Nutrition and Depression: Implications for Improving Mental Health Among Childbearing-Aged Women

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Adequate nutrition is needed for countless aspects of brain functioning. Poor diet quality, ubiquitous in the United States, may be a modifiable risk factor for depression. The objective was to review and synthesize the current knowledge of the role of nutrition in depression, and address implications for childbearing-aged women. Poor omega-3 fatty acid status increases the risk of depression. Fish oil and folic acid supplements each have been used to treat depression successfully. Folate deficiency reduces the response to antidepressants. Deficiencies of folate, vitamin B12, iron, zinc, and selenium tend to be more common among depressed than nondepressed persons. Dietary antioxidants have not been studied rigorously in relation to depression. Childbearing-aged women are particularly vulnerable to the adverse effects of poor nutrition on mood because pregnancy and lactation are major nutritional stressors to the body. The depletion of nutrient reserves throughout pregnancy and a lack of recovery postpartum may increase a woman's risk of depression. Prospective research studies are needed to clarify the role of nutrition in the pathophysiology of depression among childbearing-aged women. Greater attention to nutritional factors in mental health is warranted given that nutrition interventions can be inexpensive, safe, easy to administer, and generally acceptable to patients.

Key Words: Depression, diet, nutrition, postpartum, pregnancy, women

Women of childbearing age are at high risk for major depressive disorder (MDD). The lifetime risk for MDD in community samples has varied from 10%–25% for women (Kessler 2003), with peak prevalence between 25–44 years of age. A similar proportion of women are affected by MDD in pregnancy and the postpartum period (O'Hara and Swain 1996). During this century, MDD is occurring earlier in the life span in successive generations; therefore, an increasing number of women will become ill during their childbearing years (Kessler 2003). MDD is a leading cause of disease-related disability among women worldwide (Kessler 2003). During the perinatal period, MDD increases the risk of adverse birth outcomes (Orr and Miller 1995), insecure mother–infant attachment, and cognitive, emotional, social, and behavioral developmental problems of the offspring (Beck 1998).

MDD is underrecognized and undertreated in clinical settings (Hirschfeld et al 1997). If depression is appropriately diagnosed, the high cost and side effects of antidepressants remain important treatment barriers for many women (Cassano and Fava 2004; Simon et al 2004). Furthermore, not all depressed women respond to drug treatment, and additional therapies are needed (Fava and Davidson 1996). During pregnancy and lactation, the risks of antidepressant drug treatment appear to be low, but several domains of reproductive toxicity have not been systematically assessed. Notably, antidepressants have potent central nervous system effects, and neurobehavioral teratogenicity remains a relatively unexplored possibility (Wisner et al 1999). During pregnancy and lactation, the risk–benefit analysis must be carefully considered and the mother–baby pair monitored throughout treatment (Wisner et al 2000). Establishing effective, safe, inexpensive, and well-accepted interventions aimed at preventing and treating MDD among women of childbearing age is paramount.

The complexity of MDD is unmistakable, yet a key to its prevention and treatment may be a factor so fundamental that it has been broadly overlooked: dietary intake and overall nutritional status. Evidence for a role of nutrition in mental health originates from work that documented neurological and psychological effects of frank nutrient deficiencies. For instance, severe vitamin B12 deficiency causes loss of memory, mental dysfunction, and depression. Similarly, fatigue, confusion, dementia, and irritability are common clinical signs of folate deficiency. As discussed in detail here, these and numerous other dietary constituents are needed for countless aspects of normal brain functioning, including enzymatic activity, cellular and oxidative processes, receptor function, signal transmission, maintenance of neuronal tissue, and synthesis and function of neurotransmitters and catecholamines.

