughout breastfeeding may improve the infant's health, such as attention and cognitive functions (Helland et al., 2003; Jensen et al., 2010; Lassek & Gaulin, 2013), decrease in

allergies, respiratory illness, and eczema (Hageman et al., 2012; Oddy et al., 2006; Wijga et al., 2006), improved immune factors and responses (Dunstan et al., 2004; Furuholm et al., 2011; Urwin et al., 2013).

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). Furthermore the American Dietetic Association, Dieticians of Canada, The European Commission (EU), and the International Society for the Study of Fatty Acids and Lipids all recommend consuming at least 500 mg of *n*-3 PUFAs or 200 mg of DHA per day (Jia et al., 2015).

5.5 Reflecting Critically on the Synthesis Process

Methodology of the Synthesis Used

There were some limitations to the approach taken in this systematic review and narrative synthesis. There have been few literature reviews on this topic, but this is the first systematic review on the role of *n*-3 PUFAs in the prevention and treatment of PPD.

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.

Another limitation to this review is participation of a single reviewer. In the future, it would be beneficial to have another researcher who will conduct a search to see if any additional studies should be included, as well as evaluate the already included studies for quality. Current studies can be discussed among the researchers to achieve an agreement in relation to the scores for quality assessment and strength of evidence.

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.

Furthermore, in the case of this particular synthesis, only quantitative studies were included. Subsequently, there was high clinical and methodological heterogeneity. This prohibited the use of several techniques (although it is unlikely that any synthesis would have to use of all the tools and techniques mentioned in the guideline).

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.

5.6 Conclusions

In conclusion, based upon the findings of this review, *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.

EXECUTIVE SUMMARY

- Prevalence of PPD occurs in approximately 10–15% of women after birth and has detrimental negative consequences for both the mother and the offspring. A total of 17 studies were included in this systematic review and narrative synthesis (8 experimental and 9 observational studies);
- Although there is some evidence to suggest that *n*-3 PUFA intake is associated with reduced PPD, these results are limited to four observational studies; whereas, with the exception of one open label pilot trial, results from experimental trials did not find any association;
- Overall, 11 studies of the 17 reviewed papers found no association between *n*-3 PUFAs and PPD. The other 6 studies found a positive association between the two variables of interest and included: one ecological study (that was rated weak on the quality assessment), one open label pilot trial, one cross-sectional study and three cohort studies using small sample sizes compared to large cohort studies that found no association;
- More evidence is required to confirm the specific biological mechanisms underlying PPD with an aim to reduce the health costs and negative impact of PPD.

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APPENDIX

Appendix A: Textual Description

Experimental studies

RCT's - Treatment intervention

Freeman (2008)

Objectives

To assess the efficacy of *n*-3 PUFAs as a treatment for antenatal and postpartum depression in addition to supportive psychotherapy in an 8 week double blinded randomized placebo-controlled study.

Participants

Pregnant (12-32 weeks of gestation) and postpartum (0-6 months postpartum) women aged between 18-45 years with a current episode of major depression (had a score of 9 or higher on the EPDS). Patients receiving any antidepressant or anticoagulation, or has a history of psychosis or bipolar disorder were excluded from the study.

Description of the intervention and outcome measurement

28 participants in the treatment group received 1.9 g of EPA and DHA (1.1 g and 8.8 g respectively) in a total of four capsules per day and 23 participants in the control group received corn oil as a placebo. Their depressive state was assessed by using the HAM-D and EPDS scales and CGI at baseline and every two weeks for eight weeks.

Results and comparison

The mean and SD baseline of HAM-D and EPDS scores for the treatment group were 18.86 ± 3.43 and 17.11 ± 3.75 respectively. The endpoint HAM-D and EPDS scores for the same group were 12.82 ± 5.48 and 10.96 ± 5.92 respectively.

