

Nutrition and the psychoneuroimmunology of postpartum depression

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Abstract

Postpartum depression (PPD) is a relatively common and often severe mood disorder that develops in women after childbirth. The aetiology of PPD is unclear, although there is emerging evidence to suggest a psychoneuroimmune connection. Additionally, deficiencies in *n*-3 PUFA, B vitamins, vitamin D and trace minerals have been implicated. This paper reviews evidence for a link between micronutrient status and PPD, analysing the potential contribution of each micronutrient to psychoneuroimmunological mechanisms of PPD. Articles related to PPD and women's levels of *n*-3 PUFA, B vitamins, vitamin D and the trace minerals Zn and Se were reviewed. Findings suggest that while *n*-3 PUFA levels have been shown to vary inversely with PPD and link with psychoneuroimmunology, there is mixed evidence regarding the ability of *n*-3 PUFA to prevent or treat PPD. B vitamin status is not clearly linked to PPD, even though it seems to vary inversely with depression in non-perinatal populations and may have an impact on immunity. Vitamin D and the trace minerals Zn and Se are linked to PPD and psychoneuroimmunology by intriguing, but small, studies. Overall, evidence suggests that certain micronutrient deficiencies contribute to the development of PPD, possibly through psychoneuroimmunological mechanisms. Developing a better understanding of these mechanisms is important for guiding future research, clinical practice and health education regarding PPD.

Key words: Micronutrients: Postpartum depression: Immune system: Inflammation

Introduction

Overview of postpartum depression and psychoneuroimmunology

Postpartum depression (PPD) is characterised by sadness, fatigue, irritability and disinterest in life events⁽¹⁾. Women with PPD often experience feelings of guilt, worthlessness and anxiety related to birth and parenting; women may also think of suicide or harm toward the baby. A serious mood disorder comparable with major depressive disorder (MDD), PPD can develop as an extension of postpartum blues or arise independently in a mother whose mood has been stable until that point. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Text Revision defines PPD as beginning by 4 weeks after birth. However, in clinical practice many women are not diagnosed until 6 weeks to 3 months postpartum⁽¹⁾, and research studies on PPD often extend the time frame for diagnosis to 6 months or 1 year postpartum (see Tables 1 and 2).

Risk factors for PPD include previous mental illness, recent psychological stress, inadequate social or economic support, and a difficult birth experience⁽²⁾. Women who are experiencing significant physiological stress may also

be at risk for PPD^(3–5). However, not all women with these risk factors develop PPD. Thus, a key question is what causes certain women to shift from risk to depressive state? Over time, researchers have investigated that question from psychological, social and physiological perspectives.

The perspective framing the present review is physiological, specifically the field of psychoneuroimmunology (PNI). PNI is the study of how neuroendocrine and/or immune system dysregulation may contribute to the development of depression. Dysregulation of both these systems is acknowledged to have a role in depression for non-pregnant, non-postpartum populations^(6,7) and, recently, a psychoneuroimmunological contribution to PPD has been hypothesised as well^(3,4,8,9). This hypothesis is based on the inherently inflammatory nature of labour, delivery and postpartum healing^(10–13), which in some cases may be exaggerated and may increase the risk of depression.

Nutrition and the psychoneuroimmunology of postpartum depression

An unexplored component of psychoneuroimmunological research on PPD is how nutritional status contributes

Abbreviations: Abbreviations, COX, cyclo-oxygenase; EPDS, Edinburgh Postpartum Depression Scale; HPA, hypothalamic–pituitary–adrenal; MDD, major depressive disorder; PNI, psychoneuroimmunology; PPD, postpartum depression; T_H, T helper.

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Table 1. Observational studies of the relationship between *n*-3 PUFA and postpartum depression

| Study | Subjects (n) | Subject characteristics and stated exclusions | <i>n</i> -3 PUFA measurement | Depression measurement | Findings |
|---|--------------|---|--|---|---|
| De Vriese <i>et al.</i> (2003) ^{(40)*} | 48 | Singleton pregnancy. No: other psychiatric disorder, chronic disease, psychotropic medication use, premature labour, perinatal infection, Caesarian birth | Blood sample at delivery | SCID interview between 3 and 12 months postpartum | Baseline <i>n</i> -3 PUFA levels are lower in women who later develop depression |
| Makrides <i>et al.</i> (2003) ^{(41)*} | 380 | No reported characteristics or exclusions | Blood sample at 6 months postpartum | EPDS at 6 months postpartum | Inverse relationship between DHA levels and depression |
| Otto <i>et al.</i> (2003) ^{(42)*} | 112 | Singleton pregnancy, term delivery. No: other psychiatric disorder, chronic disease, perinatal blood transfusion, medications other than vitamins | Blood samples at 36 weeks gestation, delivery, 32 weeks postpartum | EPDS at 32 weeks postpartum | Inverse relationship between rate of DHA increase and depression. No relationship between raw DHA levels and depression |
| Browne <i>et al.</i> (2006) ⁽⁴³⁾ | 80 | Primiparous. No reported exclusions | Blood sample at 6 months postpartum. Food surveys at delivery, 6 months postpartum | EPDS, BDI-II within 6 months postpartum | No association between <i>n</i> -3 PUFA status or fish consumption and depression |
| Miyake <i>et al.</i> (2006) ⁽⁴⁴⁾ | 865 | No reported characteristics or exclusions | Food survey at time of depression screening | EPDS between 2–9 months postpartum | No association between fatty acid status and depression |

SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; EPDS, Edinburgh Postpartum Depression Scale; BDI-II, Beck Depression Inventory-II.