In addition to biologic plausibility for influencing mental health, nutrition is particularly appealing to study because it is modifiable, and there is substantial room for improving the nutritional status of childbearing-aged women in the United States. Only 23%, 43%, and 5% of women aged 20–39 met the Dietary Guidelines for Americans recommended servings of fruit, vegetables, and whole grains, respectively, in 1994–96 (U.S. Department of Health and Human Services 2003). These foods provide many of the micronutrients required for optimal human health. In contrast, intake of high-fat desserts, high-fat salty snacks, and high-fat grain-based mixed dishes (such as macaroni and cheese) have increased among women in the past 25 years (Siega-Riz and Popkin 2001), and in 1994–96, 59% of women exceeded the recommended intake of $\leq$ 10% of energy from saturated fat (U.S. Department of Health and Human Services 2003). Inadequate intakes of iron, folate, and calcium are significant problems, particularly among women of childbearing age (U.S. Department of Health and Human Services 2003). Today more than ever, Americans are eating a greater proportion of meals and snacks away from home (Nielsen et al 2002), where portion sizes are larger (Nielsen and Popkin 2003). Not surprisingly, one in three adult women in the United States is obese, and more than half are overweight (Flegal et al 1998).

Given the public health importance of MDD and the ubiquitous problem of poor diet quality among childbearing-aged women in the United States, our objective was to review and

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synthesize the current knowledge of the role of nutrition in MDD, and address implications for women of childbearing age. We begin by discussing three potential mechanisms by which nutrients could affect mental health and follow with a formal review of the literature on nutrition and MDD.

How Might Nutrition Improve Mental Health?

There are at least three mechanisms by which nutrition could be effective in improving mental health. First, modifying dietary intake or supplementing diets with single or multiple vitamins and minerals may correct existing nutrient deficiencies that contribute to poor mental health. Pregnant and lactating women are especially vulnerable to nutrient deficiencies because their needs are substantially elevated compared with nonpregnant and nonlactating women, and these needs may be difficult to meet through an ordinary diet or existing maternal stores. For instance, nutrient requirements during pregnancy are 70% higher for vitamin C and folate and 150% higher for iron compared with the nonpregnant and nonlactating state (Institute of Medicine 1998, 2000). A growing body of research suggests that failure to meet these increased nutrient needs may contribute to brain sequelae. Unfortunately, the effect of nutrition on brain pathology has only been studied in gross deficiency states. Marginal nutrient deficiency states are substantially more common, particularly in developed countries.

Second, pharmacologic doses of one or more dietary supplements may improve mental health among psychiatric patients who have a metabolic abnormality that dramatically raises nutrient requirements, such as individuals with alterations in nutrient absorption, transport, and storage. These persons may not be deficient in one or more nutrients as defined by traditional standards, but they may have considerably higher nutrient needs that can only be met with pharmacologic doses of dietary supplements. For instance, depressed patients are more likely than nondepressed people to have a point mutation in a gene coding for a key enzyme in folic acid metabolism (Arinami et al 1997; Bjelland et al 2003). Persons with such a mutation have previously been shown to have higher folic acid needs than the general population (de Bree et al 2003). Aside from this folic acid enzyme, the enzymatic and biochemical profile of individuals who have psychiatric symptoms has been neglected in the literature. It may be possible that certain dietary supplements could be used to safely and effectively improve mood or even prevent mood disorders in this at-risk population.

Third, improving the brain's nutritional milieu may augment the effectiveness of antidepressant medication (and possibly other psychotropics). Antidepressant medication is known to have varying degrees of effectiveness among depressed individuals, with the extreme being resistance to treatment, which occurs in up to 30%–40% of patients (Fava and Davidson 1996). Because nutritional deficiencies are common among individuals with MDD and nutrients are essential substrates for brain function, an individual's nutritional status may partially determine treatment effectiveness. Medication may be unable to overcome nutritional deficit(s) in a "poorly nourished" brain, and therefore would be rendered ineffective or less effective. This interaction between nutritional status and treatment effectiveness has been illustrated in several recent studies. Data suggest that n-3 polyunsaturated fatty acid (PUFA) supplements and folic acid supplements have been used independently to treat individuals with "treatment-resistant" MDD (Alpert et al 2002; Peet and Horrobin 2002). Little is known about the amount of each nutrient required for an optimal treatment effect. Traditionally defined deficiencies may not need to exist to prevent standard treatments from working optimally.