Concerning the placebo group, The mean and SD baseline of HAM-D and EPDS scores were 17.43 ± 2.19 and 15.83 ± 3.63 respectively. The endpoint HAM-D and EPDS scores for the same group were 9.91 ± 4.74 and 8.09 ± 4.96 respectively. As a result, there was a significant decreases in HAM-D and EPDS scores from baseline in both omega-3 fatty acid and control groups. But there was no significant difference on primary outcome measures of depression between omega-3 fatty acids and placebo in an 8-week study for women with perinatal depression.

Limitations

Author acknowledged that the small sample size, study length, or dose and the supportive psychotherapy may have limited the ability to detect an effect of *n*-3 PUFAs.

Rees (2008)

Objectives

To investigate whether *n*-3 PUFAs treatment is superior to placebo for the perinatal depression in six weeks randomized double-blind placebo-controlled trial.

Participants

Pregnant (in the third trimester) and postpartum women (up to six months postnatal) aged more than 21 years old, with a current episode of depression.

Patient with a psychiatric disorder, unstable medical condition, receiving antidepressant, psychological therapy or anticoagulant were excluded. A total of 26 participants were recruited, 13 pregnant women and 13 postpartum.

Description of the intervention and outcome measurement

Participants were randomized to receive either 6 g/day fish oil or placebo (sunola oil) in divided doses, every 2 weeks. The fish oil capsules contained (27.3% DHA, 6.9% EPA total *n*-3 PUFAs = 35.6% and 3.3% omega-6 fatty acids), the remainder of the capsule content composed of monounsaturated fats and a small amount of saturated fat.

HAM-D, EPDS and MADRS were used to assess the depression state of the participants from baseline until six months postpartum. At baseline assessment the clinical interview and CIDI structured interview were performed. Subjects were also required to score > 13 on the EPDS and either > 14 on the 17- item HAM-D or > 25 on the MADRS.

Results and comparison

There were no statistically significant differences between the total baseline depression scores during pregnancy and postpartum across those receiving fish oil or placebo (EPDS 17.3 vs 16.5; HDRS 19.7 vs 19.0; MADRS 30.2 vs 29.3, respectively). Mean change scores from baseline to the 6 week assessment quantified that improvement was significant ($p < 0.001$) across each of the depression measures and for both those receiving fish oil or placebo (EPDS 8.8 vs 7.5; HDRS 11.8 vs 9.3; MADRS 16.8 vs 14.1, respectively). When antenatal and postnatal groups were separated, no statistically significant differences were identified.

Limitations

Authors cited that the small sample size and the spontaneous remissions which may have masked the possible benefits of omega-3 were limitations in the study.

RCT's - Preventative intervention

Doornbos (2009)

Objectives

To evaluate the relationship between n-3 PUFA intake and depression in healthy pregnant women from week 16 of pregnancy until postpartum month 3.

Participants

Healthy pregnant women

Description of the intervention and outcome measurement

Participants received either DHA (220 mg), DHA + AA (220 mg each) or placebo daily from enrolment (weeks 14–20 of pregnancy) until 3 months after delivery. Depression was assessed with the EPDS in weeks 16 and 36 of pregnancy and 6 weeks post-partum. Erythrocyte fatty acid analysis was performed at enrolment and in week 36 of pregnancy.

Results and comparison

A total of 182 women were included in the trial; 111 participants completed all measurements. N-3 PUFA levels in erythrocytes were significantly higher in the supplemented groups. EPDS scores of 12 or higher were found in eight women (6.7 %) in week 36 of pregnancy and in seven women (5.9 %) at 6 weeks post-partum. Doornbos et al. (2009) reported median EPDS and delta EPDS scores, as the data were skewed.

In conclusion, no effects of n-3 PUFA supplementation on the incidence or severity of PPD relative to placebo were found in this study.

Limitations

Limitations mentioned by the authors were the small sample size, caused by high drop-out and the EPDS as a is a screening tool and not as an instrument to assess effects of interventions.

Llorent (2003)

Objectives

To determine the effect of DHA supplementation on plasma phospholipids DHA content and indices of depression for women who breast-feed.

Participants

Healthy pregnant women aged between 18-42 years old who planned to breast-feed their infants exclusively for at least 4 months.