* Evidence of a relationship.

Table 2. Treatment studies of the relationship between *n*-3 PUFA and postpartum depression

| Study | Subjects (<i>n</i>) and study details | Subject characteristics and stated exclusions | <i>n</i> -3 PUFA measurement | Depression measurement | Findings |
|---|--|---|---|--|---|
| Freeman <i>et al.</i> (2006) ^{(52)*} | <i>n</i> 16; length: 8 weeks; treatment: 0.5, 1.4 or 2.8 g <i>n</i> -3 PUFA per d (EPA:DHA ratio of 1.5:1) | Age 15–45 years, current episode of depression with onset within 1 month postpartum. No: psychosis or suicidal ideation, bipolar disorder, antidepressant use | N/A | EPDS and HAM-D† at baseline, treatment weeks 1, 2, 4, 6 and 8 | Treatment associated with decrease in depression, but no variance with dosage |
| Su <i>et al.</i> (2008) ^{(51)*} | <i>n</i> 40; length: 8 weeks; treatment: 1.2 g DHA + 2.2 g EPA per d | Age 18–40 years, current episode of depression with onset at 16–32 weeks gestation. No: other psychiatric disorder, psychotropic medication in previous month | Blood samples at lead-in and treatment week 8 | HAM-D, EPDS, BDI at lead-in, baseline, treatment weeks 2, 4, 6 and 8 | Treatment associated with decrease in depression at weeks 6 and 8 |
| Llorente <i>et al.</i> (2003) ⁽⁴⁵⁾ | <i>n</i> 138; length: first 4 months postpartum; treatment: 200 mg DHA per d | Age 18–42 years, gravida < 5, planning to breastfeed. No: chronic disease, smoking, dietary supplements other than vitamins | Blood samples in late 3rd trimester and at 4 months postpartum | BDI late 3rd trimester, 3 weeks, 2 months, 4 months postpartum | Treatment associated with increased DHA, but not depression |
| Freeman <i>et al.</i> (2008) ⁽⁴⁸⁾ | <i>n</i> 59; length: 8 weeks; treatment: 1.1 g EPA + 0.8 g DHA per d; all participants received psychotherapy | Age 18–45 years, current episode of depression, 12–32 weeks gestation or 0–6 months postpartum. No: active psychosis or suicidal ideation, bipolar disorder, antidepressant or anticoagulation use, substance abuse | N/A | EPDS, HAM-D, CGI every 2 weeks for 8 weeks | No relationship between treatment and depression |
| Rees <i>et al.</i> (2008) ⁽⁴⁹⁾ | <i>n</i> 26; length: 6 weeks; treatment: 0.4 g EPA + 1.6 g DHA per d | Age > 21 years, current episode of depression, 3rd trimester–6 weeks postpartum. No: other psychiatric disorder, chronic disease, antidepressant or anticoagulant use, high dietary fish intake, participation in psychotherapy | N/A | EPDS weekly during treatment period | No relationship between treatment and depression |
| Doornbos <i>et al.</i> (2009) ⁽⁴⁶⁾ | <i>n</i> 182; length: enrolment to 3 months postpartum; treatment: 220 mg DHA per d, or 220 mg DHA + 220 mg AA per d | Gravida 1 or 2, singleton pregnancy, 14–20 weeks gestation. No: diabetes, preterm delivery, vegetarian or vegan diet | Blood samples at 16 and 36 weeks gestation. Food surveys throughout study | EPDS at 16 and 36 weeks gestation, 6 weeks postpartum | Treatment associated with increased DHA and AA, but not depression |
| Mattes <i>et al.</i> (2009) ⁽⁴⁷⁾ | <i>n</i> 98; length: 20 weeks gestation to delivery; treatment: 2.24 g DHA + 1.1 g EPA per d | Gestation < 20 weeks, diagnosed atopy. No: other chronic disease, smoking, use of fish oil supplements or high dietary fish intake | Blood samples at 20 weeks gestation, delivery | BDI at 20 weeks gestation, delivery | No relationship between treatment and depression |
| Makrides <i>et al.</i> (2010) ⁽⁵⁰⁾ | <i>n</i> 2399; length: enrolment to delivery; treatment: 800 mg DHA + 100 mg EPA per d | Singleton pregnancy, < 21 weeks gestation. No: DHA therapy, anticoagulant medication, bleeding disorder, substance use, known fetal abnormality | N/A | EPDS at 6 weeks and 6 months postpartum | No relationship between treatment and depression |

N/A, not applicable; EPDS, Edinburgh Postpartum Depression Scale; HAM-D, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; CGI, Clinical Global Impressions Scale; AA, arachidonic acid.

* Evidence of a relationship.

† This study uses the abbreviation of 'HRSD' for the 'Hamilton Rating Scale for Depression'.

to the proper function of the innate immune system and hypothalamic–pituitary–adrenal (HPA) axis. In 2005, Bodnar & Wisner⁽¹⁴⁾ laid the foundation for research in this area by describing a set of micronutrients (*n*-3 PUFA, B vitamins, trace minerals, antioxidants) that become depleted during pregnancy and perhaps play a role in depression for non-pregnant, non-postpartum populations. Since then, vitamin D has also been implicated as a possible contributor to PPD⁽¹⁵⁾. The question guiding the present investigation is whether PNI might be a mechanism by which these micronutrients are associated with PPD.