Literature Review: Nutrition and MDD

Although many nutrients affect brain function, our review centers on several that we believe hold the most promise in modifying the pathophysiology of major depression. These nutrients not only have a clear role in maintaining normal brain function but are also widely viewed as nutrients of major public health importance because deficiencies commonly occur in the general population. We searched MEDLINE on Ovid (1966 to February 2004) for human studies in English with the following key words: (depression, affect) and (nutrition, diet, essential fatty acids, unsaturated fatty acids, fish oils, folic acid, antioxidants, ascorbic acid, vitamin E, carotenoids, selenium, zinc, iron, hemoglobins). We also searched PsychINFO on Ovid (1967 to February 2004) with the following key words: (depression) and (nutrition, diets, nutritional deficiencies, vitamin therapy, vitamin deficiency disorders, vitamins, folic acid, iron, zinc, ascorbic acid, fatty acids). These articles were supplemented with references cited by these manuscripts and from the authors' own files.

Essential Fatty Acids (EFAs)

Linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3) are the parent fatty acids of the n-6 and n-3 families of EFAs. Each parent fatty acid can be desaturated and elongated to a series of longer chain PUFAs. These fatty acids are termed essential because they cannot be endogenously synthesized and must be consumed through the diet. Eicosapentanoic acid (EPA 20:5n-3) and docosehexaenoic acid (DHA; 22:6n-3) are the n-3 PUFAs that are the most biologically relevant for mental health and are most predominant in the brain. Both EPA and DHA are derived almost exclusively from fish and seafood, whereas vegetable oils (e.g., canola oil) are the primary source of n-6 PUFAs.

Polyunstaurated fatty acids are key structural components of the phospholipid membranes in tissues throughout the body and are especially rich in the brain, where they determine the biophysical properties of neuronal membranes (Salem et al 2001). Fatty acids affect receptor function, neurotransmitter uptake, and signal transmission. The most prominent n-3 PUFA in the brain is DHA. By increasing membrane fluidity, high DHA concentrations enhance serotonin receptor sensitivity (Hibbeln and Salem 1995). The n-3 PUFAs are also precursors to specific prostaglandins and leukotrienes, which are potent vasodilators and inhibitors of platelet aggregation. In addition, n-3 PUFAs inhibit synthesis of cytokines and mitogens to reduce inflammation. Not surprisingly, n-3 PUFAs decrease risk of vascular disease (Simon et al 1995). The relationship between n-3 PUFAs, inflammation, and vascular disease is intriguing given that vascular factors may contribute to the pathogenesis of MDD (Alexopoulos et al 1997), and MDD is associated with both inflammation and atherosclerosis (Alexopoulos et al 1997; Maes 1999; Maes et al 1996).

Among people in the United States, the ratio of n-6 PUFAs to n-3 PUFAs has been remarkably altered from about 1:1 before 1890 to between 10:1 and 25:1 today (Leaf and Weber 1987). This dramatic shift in intake patterns, caused by a two- to threefold increase in intakes of vegetable oils at the expense of n-3 PUFAs from fish, wild game, and plants, is thought to be responsible for the increased incidence of depressive disorders in the United States in the past century (Maes et al 1996). Several comprehensive reviews of the association between EFAs and major depres-

sion have been published (Bruinsma and Taren 2000; Freeman 2000; Logan 2003). Therefore, these data are briefly summarized here.