Description of the intervention and outcome measurement

Subjects received either 200 mg/d of DHA or placebo for 4 months, starting within a week of delivery. Plasma fatty acids were measured shortly before delivery and 4 months after delivery. The BDI was completed at baseline, 3 weeks, 2 months and 4 months after delivery.

Results and comparison

Of the 138 women enrolled, eighty-nine completed all measurements. Plasma DHA levels of the DHA group and placebo at baseline were (3.15 ± 0.78) and (3.31 ± 0.70) (mg/dL of total fatty acids) respectively. After 4 months the DHA levels in plasma were 8% higher in the intervention group (3.40 ± 0.97 mg/dL), than in the placebo group (2.27 ± 0.87 mg/dL) which was 31 % lower.

However, there was no difference between groups in depression scores also this study failed to report a positive effect of DHA on PPD.

Limitations

The low amount of DHA in synaptic membranes which does not influence mood must also be considered.

Makrides (2010)

Objectives

To assess if DHA supplement during the last half of pregnancy can reduce the risk of depressed maternal mood during the postpartum period and improve early cognitive development in the offspring in a randomized controlled trial.

Participants

2399 pregnant women under 21 weeks of gestation with a mean age 28.9 years old enrolled in the study. Women were excluded if they were already taking prenatal DHA supplements, if their fetus had a known major abnormality, if were taking anticoagulant therapy and/or had a documented history of drug or alcohol abuse.

Description of the intervention and outcome measurement

96.7% of the participants who completed the trial were randomly assigned to consume either three 500- mg/d capsules of DHA-rich fish oil concentrate (providing 800 mg/d of DHA and 100 mg/d of EPA) in the treatment group or three 500-mg/d vegetable oil capsules (rapeseed, sunflower, and palm in equal proportions) in the control group.

Their depressive state was assessed by using a self-administered EPDS scale at 6 weeks and 6 months postpartum. Women with EPDA score of more than 12 was documented with a high level of depressive symptoms.

Results and comparison

The percentage of women with high levels of depressive symptoms during the first 6 months postpartum did not differ between the DHA and control groups (9.67% vs 11.19%; adjusted relative risk, 0.85; 95% confidence interval [CI], 0.70-1.02; P=.09). To conclude, the use of DHA-rich fish oil capsules compared with vegetable oil capsules during pregnancy did not result in lower levels of PPD in mothers.

Limitations

Lack of verification of high EPDS scores with a clinical diagnosis of depression, the lack of assessment of omega-3 dietary intake and the choice of supplements (DHA/EPA ratio) were the limitations highlighted by the authors

Mozurkewich (2013)

Objectives

Mozurkewich et al. tested in a double-blind, randomized controlled trial the effects of EPA- and DHA-rich fish oils on prevention of depressive symptoms among pregnant women at an increased risk of depression.

Participants

Pregnant women (>12-32 weeks of pregnancy), aged more than 18 years old and at risk for depression (EPDS score 9-19 or a history of depression) in early pregnancy. Patient with a psychiatric disorder, receiving antidepressant, psychological therapy, anticoagulant or taking *n*-3 PUFAs supplements were excluded.

Description of the intervention and outcome measurement

126 subjects who were enrolled in the study were randomly assigned to receive EPA-rich fish oil (1060 mg EPA plus 274 mg DHA), DHA-rich fish oil (900 mg DHA plus 180 mg EPA), or soy oil placebo.

Depression status was tested using BDI and Mini-International Neuropsychiatric Interview at baseline, 26-28 weeks, 34-36 weeks, and at 6-8 weeks' postpartum.

Results and comparison

One hundred and eighteen women completed the trial. There were no differences between the EPA, DHA and control groups in the mean BDI scores at baseline (8.41 vs 7.79 vs 7.15) and at endpoint (6.6 vs 5.7 vs 5.9 respectively). As a result EPA-rich fish oil and DHA-rich fish oil supplementation did not prevent depressive symptoms during pregnancy or postpartum.