Critical review: micronutrient links to the psychoneuroimmunology of postpartum depression

This broad review aims to present the current status of research related to nutrition and the PNI of PPD, rather than a detailed summary of a limited number of articles. To this end, we conducted an extensive literature search in PubMed for human studies in English, using combinations of the terms ('inflammation', 'depression', 'post-partum') with ('PUFA', 'poly unsaturated fatty acids', 'omega-3', 'folate', 'B12', 'vitamin D', 'antioxidant', 'anti-inflammatory', 'mineral', 'microelement', 'nutrition'). We also conducted a manual search for papers referenced in articles retrieved through PubMed.

Of the micronutrients that researchers have identified as associated with PPD, the fatty acid literature is the most developed and has the strongest emphasis on postpartum populations. Studies of B vitamins and depression are fewer, with little focus on women's mental health. Studies of the relationship between vitamin D or trace minerals and depression also have a limited focus on postpartum populations. Our searches did not identify any studies linking general antioxidants to psychoneuroimmunological causes of depression, so the present paper will not further discuss antioxidants.

We introduce each micronutrient with a brief overview of its biochemistry and dietary sources. Then, we present and critique evidence for the micronutrient's linkage to PNI and evidence for the micronutrient's role in depression in the general population. This presentation is followed by analysis of the micronutrient's potential role in PPD and evaluation of each micronutrient as a potential subject for psychoneuroimmunological research into the aetiology of PPD.

PUFA

Two families of essential long-chain PUFA cannot be synthesised by human bodies: *n*-3 and *n*-6 fatty acids⁽¹⁶⁾. Thus, human diets must contain either the *n*-3 and *n*-6 PUFA or their precursor molecules (α -linolenic acid for *n*-3 and linoleic acid for *n*-6). *n*-3 PUFA are concentrated in fatty fish and certain algae; their precursor α -linolenic acid is concentrated in plant sources such as flaxseed and

walnuts. (It is important to note, however, that synthesis of *n*-3 PUFA from α -linolenic acid is inefficient. Thus, human consumers rely significantly on seafood for meeting their demands of *n*-3 PUFA.) *n*-6 PUFA are concentrated in animals that are fed diets high in cultivated cereals; their precursor linoleic acid is concentrated in vegetable oil sources such as maize, soya, sunflower-seed and cottonseed.

Linkage to psychoneuroimmunology. PUFA may influence the PNI of depression through their impact on the immune system's inflammatory response. *n*-3 PUFA function in the body in the form of EPA and a further derivative, DHA. Supplementation with these molecules has been shown to decrease levels of key inflammatory cytokines TNF- α , IL-1 β , IL-6, and IL-8⁽¹⁷⁾. Further research investigating mechanisms for the anti-inflammatory effect of *n*-3 PUFA has demonstrated that EPA limits the activation of transcription factor NF- κ B, a major pathway for the formation of pro-inflammatory cytokines⁽¹⁸⁾.

Another way by which EPA limits inflammation is competitive inhibition of the cyclo-oxygenase (COX) inflammation pathway. The COX pathway converts the body's primary *n*-6 PUFA, arachidonic acid, to pro-inflammatory cytokines such as prostaglandins and prostacyclins. However, high levels of EPA directly impede production of arachidonic acid derivatives by using the COX enzyme to form EPA derivatives instead^(17,19).

Role in depression. Since the 1980s, researchers have reported a protective effect of *n*-3 PUFA against inflammatory conditions such as CVD^(17,20), cancer⁽²¹⁾ and autoimmune disease^(22,23). Because depression is often co-morbid with these diseases, researchers began asking whether *n*-3 PUFA levels that protect against inflammatory disease might also protect against depression. Early observational studies were remarkably consistent: serum and dietary *n*-3 PUFA levels are low in depressed patients, and countries with lower *n*-3 PUFA consumption have higher rates of depression^(24,25).

Following publication of these observations, psychiatric researchers began conducting intervention studies on the effectiveness of *n*-3 PUFA supplementation as a treatment for MDD. Multiple studies have shown effectiveness of *n*-3 PUFA supplementation^(26–29), but some have shown no change from placebo^(30–32). Interpretation of these results is confounded by variance in the dosages and EPA:DHA ratios used in the studies, as well as whether *n*-3 PUFA were a monotherapy or adjunct to anti-depressants and psychotherapy. Variance in the age of study populations also limits generalisability of results. However, because accumulating evidence leaned toward the effectiveness of *n*-3 PUFA supplementation, the American Psychiatric Association recommended in 2006 that practitioners consider *n*-3 PUFA monitoring and supplementation during treatment of mood disorders⁽³³⁾. That recommendation continues to be the standard of care.

Two significant mechanisms have been proposed for the apparent relationship between PUFA and depression.

The first is a psychoneuroimmunological hypothesis, that by limiting production of pro-inflammatory eicosanoids and cytokines, *n*-3 PUFA prevent the inflammatory state that characterises clinical depression^(25,34). The second mechanism is neuronal; *n*-3 PUFA help regulate the production, function and metabolism of serotonergic neurotransmitters⁽³⁵⁾.

Role in postpartum depression. In the 1990s, multiple studies characterised maternal depletion of *n*-3 PUFA, particularly DHA, during pregnancy and lactation^(36–38). Maternal stores of DHA can reduce by 50% during pregnancy and not return to pre-pregnancy levels until 6 months postpartum. Then, in 2002, an epidemiological study by Hibbeln linked low maternal *n*-3 PUFA levels with PPD⁽³⁹⁾. Hibbeln compiled a multinational dataset to compare two measures of maternal *n*-3 PUFA levels (seafood consumption and breast milk DHA content) with rates of PPD. After establishing the dataset and a conservative threshold for PPD (score of 12/13 on the Edinburgh Postpartum Depression Scale; EPDS), Hibbeln conducted multiple levels of analysis to assess the impact of confounding factors such as socio-economic status, spouse/family support, and geographical latitude/light exposure. Hibbeln demonstrated that both lower rates of seafood consumption and lower concentrations of breast milk DHA were strongly correlated with higher rates of postpartum depressive symptoms.