Concentrations of n-3 PUFAs in the blood have repeatedly been shown to be lower and the ratio of n-6 to n-3 PUFAs higher in depressed individuals compared with healthy control subjects, with blood concentrations strongly correlated with the severity of the disorder (Adams et al 1996; Edwards et al 1998; Maes 1999; Maes et al 1996; Tiemeier et al 2003). Frequent fish and seafood intake has been associated with a reduced risk of depression (Edwards et al 1998; Hibbeln 1998; Tanskanen et al 2001). In an ecologic study of 23 countries, per capita fish consumption ($r = -.81$, $p < .001$) and DHA concentrations in mothers' breast milk ($r = -.84$, $p < .001$) had strong, negative correlations with postpartum depression rates, even after controlling for maternal covariates (Hibbeln 2002). Other observational studies of perinatal women indicate that the recovery of maternal DHA status from delivery to 32 weeks postpartum was significantly slower in women who had postpartum depression compared with nondepressed control subjects (Otto et al 2003). Similarly, serum DHA and the sum of n-3 PUFAs immediately following delivery have been shown to be lower and the ratio of n-6 to n-3 PUFAs were higher among women who subsequently developed depressive symptoms at 6–10 months postpartum compared with women who lacked symptoms (De Vriese et al 2003).

In the general population, n-3 PUFAs have been used to treat mood disorders in several randomized double-blinded placebo-controlled trials (Nemets et al 2002; Peet and Horrobin 2002; Stoll et al 1999; Su et al 2003). For example, Nemets and colleagues (2002) randomized 17 women and 3 men with unipolar MDD to 2 g EPA or placebo adjunct to antidepressant therapy and found that in 4 weeks, depression scores decreased by 50% in the treatment group compared with 10% in the placebo group. Supplementation with EFA has also been used to improve depressive symptoms among people with treatment-resistant depression (Peet and Horrobin 2002). One randomized trial of EFA supplementation for MDD in the perinatal period was conducted. Llorente et al (2003) randomized 99 lactating women at delivery to 0.2 g DHA or placebo for 16 weeks. They found no difference in depressive symptoms between treated and untreated groups, but unlike many of the successful trials, the investigators used a supplement that contained no EPA and a low dose of DHA. Future research will be needed to determine whether n-3 PUFA supplements are effective in preventing or treating depression in the perinatal period and whether n-3 PUFAs augment the action of antidepressants or have antidepressant properties independent of medication. Deficiencies in n-3 PUFAs are present among depressed persons even after successful antidepressant therapy (Edwards et al 1998).

Folate and Vitamin B12

Folate and vitamin B12 are essential for normal central nervous system function and may modulate mood through several mechanisms. Folate and vitamin B12 are needed for single-carbon metabolism involved in the synthesis and metabolism of serotonin and other monoamine neurotransmitters and catecholamines (Bottiglieri 1996). Folate helps maintain normal brain concentrations of tetrahydrobiopterin, a cofactor in the synthesis of serotonin and catecholamines (Hamon et al 1986). Additionally, a deficiency of either folate or vitamin B12 causes elevated homocysteine concentrations, which may contribute to the pathogenesis of MDD by mediating a vascular response (Clarke et al 1998; Reynolds et al 1984).

Patients diagnosed with MDD tend to have lower concentrations of serum or red cell folate than healthy control subjects (Alpert et al 2000; Bjelland et al 2003; Morris et al 2003; Rosche et al 2003). Poor folate status has been associated with severity of depression and prolonged episodes of MDD (Alpert et al 2000). Dietary folate may be lower among depressed men than healthy control subjects (Tolmunen et al 2003) but has not been studied in women. Two studies indicated that a point mutation in a gene that codes for a key enzyme in folate metabolism is a risk factor for depression (Arinami et al 1997; Bjelland et al 2003).

Particularly intriguing are data that suggest an interaction between folate and the efficacy of antidepressant medication. Several trials indicate that poor folate status reduces the response to antidepressants. Investigators reported that the nonresponse rate to an open-label 8-week course of fluoxetine was significantly higher among depressed patients with deficient or marginal serum folate concentrations ($\leq$ 2.5 ng/mL) compared with patients with adequate folate status (35% vs. 20%; Fava et al 1997). Nonresponders to the 8-week trial were subsequently randomized to either a higher dose of fluoxetine, despiramine augmentation of fluoxetine, or lithium augmentation of fluoxetine for a total of 4 weeks. The investigators found that poor folate status at the start of the initial 8-week treatment was associated with further treatment resistance after the 4-week randomized trial. Specifically, 45% of patients with normal folate responded to the new treatment, whereas only 7% of patients with low folate had an adequate response (Papakostas et al 2004a). Finally, patients whose depression had remitted at the end of the 8-week fluoxetine trial and had their dose increased to 40 mg/day were followed for a 28-day continuation period of treatment. Relapse rates during the continuation period were significantly higher among the low-folate group compared with the group with adequate folate at baseline (43% vs. 3%; Papakostas et al 2004b). Similar poor response in relation to low folate has been reported for treatment with sertraline (Alpert et al 2003) and desipramine (Wesson et al 1994). Furthermore, a number of double-blinded, placebo-controlled randomized trials have successfully used folic acid to augment antidepressant medication (Alpert et al 2000, 2002; Coppen and Bailey 2000).