Limitations

Authors acknowledged that the lack of verification of high depression scores of self-reporting scales with a clinical diagnosis of depression, the lack of adherence in 14% of participants and the small amount of fish oil existed in the placebo capsules for masking as well as a small amount of alpha linolenic acid may be converted to DHA and EPA, thus possibly serving as an active placebo were the weakness of the study.

Pilots Trials

Freeman (2006) - Treatment Intervention

Objectives

To assess the role of *n*-3 PUFAs in the treatment of PPD in 8 weeks randomized dose-ranging pilot trial.

Participants

Women aged between 15–45 years who had a major depressive episode within 1 month of delivery and who had a score of 15 or higher on the HAM-D or 9 or higher on the EPDS. Patients receiving antidepressant medication, had Psychosis symptoms or a history of mania were excluded from the study.

Description of the intervention and outcome measurement

Women randomly received a combination of EPA and DHA (ratio 1.5:1) at total concentrations of 0.5 (six participants), 1.4 (three participants), or 2.8 g/day (seven participants). Their depressive state was assessed by using the HAM-D and EPDS scales at baseline and at weeks 1, 2, 4, 6, and 8.

Results and comparison

Sixteen women (mean age 31 years, 69% Caucasian, 69% had past histories of major depressive episodes) were enrolled. The Mean baseline HAM-D and EPDS scores were 19.1 and 18.1, respectively (SD unavailable) and the Mean HAM-D and EPDS scores after treatment were 10.1 and 9.3, respectively. In comparison to the baseline scores, the post-treatment scores decreased but the changes were not statistically significant.

Limitations

The authors acknowledged the small sample size and the lack of placebo group as major limitations of the study.

Marangell (2004) - Preventative Intervention

Objectives

To assess the role of *n*-3 PUFAs in the prevention of post-partum depression in a preliminary, small, open-label pilot.

Participants

Pregnant women ≥ 18 years of age with a past history of a postpartum depressive episode were included in the study. Candidates were excluded if they were depressed at the time of clinical interview, if they were taking psychotropic medications, if they had a history of non-response to two or more antidepressants and/or had serious illnesses.

Description of the intervention and outcome measurement

Subjects were assigned to take 10 study capsules with a total dose 2960 mg per day (173 mg of EPA and 123 mg of DHA).

Depression was measured using HAM-D and EPDS at baseline (34-36 weeks of pregnancy), 2 weeks after the baseline, Week 2, 4, 8 and 12 postpartum.

Results and comparison

This study failed to show positive results for the use of *n*-3 PUFAs monotherapy starting at 34 to 36 weeks gestation for the prevention of PPD in patients with a prior PPD history.

Limitations

Authors highlighted the small sample size, lack of control group unknown optimal dose of *n*-3 PUFAs in the treatment or prophylaxis of major depression as major limitation in this trial.

Observational studies

Ecological studies

Hibbeln (2002)

Objectives

To assess if DHA status in mothers' milk and seafood consumption would predict prevalence rates of PPD across countries in a detailed cross sectional, ecological analysis.

Inclusion criteria

Studies reported the prevalence rates of major postpartum depressive symptoms, used the EPDS instrument to assess PPD, were published as primary data and reported appropriate methodology regarding sampling and data analysis.

Description of the study

Existing data on the prevalence of PPD, measured using the EPDS, were compared with published data on the DHA, EPA and AA content in mothers' milk and to seafood consumption in 23 countries.

Confounders

While this study attempted to control for confounding, such information was not uniformly available, precluding the use of multivariable analyses.

In this study, the risk factors that predicted the prevalence rates of PPD in simple correlations included; low socioeconomic status, young maternal age, the percentage of women without partners, percentage with a secondary education.

Results

n = 14 532 mothers. PPD was inversely correlated with DHA concentrations in breast milk ($r = -0.84$, $P < 0.0001$) and fish consumption ($r = -0.81$, $P < 0.0001$) across 16 and 22 countries, respectively but AA and EPA content of mothers' milk were unrelated to PPD prevalence.

