

Role of docosahexaenoic acid in maternal and child mental health¹⁻⁴

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ABSTRACT

Mental health problems in women and children represent a significant public health problem worldwide, especially in developing countries. The role of nutrition as a cost-effective approach in the prevention and management of these conditions has received recent attention, particularly nutrients such as iron, zinc, and n-3 (omega-3) fatty acids, which play a role in brain structure and function. The objective of this article was to review current evidence on the relation between n-3 fatty acids, especially docosahexaenoic acid (DHA), and maternal and child mental health disorders. Human studies published in English were identified from Medline databases (1966 to June 2008) by using key search terms and review articles. A summary of the role of DHA in the human brain is followed by a review of human studies, both observational and intervention trials, that examine the relation between n-3 fatty acids such as DHA and depression and child mental health disorders. Observational studies support a direct association between poor n-3 fatty acid status and increased risk of maternal depression and childhood behavioral disorders such as attention-deficit hyperactivity disorder (ADHD). However, evidence from intervention trials is weak. Most of the studies reviewed had small sample sizes and were conducted in clinically diagnosed samples, with no placebo-controlled groups. Little is known about the benefits of DHA in the prevention of maternal depression and ADHD. Large, well-designed, community-based prevention trials are needed. *Am J Clin Nutr* 2009;89(suppl):958S-62S.

INTRODUCTION

Mental health disorders are an important cause of dysfunction throughout the world, accounting for 8.1% of the Global Burden of Disease (1) and disproportionately affecting women, children, and adolescents (2, 3). Recent reports stress the need for research about the causes and consequences of mental health disorders and for the application of this knowledge to policies and programs (4). In this effort, researchers have begun to focus on the role of nutrition in mental health, and evidence indicates that essential fatty acids (FAs) such as docosahexaenoic acid (DHA; 22:6n-3) may play an important role in the prevention and treatment of certain mental health disorders (5, 6).

The FAs that are biologically relevant for mental health include the long-chain n-3 FAs that are present in cell membranes in the brain and neural tissue, namely DHA and eicosapentaenoic acid (EPA; 20:5n-3). Although preformed DHA and EPA are present in cold water fish, such as salmon and tuna, their role in humans remains unclear. DHA and EPA can be synthesized from

the parent n-3 FA α -linolenic acid (ALA) in the liver through a series of elongation and desaturation steps. There have, however, been recent concerns that the efficiency of this process may be low (8%) because both n-6 and n-3 FAs share and compete for the same enzymes that are used for desaturation and elongation. In addition, n-6 FAs such as linoleic acid are widely present in vegetable oils, seeds, nuts, margarine, grains, eggs, and some meats, whereas n-3 polyunsaturated FAs (PUFAs) are found primarily in canola and soybean oil, flaxseed, walnuts, eggs, some meats, and cold water fish (7). Intakes of n-6 FAs have increased, resulting in a high ratio of n-6:n-3 FA intakes in the diet that may be associated with an increased risk of mental health disorders (5, 8).

The objective of this article was to review and summarize the literature on the relation between DHA and mental health disorders affecting women and children. After a brief summary of current knowledge on the role of n-3 FAs, especially DHA, in the structure and function of the human brain, evidence from observational and intervention studies that link DHA with maternal and child mental health is reviewed.

METHODS

We searched the Medline database from 1966 through June 2008 using the following search terms: *omega-3 fatty acids, DHA, fish oil, child, maternal, postpartum, perinatal, depression, mood, behavior, and ADHD*. We combined search terms such as DHA and omega-3 fatty acids with terms such as postpartum depression, mood, and ADHD. The search was limited to studies conducted in humans and published in the English language. We also identified articles from the bibliographies of relevant articles found in Medline.

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Long-chain PUFAs and the human brain

The n-3 and n-6 PUFAs comprise $\approx 14\%$ and 17% of the total FAs in the human brain and are predominantly DHA and arachidonic acid (AA; $20:4n-6$), respectively. Saturated FAs account for nearly one-third of all FAs; monounsaturated FAs and other PUFAs account for the remainder (6). Both DHA and AA accumulate rapidly in neural tissues during the brain growth spurt that occurs during gestation and the first year of life. Fetal accretion of n-3 PUFAs is particularly high during the last trimester ($\approx 50-60$ mg/d), and, although prenatal supplementation with preformed DHA has been shown to improve maternal and infant n-3 PUFA status, little is known about the long-term benefits to maternal and child health (9, 10). There is, however, considerable evidence from animal studies regarding the role of DHA in brain structure and function (6, 11). One advantage of animal models is that we can ethically restrict the dietary intakes of the parent n-3 FA ALA, which is an essential FA in humans. Studies in rats have shown that parental restriction results in reduced brain DHA concentration and FA status in the offspring, which is accompanied by poor cognitive and behavioral test performance (11, 12). There is also some evidence of programming during critical periods of development; studies in rats have shown that restriction of n-3 PUFAs during pregnancy and early infancy may result in impaired neural function and performance that cannot be reversed by subsequent dietary improvements (6). However, many methodologic problems make it difficult to extrapolate the findings to humans, eg, small sample sizes, variance in test type, and limited evidence of dose-response effects.