Vitamin B12 concentrations in blood have been shown to be lower in depressed patients than nondepressed patients in most (Baldewicz et al 2000; Bjelland et al 2003; Penninx et al 2000; Tiemeier et al 2002) but not all (Fava et al 1997) studies. We are not aware of any studies that have used vitamin B12 supplements for the treatment or prevention of MDD. Unlike folate, vitamin B12 does not appear to modify the response to antidepressant treatment (Papakostas et al 2004a, 2004b).

Antioxidants

The brain is a major consumer of oxygen. Therefore, it is an important substrate for oxidation by reactive oxygen species. In particular, neuronal membranes are extremely susceptible to lipid peroxidation due to their high polyunsaturated fatty acid content. Peroxidation of nerve endings alters neurotransmitter transport and subsequently affects central nervous system functioning (Rafalowska et al 1989). In addition to causing neuronal damage, reactive oxygen species can cause oxidative stress and vascular changes, all of which have been observed in MDD (Krishnan and McDonald 1995). Antioxidants serve as the body's defense mechanism against oxidative stress, but interestingly, the antioxidant concentration of the brain is low (Mahadik and Mukherjee 1996), which may favor a pro-oxidant environment. High-dose antioxidant supplementation has been shown to slow

the progression of neuronal damage and vascular disease (Grundman 2000), and therefore may be effective in preventing or treating MDD. Surprisingly, few studies have assessed the relation between antioxidants and MDD.

Vitamin C (ascorbic acid) is a potent antioxidant required for prevention of oxidative stress. In fact, no other antioxidants are reduced until ascorbic acid is depleted. In small studies, high-dose ascorbic acid supplements (3 g/day) have been shown to reduce severity of MDD (Cocchi et al 1980; Naylor and Smith 1981), as well as depressive scores in healthy individuals (Brody 2002). Lower doses of vitamin C or dietary vitamin C have not been studied.

Vitamin E refers to a family of tocopherols that are the major lipid soluble antioxidants that protect membranes from peroxidation. A cross-sectional hospital-based observational study reported that a group of men and women with MDD had lower concentrations of serum vitamin E than healthy control subjects and that there was a significant, positive correlation between serum vitamin E and the duration of MDD (Maes et al 2000). Similar results among men only were reported by another group (Shibata et al 1999). A community-based longitudinal study of elderly men and women revealed no relation between vitamin E and subsequent depressive symptoms (Tiemeier et al 2002). Conflicting results could be due to different study populations, study designs, analytical strategies, and definitions of the outcome (MDD vs. depressive symptoms).

Carotenoids are antioxidants in vitro, but to our knowledge, they have not been studied in relation to MDD.

Selenium

Selenium is thought to play an important role in brain function because its metabolism in the brain is vastly different than in other organs (Whanger 2001). Specifically, during times of deficiency, the brain retains selenium at the expense of tissues such as muscle, kidney, and liver (Whanger 2001). Indeed, selenium is an important modulator of mood. Metabolic feeding trials have shown that individuals fed marginal selenium diets reported more symptoms of depression and hostility than individuals fed higher selenium diets (Finley and Penland 1998; Hawkes and Hornbostel 1996). In randomized trials, supplementation of 100–150 μg selenium/day for 5 or 6 weeks significantly improved mood scores compared with placebo (Benton and Cook 1991; Scott 1993), and subjects with baseline diets lower in selenium evidenced a greater improvement (Benton and Cook 1991). In a randomized trial of HIV-infected patients, researchers found that supplementation with 200 μg/day selenium caused a 20-fold reduction of depressed–dejected mood state and a trend toward improvement in quality of life scores (Shor-Posner et al 2003).