In the years immediately following publication of Hibbeln's data⁽³⁹⁾, multiple observational studies were conducted to compare postpartum subjects' *n*-3 PUFA levels with depressive symptoms (Table 1). Three of five studies during this period reported an inverse correlation between *n*-3 PUFA levels and PPD^(40–42), while the other two showed limited or no relationship^(43,44). There are no systematic methodological distinctions among the studies that might explain why some showed a relationship and some did not. Areas of consistency in study design are: use of EPDS to assess depression; and use of blood samples rather than diet to assess *n*-3 PUFA levels (four of five studies). Areas of inconsistency in study design are: prospective cohort *v.* cross-sectional design; timeline for assessing *n*-3 PUFA status and screening for depression; and threshold on the screening tool used for considering a woman 'depressed'.

Since publication of Hibbeln's data⁽³⁹⁾, eight interventional studies (Table 2) have been published that examine the link between *n*-3 PUFA and perinatal depression (second trimester of pregnancy to 4 months postpartum). The studies are all placebo-controlled, randomised and blinded. Of the eight studies, six report no effect of *n*-3 PUFA supplementation on perinatal depression^(45–50), while two studies report an inverse association between *n*-3 PUFA supplementation and perinatal depression^(51,52). Yet, as with observational studies of *n*-3 PUFA and PPD, there is no straightforward explanation for these mixed results. An area of consistency in study design is the use

of EPDS to assess depression. Areas of inconsistency in study design are: when in the perinatal period intervention occurred; dosage and ratio of EPA:DHA used in treatment; whether blood samples confirmed an impact of *n*-3 PUFA supplementation; sample size; inclusion/exclusion of participants with confounding factors; and timeline for assessing *n*-3 PUFA status and screening for depression.

Assessment of research potential *n*-3 PUFA and the psychoneuroimmunology of postpartum depression. Recent results from clinical trials have cast doubt on the potential of *n*-3 PUFA to prevent depression for a general postpartum population⁽⁵⁰⁾. However, meta-analysis results⁽⁵³⁾ suggest that *n*-3 PUFA consumption may help prevent PPD for certain ethnic populations, and that specific *n*-3 PUFA may have different effects for prevention than treatment. Thus, it is valuable for research to continue on the relationship between *n*-3 PUFA and PPD. Based on the role of *n*-3 PUFA in modulating inflammation, investigation of psychoneuroimmunological mechanisms for the relationship is one avenue by which research should proceed.

B vitamins

B vitamins are a family of eight water-soluble molecules that have similar structures and act as enzymes for metabolic processes throughout the body, particularly in the haematological, nervous and integumentary systems. B vitamins are both numbered and named (for example, vitamin B₂ is 'riboflavin'; vitamin B₉ is 'folate') and are found in a wide variety of unprocessed foods. Gross deficiencies in B vitamins can cause chronic problems ranging from anaemia (microcytic, vitamin B₆; macrocytic, vitamins B₉ and B₁₂), to peripheral nervous system impairment (vitamins B₁ and B₁₂), to severe psychological disturbance (vitamins B₁, B₃, B₆ and B₁₂).

Linkage to psychoneuroimmunology. The linkage between B vitamins and PNI is limited, as B vitamins do not have a direct influence on the immune system or HPA axis. What B vitamins do influence are the background levels of cardiovascular inflammation, by managing levels of the pro-inflammatory amino acid homocysteine⁽⁵⁴⁾. Vitamins B₉ and B₁₂ convert homocysteine to methionine, an amino acid needed for the translation step of protein synthesis, and vitamin B₆ helps condense homocysteine into a precursor of the amino acid cysteine^(55,56).

Role in depression. Depression in general populations has been linked to low levels of B vitamins and/or high levels of homocysteine. The implicated B vitamins vary depending on the study population, such as vitamin B₁₂ showing strong correlation with depression in elder populations^(57–59) and vitamin B₉ showing correlation with depression in adult and adolescent populations^(55,60). Because almost all studies use a cross-sectional design, however, analysis raises the question of whether low B vitamin and high homocysteine levels cause depression, result from depression or are co-morbid with depression.

Longitudinal studies that would elucidate this relationship have not been conducted. The results of treatment studies using B vitamins as preventive and adjunctive therapy for depression have been mixed, depending on dosage levels prescribed and participants' general health status^(61–63).

In the absence of evidence clarifying the relationship between B vitamins and depression, causal mechanisms have been proposed but not thoroughly investigated. A neuronal hypothesis suggests that low levels of vitamins B₆, B₉ and B₁₂ might cause decreased synthesis of the neurotransmitters serotonin, dopamine and noradrenaline^(62,64). A second, 'vascular hypothesis' of depression suggests that B vitamin deficiency allows hyperhomocysteinaemia, which in turn is associated with vascular damage and a state of chronic inflammation. In addition, damage to the carotid and intracerebral arteries can cause persistently low O₂ delivery to the prefrontal cortex, resulting in depression and generally poor mentation. However, research in recent years has suggested that hyperhomocysteinaemia may be co-morbid with CVD rather than a cause of it^(54,57), calling into question the vascular hypothesis for how B vitamin deficiency relates to depression.