The evidence from human studies on the role of DHA in maternal and child mental health has focused primarily on depression or depressed mood and child behavior. The first section of this review focuses on the evidence from human studies that links n-3 FA status and intakes with depression in women and children, which is followed by a section on n-3 FAs and child mental health and behavior problems.

n-3 PUFAs and depression

Potential biological mechanisms

Major depressive disorders are characterized by alterations in neurotransmitter concentrations and function, especially lower concentrations of dopamine and serotonin (13). n-3 PUFAs can influence depression through their effects on membrane fluidity and/or modulation of the inflammatory response system, as shown in **Figure 1**. PUFA deficiency alters the FA composition of key organ membranes, including the brain, which affects membrane viscosity. Alterations in membrane viscosity can influence various steps in the metabolism of the neurotransmitter serotonin 5-hydroxytryptamine, which plays a key role in the pathophysiology of depression. Although studies have shown that depressed patients have reduced concentrations of n-3 PUFAs, especially DHA, in red blood cell membranes and an increased AA:EPA ratio in serum phospholipids and cholesteryl esters, these changes may be due to reduced intakes of n-3 PUFAs in depressed patients (14). An alternate pathway is the role of PUFAs in the synthesis of markers of immune function, which have been implicated in depression. An elevated n-6:n-3 ratio may be causally associated with increased concentrations of eicosanoids and proinflammatory cytokines such as tumor necrosis factor, which are seen in depression (14).

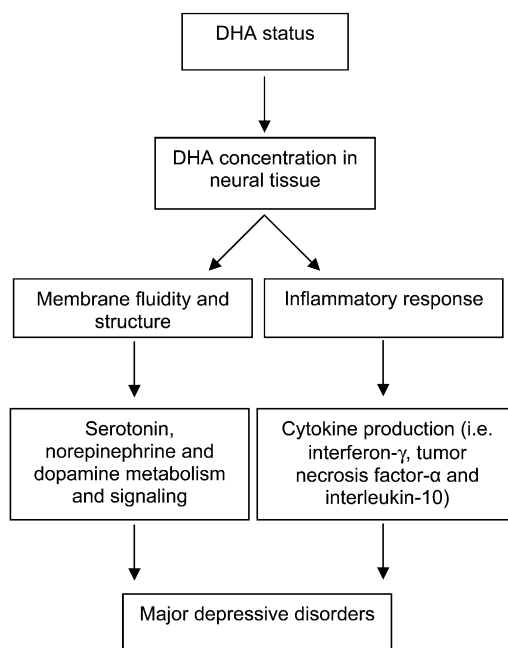


FIGURE 1. Mechanisms of action for docosahexaenoic acid (DHA) in major depressive disorders.

Observational studies

Of particular interest to maternal mental health are the results of an ecological analysis in which Hibbeln (15) reported an inverse relation between seafood consumption, a key source of n-3 PUFAs, and the prevalence of postpartum depression (PPD) in several countries. These investigators also found a similar relation between human milk DHA content and the prevalence of PPD, which supports the argument that women are less likely to suffer from PPD as their DHA status improves, presumably because of higher intakes of seafood—an important dietary source of n-3 FAs. Several recent observational studies have examined the relation between DHA intakes or status during pregnancy and the risk of PPD and have reported mixed findings. Two studies from England and Australia (16, 17) found that low DHA status and intakes during pregnancy were associated with an increased risk of PPD. In contrast, a study from Japan (18), where seafood consumption is much higher, failed to find a dose-response relation between n-3 and n-6 intakes during pregnancy and risk of PPD after adjustment for several confounding factors such as age, gestation, education, and income. PPD was evaluated by using the Edinburgh Postnatal Depression Scale in most of these studies. Although these studies suggest a relation, more definitive conclusions can be made only from well-designed controlled trials of n-3 FA supplementation—studies that are difficult and expensive to conduct. In addition, because seafood is also a source of neurotoxic contaminants, such as mercury and polychlorinated biphenyls, these potential dangers must be considered before recommendations are made (19).