The mechanism by which selenium affects mood is not certain. Small changes to thyroid function have been associated with depressive symptoms (Henley and Koehnle 1997). Interestingly, selenium is required for synthesis and metabolism of thyroid hormones (Rayman 2000). A deficiency is thought to compromise thyroid-hormone metabolism and may mediate the effects of altered selenium status and depression (Sher 2000). Similarly, selenium deficiency reduces immune function (Rayman 2000), which is also characteristic of individuals with MDD (Maes et al 1991). Finally, selenium is an essential component of the antioxidant enzyme glutathione peroxidase, which scavenges hydrogen peroxide, thereby protecting nerves from lipoperoxidation and tissue damage.

Iron

Iron deficiency alters myelination, neurotransmitter metabolism, and function (Beard and Connor 2003), cellular and oxidative processes (Beard 1995), and thyroid hormone metabolism (Zimmermann and Kohrle 2002). Decreased brain iron stores may impair the activity of iron-dependent enzymes that are necessary for the synthesis, function, and degradation of dopamine, serotonin, and noradrenaline (e.g., monoamine oxidase and aldehyde oxidase; Oski 1979). Fatigue, irritability, apathy, and an inability to concentrate are common symptoms of iron deficiency. Randomized trials have shown that among women of childbearing age, iron deficiency causes deficits in cognitive function such as memory, learning, and concentration (Ballin et al 1992; Bruner et al 1996). Iron deficiency without anemia is associated with higher depressive scores among young women taking oral contraceptives (Rangan et al 1998). A recent study reported significantly higher depressive symptoms at postpartum day 28 among women who were anemic on postpartum day 7 compared with nonanemic women and a negative correlation between hemoglobin concentrations and depressive symptoms (Corwin et al 2003). In a randomized, placebo-controlled trial of iron supplementation from 10 weeks to 9 months postpartum in South Africa, investigators reported that iron improved depressive symptoms among anemic mothers (Beard et al 2005).

Zinc

After iron, zinc has the second highest concentration of all transition metals in the brain (Huang 1997). Most zinc is localized within synaptic vesicles of specific neurons (Frederickson 1989), where it is thought to modulate synaptic transmission and may itself act as a neurotransmitter (Huang 1997). Zinc is also needed for DNA synthesis and cell membrane stabilization. It is essential to the structure and function of regulatory, structural, and enzymatic proteins. Zinc deficiency causes immunosupression, which is also a common occurrence in MDD (Maes et al 1991). Clinical manifestations of zinc deficiency include behavioral disturbances such as depression and dysphoria (Solomons 1988). Blood zinc concentrations are lower in individuals with MDD compared with control subjects (Hansen et al 1983; McLoughlin and Hodge 1990). Maes and colleagues studied serum zinc in 48 unipolar MDD patients and 32 control subjects and found that zinc concentrations were correlated with severity of depression (Maes et al 1994).

Summary

Nutritional status plays an important role in mental health, and poor nutrition may contribute to the pathogenesis of MDD. Data support a relationship between MDD and poor EFA and folic acid status, with a strong likelihood that these nutrients can be used effectively to treat MDD or to augment existing treatments. Other nutrients, including dietary antioxidants and certain trace elements, have not been studied as rigorously, but have strong biologic plausibility in affecting normal brain function and modulating mood. Although the nutrients discussed here have varying physiologic roles in maintaining mental health, what unifies them is that a deficiency of each is relatively common among individuals who consume a typical Western diet. Although nutrient deficiencies are prevalent among all Americans, they disproportionately affect low-income individuals. What is especially intriguing is that socially and economically disadvantaged women are also those at high risk of MDD (Murphy et al 1991), which suggests that poor nutrition may be an important contributor to mood disorders in this population.