Role in postpartum depression. Few studies have investigated the relationship between B vitamins and PPD, and those that have do not provide evidence of a likely link. In an early prospective cohort study (*n* 131), Rouillon *et al.* recorded serum vitamin B₉ status on the third day postpartum and measured PPD at 1, 2 and 3 months postpartum⁽⁶⁵⁾. The authors found no correlation between vitamin B₉ status and PPD. Later, Miyake *et al.*⁽⁶⁴⁾ used a FFQ to characterise dietary intake of vitamins B₂, B₆, B₉ and B₁₂ in a prospective cohort of 865 women. The only inverse association identified between B vitamin intake and PPD occurrence (measured between 2 and 9 months postpartum) was between vitamin B₂ and PPD. However, this inverse relationship was only significant (CI = 95%) for the third quartile of vitamin B₂ consumption.

Assessment of research potential: B vitamins and the psychoneuroimmunology of postpartum depression. Currently, there is no strong evidence correlating B vitamin levels with PPD. Much work remains to characterise a possible link between B vitamins and PPD, particularly longitudinal research that measures levels of vitamins B₂, B₆, B₉ and B₁₂ throughout the postpartum period. In addition, B vitamins do not have an identified neuroendocrine or immune function through which B vitamin deficiency might contribute to the PNI of PPD. Thus, we hesitate to recommend research on B vitamins and the PNI of PPD.

Vitamin D

Vitamin D is a steroid hormone synthesised by the skin in response to UVB light. To become biologically active, the molecule undergoes a first hydroxylation reaction in the liver. Then, specialised cells in the kidneys, brain and

immune system complete a second hydroxylation reaction, creating the body's functional form of vitamin D, calcitriol^(66,67). Dietary sources of vitamin D include fortified dairy or cereal products, fatty fish, eggs and beef liver.

Vitamin D works at a cellular level by activating the vitamin D nuclear receptor. Genes under the influence of the vitamin D nuclear receptor contribute to Ca transport, bone remodelling, cell cycling, cell differentiation and apoptosis. While vitamin D's role in Ca regulation and bone health has long been recognised, its role in cellular proliferation and development has been a subject of increasing interest over the last 10 years⁽⁶⁶⁾.

Linkage to psychoneuroimmunology. Vitamin D exerts influence over both cellular and humoral immune responses. Early animal studies showed that vitamin D inhibits CD4 and T helper (T_h) cell activation in autoimmune disease models⁽⁶⁸⁾. Later studies produced more specific findings, indicating that vitamin D shifts the body's production of T lymphocytes away from T_h1 toward T_h2 cells. As a result, T_h1 production of inflammatory cytokines interferon- γ and IL-2 decreases, while T_h2 production of cytokines such as IL-4, IL-5 and IL-10 increases. These cytokines in turn stimulate B cell production⁽⁶⁷⁾. Vitamin D also decreases NF- κ B activation of macrophages, thereby reducing macrophage production of pro-inflammatory cytokines⁽⁶⁷⁾.

In addition to impacts on the immune system, vitamin D interacts with elements of the HPA axis. In hippocampal cells cultured from young rats, researchers have examined the interaction between vitamin D and glucocorticoids⁽⁶⁹⁾. Normally, glucocorticoids prevent the differentiation of hippocampal cells, and if glucocorticoids stimulate the cells for extensive periods, apoptosis occurs. However, vitamin D exerts two effects on this glucocorticoid system: when applied to hippocampal cells concurrently with glucocorticoids, it allows morphological changes in the cells; when applied to hippocampal cells before long-term glucocorticoid exposure, it significantly decreases the extent of apoptosis.

Role in depression. Four cross-sectional studies in non-psychiatric populations have examined the relationship between vitamin D levels and depression. Of these, three found that a low serum vitamin D level was associated with depressive symptoms^(70–72). However, in a study of similar sample size and design, researchers found no association between vitamin D levels and depression⁽⁷³⁾. Other cross-sectional studies have examined vitamin D levels in patients already identified with depression, comparing those depressed patients with non-depressed controls. Three of these studies identified a low vitamin D–depression link^(74–76), while two other studies found no significant difference in vitamin D status between depressed and non-depressed patients^(77,78).

Two double-blind, randomised treatment trials have specifically examined the relationship between vitamin D and depression. In a 1-year-long prospective study in an overweight/obese population, researchers found significant improvement in depressive symptoms with ongoing,

high-level supplementation of vitamin D⁽⁷⁹⁾. The other treatment study used a very different design, investigating whether annual oral administration of high-level, single-dose vitamin D could make an impact on mood⁽⁸⁰⁾. (The rationale for single-dose administration was its reported effectiveness as a treatment for seasonal affective disorder.) However, the study found no prevention effect for depressive symptoms between the treatment and control groups.

Three general concerns limit interpretation of research on vitamin D and depression. As discussed in regard to studies of B vitamins, cross-sectional designs do not support a distinction among cause/effect/co-morbid relationships. Next, most of these studies failed to adjust for other factors known to influence depression, such as smoking, CVD and diet/exercise. Finally, many of these studies focused on middle-aged or older adults. Patterns and mechanisms of depression in elder populations cannot be assumed to be consistent across the lifespan.

The studies discussed above have generated significant interest in the relationship between vitamin D and depression. However, researchers have proposed few hypothetical mechanisms for the low vitamin D–depression relationship. The dominant hypothesis in the literature is neuronal, focusing on vitamin D's influence on hypothalamus function and the production of neurotransmitters^(71,81,82). To our knowledge, a psychoneuroimmunological hypothesis has been mentioned only briefly, even though vitamin D's contribution to immune function is well established^(15,82).