Intervention studies

Most studies that have examined the effects of increasing the intakes of n-3 PUFAs, especially DHA, on depressed mood or depression have been done in clinical settings in subjects with

a diagnosis of depressed mood, clinical depression, or PPD. In a recent systematic review, Appleton et al (20) identified 18 randomized controlled trials, of which 12 were included in a meta-analysis. Most study subjects had a clinical diagnosis, including unipolar depression, bipolar disorder, schizophrenia, chronic fatigue syndrome, or PPD. Most studies included women, and only one was conducted in children. The number of subjects ranged from 11 to 452, and the duration of the interventions ranged from 28 to 180 d. Varying doses and combinations of EPA and DHA were used, ranging from 0.2 to 9.6 g PUFA/d and a median of 2.0 and 0.8 g/d, respectively. The overall effect was small (0.13; 95% CI: 0.01, 0.25), and nearly 50% of the studies found no effects. A significant effect was found (0.57; 95% CI: 0.37, 0.77) in the subset of 8 studies conducted in subjects with a diagnosis of depression.

Although there has been considerable interest in the role of n-3 FAs and mental health, little is known about their effects on maternal mental health. Many women of reproductive age, especially during pregnancy and lactation, are at increased risk of both low PUFA status, due to increased requirements, and PPD, which in turn increases the risk of adverse birth outcomes and developmental problems for the offspring (21). The reduced responsiveness of pregnant and lactating women to antidepressant therapy and the possible risk of teratogenicity further emphasize the need for safe and inexpensive interventions (5). The increased demands for several nutrients, including DHA, during this vulnerable period suggest a role for nutrition. Observational data suggest that PPD may be associated with n-3 FA intakes and status, but there are few well-controlled trials that have evaluated the effects of increasing the intakes of FAs, especially DHA, on depressive symptoms in postpartum women. The findings are mixed and difficult to interpret because of differences in study design. Most studies were small and typically provided fish oil-based supplements that contained high doses of EPA and DHA (1-3 g/d) as an adjuvant to ongoing treatment of PPD (22). Two small intervention trials (23, 24) conducted in women ($n < 20$) with PPD showed reductions in depressive symptoms over time, but lacked a control group, which make it impossible to attribute changes to the intervention. Two placebo-controlled trials that examined the effects of supplementation during the postpartum period found no group differences in depressive symptoms (25, 26). The trials varied in both dosage and duration (25, 26). A study by Su et al (27) examined the effects of prenatal supplementation with n-3 FAs administered for 8 wk beginning at 24 wk of gestation among women with a history of depression ($n = 118$). They found significant decreases ($\approx 50\%$) in mean scores on both the Hamilton Rating Scale for Depression (HRSD) and the Edinburgh Postnatal Depression Scale between those who received n-3 FAs and those who received a placebo, which indicated no benefits of n-3 PUFAs and suggested that the timing of the intervention may be important. We did not identify any studies conducted in developing countries, where maternal mental health disorders are often underrecognized and receive little or no attention.

n-3 PUFAs and child mental health

Potential biological mechanisms

The role of n-3 PUFAs in child mental health has received recent attention related to the treatment of attention-deficit hy-

peractivity disorder (ADHD). A few studies have also examined the relation between n-3 PUFAs and children's behavioral problems, depressed mood, and clinical depression. Although the exact mechanisms by which PUFAs, especially DHA, affect behavioral disorders such as ADHD remain unclear, plausible evidence suggests why DHA may be involved in these disorders. DHA is important for both membrane fluidity and neurotransmitter function, especially synaptic signal transduction, particularly during the perinatal period (12, 28, 29). Deficits in frontal cortex dopamine neurotransmission seen in patients with ADHD could therefore be associated with lower brain DHA concentrations (6). Children with ADHD have also been shown to have lower plasma or red blood cell DHA concentrations and symptoms such as increased thirst and urination that are characteristic of essential fatty acid deficiency (30-34), which suggests alterations in FA metabolism that may share a common genetic susceptibility. These findings also suggest a possible role for DHA as an adjuvant therapy. Similar processes may play a role in other behavioral disorders and depression.