Limitations

Data concerning the risk factors of PPD were not available for all countries which prevent the authors to make causal inferences and the exclusion of countries with extreme values on these confounders resulted in weakened correlations.

Cross sectional studies

De Vriese (2003)

Objectives

To determine whether the postpartum fatty acid profile differs in women who develop PPD compared to controls.

Participants

Healthy pregnant women singleton pregnancies were included in this study. Participants with psychiatric disorder other than depression, chronic disease, or who received major psychotropic medication use were not considered for the study.

Description the study

A maternal blood sample was obtained shortly after delivery for the n-3 fatty acid measurement.

PPD was diagnosed retrospectively according to DSM criteria (American Psychiatric Association, 1994) 24 to 40 weeks after delivery. Of the 48 participants, 10 pregnant women developed PPD and 38 pregnant women did not develop PPD.

Results and comparison

Lower concentrations of DHA and total N -3 PUFAs and a higher ratio of N -6 to N-3 PUFAs were observed among ten participants with PPD as compared to 38 non-depressed controls; each difference was statistically significant.

Limitations

Failure to control for potential confounders is a limitation in this study.

Case-control study

Browne (2006)

Objective

To determine whether or not prenatal fish consumption and omega-3 status after birth were associated with postnatal depression.

Participants

Eighty first-time mothers were enrolled in this study.

Description if the study

Forty one respondents with scores of ten or above on the BDI-II, and/or nine or above on the EPDS were included as cases and they were interviewed via telephone using the depression module from the CIDI. Thirty nine non-depressed women were included in

the control group. Participants in the case group who met and don't the CIDC criteria were categorized in a "diagnosis of depression group" and "screened high group" respectively.

Fish consumption was measured during pregnancy using a FFQ with frequency categories ranging from less than once per month to once or more times per day. A blood sample was provided within 6 months postpartum to determine the omega-3 status. PPD was assessed using CIDC.

Confounders

The alcohol consumption, breastfeeding, dietary supplement use, education qualification, ethnicity, fish consumption, household income and smoking status (before and after birth) differed across groups were analysed to control differences across groups. Only household income and current breastfeeding were significantly different and they were entered as covariates in logistic regression analyses. Results of these analyses found no evidence of an association between any of those variables and depression status (diagnosis and screened depressed groups).

Results and comparison

There was no association between prenatal fish consumption and PPD ($P > 0.29$). There was also no association between post-natal omega-3 status and PPD even after adjusting for household income and current breastfeeding.

Limitations

Prenatal fish consumption was measured using only a FFQ and no regular consumption of oily fish (rich in omega-3s) among participants were the limitations highlighted by the authors.

Cohort studies

Da Rocha (2012)

Objectives

To assess whether an unbalanced dietary intake of omega-6/omega-3 ratio >9:1 has possible effect in the prevalence of PPD.

Participants

Pregnant woman

Description of the study

Of the 255 pregnant women who enrolled the cohort 41.6% (106 women) completed the study. The dietary intake in the first trimester of pregnancy was assessed by means of a FFQ. EPDS was applied at least 30 days following delivery for the assessment of PPD.

Confounders

The following variables were adjusted as potential confounders: age, schooling, time elapsed since delivery and lipid consumption

Results and comparison

The prevalence of PPD observed in 26.4% of participants (n = 28; CI 95%: 18.0–34.8) and the greater prevalence ratio of PPD were observed in women with food intake in the first trimester for the omega-6/omega-3 ratio >9 : 1 (PR= 2.73; CI 95%: 1.44–5.18). The prevalence of PPD was 2.5 greater among Brazilian women whose dietary ration of omega-6/ omega-3 in the first trimester was greater than 9:1, as they would be expected to have a low omega-3 index in the 28th gestation week. The results remained statistically significant even when the analysis were adjusted for the effect of several confounding

factors such as age, schooling, pre-pregnancy BMI, lipid consumption and time elapsed since delivery.

Limitations

Authors acknowledged that the inclusion of women with history of depression, the lack of follow up and lack of dietary data were considered as limitation in this study.