Role in postpartum depression. One study has investigated the association between vitamin D and PPD. Researchers monitored vitamin D levels and depressive symptoms for ninety-seven women on a monthly basis for 7 months⁽¹⁵⁾. Using a dichotomous model with a cut-off score of 9 on the EPDS and 32 ng/ml vitamin D, depression was consistently higher for women with lower vitamin D levels than higher vitamin D levels. Limitations of the study include its use of a convenience sample, no participant exclusions for other factors influencing depression (social support, etc.) and no clinical assessment of depression following screening with the EPDS.

Assessment of research potential: vitamin D and the psychoneuroimmunology of postpartum depression. The contributions of vitamin D to immune and HPA axis function suggest that vitamin D could be an appropriate focus for PNI of PPD research. However, because the only research linking vitamin D to PPD is a small pilot study, any investigation of vitamin D's link to the PNI of PPD needs to begin with extensive characterisation of the vitamin D–PPD relationship.

Trace minerals

Dietary minerals are elements present in the human body that are not common components of organic molecules. Some dietary minerals occur in relatively large quantities

and play structural (Ca) and electrolyte (Na, K, Cl) roles. Other dietary minerals occur in trace amounts and function as enzymic cofactors and cell-signalling molecules. Food sources for dietary minerals vary widely. Some are concentrated in animal products (Fe, Ca, P), while others are concentrated in vegetarian sources (K, Mg).

If no supplements are consumed and excretion mechanisms function adequately, the human body rarely reaches a toxic concentration of minerals. Mineral deficiency, however, is common. Humans can become deficient in dietary minerals due to inadequate intake, overactive bladder or bowel excretion, or a pathogenic body condition (for example, low Fe due to chronic bleeding). In addition, women's bodies can become depleted of minerals during pregnancy and lactation, due to transfer of minerals to the fetus and infant. When deficiencies occur, symptoms vary according to the mineral and to the level of deficiency.

Of specific interest for the present study are the trace minerals Zn and Se. Both minerals play multiple roles throughout the body (particularly as enzyme cofactors and by contributing to the structure of amino acids), and both minerals have been associated with depression^(83,84). Both minerals can be ingested in adequate amounts from a well-rounded diet; Zn is particularly concentrated in red meat, seeds and beans, while Se is concentrated in nuts, meat and fish. In the sections below, we discuss each mineral in turn.

Linkage to psychoneuroimmunology. Zn deficiency has been linked to immunosuppression through treatment studies, prevention studies and laboratory studies of animal models^(84–86). One mechanism by which Zn deficiency contributes to immunosuppression is altering the balance between pro- and anti-inflammatory cytokines⁽⁸⁷⁾, such as allowing greater production of NF- κ B⁽⁸⁷⁾ and IL-1 β ⁽⁸⁸⁾. A second mechanism by which Zn deficiency causes immunosuppression is altering the number and productivity of B cells and T cells, a process that possibly involves the HPA axis⁽⁸⁹⁾.

Se's primary function in the immune system is anti-inflammatory, mediated by the selenoprotein glutathione peroxidase^(83,90). A key antioxidant with variants across species, glutathione peroxidase reduces H₂O₂ and thus limits the COX pathway production of pro-inflammatory cytokines. Se also contributes to cellular immunity by stimulating T cell clonal expansion and potentiating the action of natural killer cells (first identified in 1994⁽⁹¹⁾, now a foundation for Se research in virology^(92,93) and oncology^(94–98)).

Role in depression. Low levels of Zn have been linked to mood disorders since the 1980s. This relationship has been consistent for populations of different ages, from young adult⁽⁹⁹⁾ to adult⁽¹⁰⁰⁾ to elderly⁽¹⁰¹⁾. Some studies even support a tentative relationship between Zn and mood regulation in infants and young children⁽¹⁰²⁾. Yet, it is important to note that longitudinal studies have not yet been conducted that would clarify a cause/effect/co-morbid relationship between Zn and depression.

In the absence of longitudinal data, treatment studies are one way to elucidate the Zn–depression relationship. Nowak *et al.* reported results from a small (n 20) double-blind, placebo-controlled study of Zn as an adjunct to standard antidepressant therapy in a non-hospitalised adult MDD population⁽¹⁰³⁾. Depressive symptoms after 6 and 12 weeks of treatment were reduced in those receiving both Zn supplements and antidepressant medication, compared with the control group receiving placebos and antidepressants. Later, Sawada & Yokoi⁽⁹⁹⁾ tentatively expanded these findings to a non-MDD population. Sawada & Yokoi's small (n 31) double-blind, placebo-controlled pilot study tested the impact of Zn supplementation on the mood of healthy young adult women. Results showed a significant decrease in anger-hostility and depression-dejection scores, but no significant changes in other mood components (for example, tension-anxiety, vigour, fatigue and confusion).

Efforts to understand the mechanisms by which Zn deficiencies might contribute to depression have focused on neuronal hypotheses; Zn has not yet received attention from the PNI research community. The neuronal hypotheses are based on evidence that half of the brain's free Zn is stored in synaptic vesicles of hippocampal glutamatergic neurons. Physiologically normal levels of Zn may regulate glutamate release from these neurons⁽¹⁰⁴⁾, protecting neuron health in an area of the brain whose atrophy has been linked to mood disorders⁽¹⁰⁵⁾.