Observational studies

Cross-sectional studies have reported that the frequency of behavioral problems in boys is inversely associated with n-3 PUFA status (30, 31). For example, Stevens et al (30) found that the frequency of hyperactivity, conduct disorder, anxiety, impulsivity, and impulsivity-hyperactivity, based on the Connor's Parent Rating Scale, was significantly lower in boys with high FA concentrations (mean = 4.11% of total FAs) than in those with low status (mean = 2.78% of total FAs). Similar findings were found for parent ratings of temper tantrums and sleep-related problems. The analyses, however, were not adjusted for potentially confounding factors such as maternal depression, which may be associated with the outcomes, and no significant differences in teacher rating scales were observed. Several case-control studies (32-34) have reported low blood concentrations of DHA and AA in children with ADHD compared with age-sex matched control subjects. For instance, Colter et al (34) compared 11 adolescents with ADHD with 12 age-matched control subjects and found that, although both groups consumed similar amounts of n-3 and n-6 FAs, the children with ADHD had significantly lower blood concentrations of DHA and a lower ratio of n-3:n-6 FAs than did the control subjects. n-3 FA status was inversely correlated with scores on several Connor's behavioral scales, which indicated behavioral vulnerability among children with low n-3 FA status. Finally, several recent longitudinal studies found a negative association between DHA status early in life and subsequent behavior problems in young children (26, 35, 36).

Intervention trials

The value of providing n-3 FA supplements, especially DHA, to children with behavioral problems such as ADHD has been a major area of interest in recent years. However, most of the studies have had small sample sizes and mixed findings (37). For example, Voigt et al (38) found no improvements in symptoms after supplementation with 345 mg/d DHA for 4 mo. Similarly, Hirayama et al (39) found no differences in ADHD symptoms between children ($n = 40$) who were randomly assigned to consume DHA-containing foods (3.6 mg/wk) and those assigned to

consume control foods. In contrast, ADHD-related symptoms in children with learning difficulties (eg, dyslexia) decreased after 12 wk of supplementation with a highly unsaturated FA mixture (40). Similarly, fish-oil supplementation for 3 mo significantly improved literacy skills and behavior among children ($n = 117$) with developmental coordination disorders (41). Sorgi et al (42) reported significant improvements in behavior among children ($n = 9$) who received 16.2 g EPA/DHA concentrates for 8 wk, but there was no control group. A recent study from India, a developing county, reported significant improvements in the hyperactivity scores of children with ADHD after they consumed for 3 mo supplements containing flaxseed oil, which is rich in the parent n-3 FA ALA (200 mg/d) (43). Improvements were seen in impulsivity, restlessness, inattention, self-control, and learning problems, based on a validated parent rating scale. Improvements were also seen in erythrocyte membrane FA concentrations, especially DHA and EPA, which indicates that the precursor ALA can be effectively converted. The absence of a control group was a major weakness.

Two recent studies that included a control group have reported promising findings (44, 45). Germano et al (44) evaluated the effects of supplementing children with ADHD ($n = 31$) with high doses of EPA and DHA (2.5 g/d per 10 kg body weight) and found significant improvements in inattention and hyperactivity over time, but the loss to follow-up was high ($\approx 50\%$). Significant improvements were also seen in a randomized controlled study conducted in Australia (45). Children aged 7–12 y ($n = 132$) who had ADHD scores above the 90th percentile based on parent's ratings on the Connor's ADHD index were randomly allocated to 3 groups: 1) treatment with PUFAs alone (500 mg/d), 2) treatment with PUFAs and micronutrients, and 3) placebo for 15 wk. After the intervention, all children received PUFAs plus micronutrients (vitamin A, B-complex vitamins, vitamin C, vitamin D, iron, and zinc) for weeks 16–30. None of the children received stimulant medication. At 15 wk, significant improvements were seen in 9 of 14 ADHD scales (Connor's Parent Rating Scales) in the PUFA group compared with the placebo group. The findings were confirmed for inattention, hyperactivity, and impulsivity in a subsequent crossover design. There were no benefits derived from the micronutrient supplement beyond those observed for the PUFA supplement.

SUMMARY

There is plausible evidence from animal studies and observational studies in humans that support an important role for DHA in maternal and child mental health. Although the results of the intervention trials in humans provide some support for a relation between DHA status and mental health, many of these studies lack a placebo-controlled group, which makes it difficult to attribute changes in mental health symptoms or behavior to the intervention. The need for well-designed studies is further heightened by recent concerns that promoting the consumption of seafoods that are naturally rich sources of the n-3 FAs may increase the exposure to environmental toxins that can cause neurologic damage, such as mercury and polychlorinated biphenyls (19). The effects of the total n-6:n-3 ratio and interactions with other key nutrients, such as iron and zinc, also need to be evaluated. Finally, the role of DHA during critical windows of development needs further evaluation in well-designed longitudinal follow-up

studies in light of the effects of DHA on immune function and on neurotransmitter synthesis and function, which are altered in several mental disorders. (Other articles in this supplement to the Journal include references 46–51.)

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