Implications for Women of Childbearing Age

Nutritional interventions for improving mental health may be particularly salient among women of childbearing age. Women have roughly twice the risk of MDD as men (Kessler 2003). Diet quality among women is often poor, and half of American women are overweight (Flegal et al 1998). Furthermore, women of childbearing age are particularly vulnerable to nutritional deficiencies because pregnancy and lactation are major nutritional stressors to the body. In fact, for many nutrients, requirements reach a lifetime high during pregnancy or lactation. The high demands combined with inadequate intakes often lead to nutrient depletion by the end of gestation and a failure of stores to recover postpartum. For instance, maternal DHA status begins to decline by the second trimester as DHA stores are mobilized and transferred to the fetus (Al et al 2000). DHA stores are ultimately depleted in a majority of uncomplicated pregnancies and do not recover to first-trimester concentrations by 6 months postpartum (Al et al 2000). Similarly, among women with good iron status at the start of pregnancy, at least 80% who are not supplemented are iron deficient at delivery and 44% are anemic (Eskeland et al 1997). Furthermore, one third of women supplemented with iron during pregnancy are deficient at term (Eskeland et al 1997). Poor prenatal iron status increases the risk of postpartum iron deficiency and anemia (Bodnar et al 2002). Successive pregnancies (particularly those with a short interpregnancy interval) may compound the problem and cause multiple marginal nutrient deficiencies.

If we are to advance our understanding of the role of nutrition in MDD prevention among childbearing-aged women, we must fill the important gaps in our knowledge. It is currently unknown how nutrition specifically affects women's mental health during pregnancy, postpartum, and more generally the childbearing years. Most previous studies sampled small hospital-based groups of Caucasian men and nonpregnant and nonlactating women, then did not stratify results by gender. Such studies not only have limited generalizability, but also prevent us from determining if nutrition has a differential impact on mood in women. Additionally, the literature is dominated by cross-sectional studies, which measure nutritional status (most often by a biochemical marker) and depression simultaneously. Cross-sectional studies cannot disentangle cause from effect. Because changes to appetite and body weight are among the diagnostic criteria for MDD (American Psychiatry Association 1994), poor nutrition may be simply a consequence of the disorder. Longitudinal studies are needed to determine whether poor nutritional status precedes the onset of depressive symptoms. Dietary intake was ignored by nearly all previous investigations but, if studied in conjunction with biochemical measurements of diet, can help to distinguish if reduced blood concentrations of nutritional biomarkers in MDD are caused by reduced intake or altered metabolism or enzymatic function. Previous studies have rarely adjusted for confounders, leading to potentially biased results.

In the future, large, population-based samples of racially/ethnically and socioeconomically diverse women should be followed longitudinally to determine whether nutritional status at baseline predicts subsequent depressive symptoms. Studies of pregnant women followed from early in gestation through 6 to 12 months postpartum should be a priority. Serial measurements of diet, supplement use, biochemical indices, depressive symptoms, and antidepressant use should be obtained. A longitudinal design with repeated measures is especially valuable for studies of perinatal women because their nutritional status changes rapidly, and MDD may be diagnosed and may resolve at any number of time points. In addition to EFA, folic acid, and vitamin B12, investigators should assess antioxidants, selenium, zinc, and iron because these nutrients have received less attention in the literature but hold substantial promise in modulating mood. Confounders and effect modifiers of the nutrition–MDD relation, including socioeconomic status, race/ethnicity, parity, body mass index, access to health care, physical activity, and dietary supplement use should be measured and addressed in the analysis. Interactions between nutrition and medication effectiveness may be particularly fruitful lines of investigation.

Although more research is needed to clarify the role of nutrition in the pathophysiology of MDD among childbearing-aged women, clearly the potential for dietary modification to improve mental health is compelling. Nutrition interventions are relatively inexpensive, easy to administer, and generally acceptable to patients. Indeed, nutritional modification may benefit psychiatric conditions and countless aspects of human well-being, as well as have the potential for tremendous public health impact.

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