Markhus (2013)

Objectives

To assess if the low *n*-3 PUFAs status in pregnancy could be a risk factor for PPD using data of a community based prospective cohort.

Participants

Pregnant women in their 24 weeks of gestation within the period November 2009 - June 2011.

Description of the study

The fatty acid status was assessed through an the electronic questionnaire (seafood intake, demography, socioeconomically status, psychological status) in pregnancy and a blood test in the 28th gestation week. Participants were screened for PPD using the Norwegian version of the EPDS three months after delivery.

Results

From the 72 women who enrolled in the cohort, 69 (96%) provided venous blood in the 28th gestation week for the assessment of the fatty acid status in red blood cells, 55 (76%) answered the electronic questionnaire in pregnancy and 43 (61%) were screened for PPD at three months postpartum using the EPDS. 6.9% of the mothers of the study population (*n*= 43) scored ≥ 10 on the EPDS.

Lower omega-3 index in pregnant women in their late pregnancy (week 28) was associated with higher levels of depressive symptoms postpartum, in a simple nonlinear regression model thus they concluded that omega-3 status in pregnancy could be a possible biological risk factor for PPD.

Limitations

Authors acknowledged that the selective dropout, the uncontrolled confounder effects (as this group of participants did not provide data concerning any potential confounders) and the measure of depression were limitation to the study.

Miyake (2006b)

Objectives

To investigate the relationship of consumption of selected high-fat foods and specific types of fatty acids with the risk of PPD through analysing data from a large prospective cohort study of pregnant women and their offspring in Japan.

Participants

Pregnant women

Description of the study

n = 865 participants completed a diet history questionnaire during pregnancy and PPD was assessed using a self-administered Japanese version of the EPDS between 2 and 9 months post-partum.

Confounders

An adjustment was done for age, gestation, parity, cigarette smoking, family structure, family income, education, changes in diet in the previous month, season when data at

baseline were collected, body mass index, time of delivery before the second survey, medical problems in pregnancy, baby's sex and baby's birth weight.

Results and comparison

Of the 865 participants, 14% of population (121 women) have developed PPD. The multivariate ORs (95% CI) for post-partum depression in successive quartiles of n-3 PUFAs were 1, 0.68 (0.39–1.18), 0.58 (0.33, 1.02) and 0.90 (0.53, 1.53). The adjustment of confounders didn't change the findings.

This study failed to prove an inverse relationship between fish and n-3 polyunsaturated fatty acid intake symptoms of PPD.

Limitations

Authors highlighted the wide range (2 to 9 months) for postnatal depression screening, the EPDS self-report rating scale and the single self-administered semi-quantitative dietary questionnaire as potential limitations to this study

Otto (2003)

Objectives

To assess if the plasma phospholipids status in women is related to the prevalence of PPD. Other objective was to study breastfeeding and depression

Participants

Pregnant women with a singleton pregnancy and term delivery (≥ 37 weeks). Subjects who had any medical instability, received medication or had blood transfusion in the perinatal period were excluded.

Description of the study

Venous blood samples were collected at week 36 of pregnancy, immediately after delivery, and 32 weeks postpartum for fatty acids analysis.

PPD was assessed retrospectively at delivery and then again at 32 weeks postpartum using the validated Dutch version of The EPDS questionnaire.

Confounders

The following variables were controlled in this study: maternal age at moment of testing, educational level, parity, smoking or alcohol use. No correlation was found between the EPDS score treated as a continuous variable and any of the population characteristics which were not significantly different between the two groups.

Results and comparison

Of the 112 participants in this study, 21% (=24 women) had a total EPDS score of 10 or above and were diagnosed as “possibly depressed” in the postpartum period.

Ratio of DHA to omega-6 fatty acids was significantly lower in the 24 “possibly depressed” women (EPDS>10) compared with the 44 “not likely depressed” women (EPDS<10) (2.34 ± 5.56 versus 4.86 ± 5.41 , respectively; OR = 0.88; P = 0.03).

In conclusion, women consuming inadequate levels of essential fatty acids (and lower levels of DHA in particular) in pregnancy may be more likely to experience postpartum depressive symptoms.