The relationship between low Se levels and depression has primarily been explored through treatment studies. In the 1980s, Se was part of three antioxidant interventions for geriatric populations⁽¹⁰⁶⁾. In these studies, subjects treated for up to 1 year with combinations of Se and other antioxidants (vitamins A, C and E) showed improvement in measures of mood and cognitive function. However, the studies did not allow specific impacts of Se to be identified. Then, in 1991, Benton & Cook⁽¹⁰⁶⁾ reported research investigating whether Se supplementation alone would make an impact on mood. Results of that placebo-controlled, double-blind study involving fifty subjects indicate that Se supplementation causes significant improvement in mood only for subjects with a low baseline Se level, and minimal or no change in mood for subjects whose baseline Se status is marginal or adequate. However, these minimal impacts were not observed in a later, very small (n 11) study⁽¹⁰⁷⁾.

In 1998, Finley & Penland⁽¹⁰⁸⁾ identified the most significant treatment effect to date for Se's impact on mood. In this study (n 30), subjects consuming a prescribed high-Se diet (utilising pastured meat and grains raised in high-Se soil) showed increased plasma Se and reported less mood disturbance over time than those consuming a low-Se diet. The result was robust across multiple subscale measures of mood (elated–depressed, composed–anxious, etc.). However, participants in the study's treatment groups did not have similar baseline mood scores; the high-Se group had a higher number of participants with baseline

mood disturbance. Thus, the question must be asked whether Se is particularly helpful for individuals already experiencing disturbed mood, or whether Se can limit mood disturbance in the general population.

As a follow-up to these intervention studies, in 2006 Rayman *et al.* included a mood assessment protocol in their pilot (n 501) for the UK PRECISE study (UK PREvention of Cancer by Intervention with SElenium)⁽¹⁰⁹⁾. The pilot study was a 6-month, double-blind, randomised trial for Se supplementation in otherwise healthy older adults (age 60–74 years). The study found no relationship between mood and Se supplementation status.

Mechanisms by which Se deficiency might contribute to depression have been proposed but not explored. One idea is that, due to selenoprotein glutathione peroxidase's role in processing thyroid H_2O_2 , Se deficiency may make an impact on mood by decreasing thyroid function⁽¹¹⁰⁾. A neuronal explanation of the Se–depression link is based on evidence that Se concentration influences dopamine metabolism⁽¹¹¹⁾; however, animal studies suggest that only severe Se deficiency is likely to make an impact on dopamine levels⁽¹⁰⁹⁾. To our knowledge, a psychoneuroimmunological mechanism for a Se–depression link has not yet been proposed in the literature.

Role in postpartum depression. One study has investigated the association between Zn and PPD. Working with a cohort of sixty-six women, all of whom were receiving Zn supplements, Wójcik *et al.* measured serum Zn and screened for depression at three points in time: 1 month before delivery, 3 d postpartum and 30 d postpartum⁽¹¹²⁾. Wójcik *et al.*⁽¹¹²⁾ was able to support in a postpartum population the earlier conclusion of Maes *et al.*⁽¹¹³⁾ for adult MDD: Zn levels vary inversely, along a continuous spectrum, with the severity of depressive symptoms.

One study likewise has investigated the relationship between Se and PPD. Mokhber *et al.*⁽¹¹⁴⁾ reported the results of a placebo-controlled, randomised, double-blind Se supplementation trial (n 218) during the last 6 months of pregnancy. Pre-/post-treatment serum Se was measured, and screening for PPD occurred 8 weeks after delivery. Results demonstrated a significant increase in serum Se in the treatment group, indicating that low Se levels are responsive to intervention. Mokhber *et al.* also reported that mean depression scores were significantly lower in women receiving Se supplementation, even after thorough analysis of social support factors.

Assessment of research potential: trace minerals and the psychoneuroimmunology of postpartum depression. In conclusion, the trace minerals Zn and Se are an appropriate focus for PNI of PPD research. However, the research on trace minerals and MDD that would support a PNI of PPD investigation is in its infancy. Thus, it is unlikely that research on the PNI of PPD would make significant progress toward understanding Zn and Se's contributions to PPD unless concurrent work occurs on the biochemical aspects of how trace minerals relate to MDD.

Discussion

We have reviewed evidence linking women's micronutrient status to the development of PPD, focusing on the potential contribution of micronutrient status to a psychoneuroimmunological mechanism of PPD. Although data regarding a micronutrient–PPD link and PNI of PPD mechanism are provocative, available evidence cannot support strong conclusions in either area. The strength of conclusions is limited by two factors. First, for each micronutrient of concern, studies have produced conflicting results – yet meta-analysis to resolve these conflicts is not possible because the studies vary so greatly in design (for example, definitions of depression, measurement of micronutrient status, guidelines for participant exclusion). Thus, researchers and clinical practitioners have no formal tool to assess the balance of evidence for or against a micronutrient–PPD link. Second, the studies were not designed to test particular mechanisms for how each micronutrient could contribute to PPD. Thus, conclusions for any single study are limited to a statement for or against the micronutrient–PPD link, offering no further insight about how the micronutrient may relate to PPD. Without consideration of a mechanism of action, studies have not been structured to identify special conditions under which a relationship might exist, such as in particular patient populations (history of mental illness, inflammatory disease, limited social support), according to the degree of micronutrient deficiency (before, during, after pregnancy) or according to the type of micronutrient consumed (dietary, supplement, pharmaceutical-grade, etc.).

In light of these limitations in the body of literature on micronutrients and PPD, we propose three principles to guide future investigations. First, studies conducted by various research groups need to comply with more stringent design recommendations (see below). Meeting these standards will enable the findings of future studies to be compiled into meta-analysis projects. Second, studies need to investigate underlying mechanisms about a micronutrient's relationship with PPD. This will help tease out the aetiology of each micronutrient's contribution, if any. By better understanding the aetiology, we can better investigate the conditions in which the micronutrient is likely to exert significant impact. Then, we can design more effective interventions for women at risk of PPD. Finally, researchers are encouraged to keep in mind that single-nutrient interventions generally have less impact on mood than broad-spectrum nutritional interventions (prescribed diet, nutritional counselling, etc.). Single-nutrient interventions may even have negative effects, such as recent evidence that fish oil supplements for lactating women may be associated with decreased cognitive abilities in children at 7 years of age⁽¹¹⁵⁾. Thus, future research needs to build a picture of how multiple micronutrients contribute to PPD.

Research design recommendations

Research designs should take into account several considerations. First, research needs adequate sample size and ethnically diverse patient populations. Working from the perspective of the PNI of PPD, patients with histories of immune disorders or inflammatory diseases should not be included, as these patients' basic inflammatory milieu is significantly different from the general population.

Second, if possible, research should be longitudinal. This prevents the cause/effect/co-morbid uncertainty inherent in cross-sectional research. This is especially important from a PNI of PPD perspective, because plasma levels of micronutrients are often influenced by an inflammatory state⁽¹¹⁶⁾. Thus, longitudinal data are important for resolving uncertainty not just about the link between micronutrients and PPD, but also the link between micronutrients and biochemical markers of psychoneuroimmunological aetiology.

Third, observational research should stretch from early pregnancy to 1 year postpartum to identify when changes in micronutrient levels occur. This information would help prevention researchers time their interventions for presumed maximum effect.

Fourth, research needs to use a consistent method for monitoring micronutrient status. Dietary recall is not a preferred method for assessing micronutrient status, as it builds uncertainty into the study design. Using PUFA measurement as an example, validation studies for food questionnaires show that fish consumption as a measure of *n*-3 PUFA status only correlates with plasma measurements at the quartile level^(117,118). As an alternative, we recommend monitoring blood levels, which reflect the availability of micronutrients for biological processes. Blood sampling is, however, logistically difficult, and episodic sampling may need to be used in combination with dietary recall for a longitudinal study. Nonetheless, improved accuracy on micronutrient status is an important component of increasing the strength of study conclusions. In addition, blood sampling facilitates research on mechanisms of a micronutrient–PPD link. For example, measuring cytokine and cortisol levels at the same time allows investigation of a PNI of PPD hypothesis.

Fifth, to facilitate comparison of study results, research needs to use a common measurement tool and timeline for screening for PPD. We suggest a tool created specifically for postpartum populations, such as the EPDS⁽¹¹⁹⁾ or Postpartum Depression Screening Scale⁽¹²⁰⁾. We recommend a timeline of PPD identified in the first 3 months postpartum.

We recognise that studies complying with all these suggestions will be difficult to carry out on a very large scale. There is a trade-off between large studies that can rigorously quantify the micronutrient–PPD relationship, and small studies that can investigate causal mechanisms for the relationship. As a result, it might be advisable

to initiate moderately sized (n 1000) studies of the micronutrient–PPD relationship, focusing on specific populations or mechanisms of interest.

Limitations

One limitation of the present review is that the literature search was conducted only in the PubMed database and only included English-language articles. Another limitation is that the review did not establish level-of-evidence criteria for research results included in the analysis. Thus, the present review can provide only general direction to readers, unlike a systematic review that could provide a more solid foundation for research and clinical decision-making. A third limitation is that the present review's focus on physiological mechanisms resulted in some data not being included. For example, Strøm *et al.*⁽¹²¹⁾ conducted a large study on the relationship between n -3 PUFA or fish consumption and PPD. The authors measured PPD on the basis of (1) psychiatric admissions or (2) anti-depressant prescriptions. These measures of PPD capture only the most severe cases, unlike depression-screening scales that are sensitive to developing or mild cases of PPD. The Strøm *et al.* data⁽¹²¹⁾ were not included in the present review because our focus on physiological contributors to PPD required the higher degree of sensitivity that screening scales provide.

To address these limitations, we recommend conducting a systematic review of articles related to the causal mechanisms for a micronutrient–PPD link. This review should include non-English publications. The review should also summarise data from studies that do not use a screening scale to measure the incidence of PPD.

Research significance

At this time, evidence is not strong enough to safely prevent or treat PPD with dietary interventions or supplements alone. Further research on the link between micronutrients and PPD, specifically the PNI of PPD, is necessary before clinicians can design diet and supplementation plans to prevent and treat PPD. 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 d), with the EPA:DHA ratio undefined⁽¹²²⁾. For B vitamins and trace minerals, there is no recommended dosage for mood disorders. 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. These interventions would be relatively inexpensive, and women reluctant to take anti-depressant medication might be more willing to enter treatment^(1,123–125).

The potential association of micronutrients with PPD is also significant for health and agriculture policy. A demonstrated link between micronutrient status and PPD could

be the basis for health education initiatives, including additional labelling of micronutrients in processed foods. Also, a demonstrated link could support inclusion of more micronutrient-rich foods in government benefit programmes, such as the Women, Infants, and Children nutritional support programme in the USA.

In conclusion, limited evidence suggests that certain micronutrient deficiencies may be factors causing some women to move beyond risk to develop PPD. How these deficiencies influence immune and HPA axis function is an intriguing direction for research from a PNI of PPD perspective.

Acknowledgements

The present review was supported in part by funding from the National Institutes of Health (R01NR011278).

E. R. E.-B. was the primary researcher and writer for this paper. E. J. C. oversaw the project and reviewed drafts when the paper was prepared for publication.

The authors declare no potential conflicts of interest for themselves or their institution.

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