Parker (2014)

Objectives

To investigate whether there was a relationship polyunsaturated fatty acids status and perinatal depression especially in the postpartum period.

Participants

Pregnant adult women of 18 years of age and more with a pregnancy age between 34 and 37 weeks.

Description of the study

Two tools of depression measurement were used at baseline to assess depression at baseline and 3 months postpartum, one was the EPDS and the second was either DSM-IV criteria for a major depressive episode via administration of the Mini International Neuropsychiatric Interview (MINI) and/or antidepressant medication. Subjects provided blood samples at 36 weeks of pregnancy for the 9 different fatty acids measurement.

Confounders

After examination of the following variables: age, education level, income level, marital status, number of children, neuroticism scores, the presence or absence of a lifetime mood disorder, coffee drinking, cigarette smoking and alcohol intake, as well as stress levels during pregnancy; the authors found that those who rated as EPDS cases had higher neuroticism scores, previous depressive episode, higher levels of stress during pregnancy, and older.

Results and comparison

A total of 772 women were rated for depression at baseline and postpartum through the EPDS with 635 non-depressed and 138 depressed women at 3 months postpartum.

In the third month post-natal assessment period, women did not differ on most of the PUFA variables measured at that time. EPDS assigned depressed women compared with non-depressed women had significantly higher omega-6 levels (27.2% vs. 26.8%), lower omega-3 levels (9.1% vs. 9.4%) and lower EPA (0.5% vs. 0.6%).

As a result of this study, PUFA status in late pregnancy is slightly related with the risk of PPD when depression was quantified by the EPDS, no association found between post-natal depression diagnosed by DSM criteria and any fatty acid variables.

Limitation

Authors highlighted the following limitations:

Inability to draw a cause and effect conclusions because of the observational design of the study. Lack of record of the women who declined to participate and the reason of refusing, thus cannot be certain that the study sample is entirely representative of the Australian population despite the large sample size.

Strom (2009)

Objectives

To determine the association between intake of fish and n3 PUFAs during pregnancy and PPD using data from large prospective cohorts in Denmark.

Participant

Danish pregnant women between 12 and 30 weeks of gestation.

Description of the study

Of all Danish pregnant women, 35 % women between 12 and 30 weeks of gestation entered the cohort. In this study, authors used data from the recruitment form, the telephone interview conducted in gestation week 12 and the food-frequency questionnaire (FFQ) mailed to the participants at 25 wk of gestation.

The depression status was assessed through "PPD admission" which was defined as an admission to psychiatric hospital or psychiatric ward because of depression up to 1 year

post-partum and "PPD prescription" which was defined as a woman who filled a prescription for an antidepressant.

Confounders

The following covariates were identified in this study: age, parity, pre-pregnancy body mass index, total energy intake, alcohol intake during pregnancy, smoking during pregnancy, occupation, level of attained education, homeownership, marital status, social support (combining information on social network, financial and practical help) and history of depression.

No association between fish dietary intake and the history of depression, but a strong relationship was observed between fish intake and socio-demographic and behavioural characteristics of the women.

More cases existed for both PPD-admission and PPD-prescription in women who were single, were smokers, had poor social support, had a history of previous depression, and had a lower socioeconomic status. Moreover, there were more cases of PPD-prescription in under- and overweight women, PPD-prescription was most recurrent in the oldest age group, whereas PPD-admission was most frequent among young women.

Results and comparison

Over all the 54,202 women enrolled in this study, the number of cases of PPD-admission in the study population was 159 (0.3%), and there were 866 cases of PPD-prescription (1.6%).

They found no association between fish intake and hospital admission for PPD, but a higher risk for PPD-prescription (antidepressant) among postpartum women who consumed low relative to high amounts of fish.

Limitations

Several limitation in this study were mentioned by the authors such as the small percentage of women who developed PPD(0.3%), small percentage of women with a history of PPD (5%), the primary outcomes included hospital admission for PPD and antidepressant prescription which would not capture women with depression who did not seek treatment.