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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First published online January 28, 2009; doi: 10.3945/ajcn.2008.26692F.
Long-chain PUFAs and the human brain

The n–3 and n–6 PUFAs comprise ~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 (~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).

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...
Potential biological mechanisms

n–3 PUFAs and child mental health

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. For example, Voigt et al (38) found no improvements in symptoms 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 country, 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 \((200 \text{ mg/d})\) (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). Gervino et al (44) evaluated the effects of supplementing children with ADHD \((n = 31)\) with high doses of EPA and DHA \((2.5 \text{ g/d per 10 kg body weight})\) and found significant improvements in inattention and hyperactivity over time, but the loss to follow-up was high (~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 \((500 \text{ mg/d})\), 2) treatment with PUFAs and micronutrients, and 3) placebo for 15 wk. After the intervention, all children received PUFAs plus micronutrients \((\text{vitamin A, B-complex vitamins, vitamin C, vitamin D, iron, and zinc})\) for weeks 16–30. None of the children received stimulant medication. At 15 wk, significant improvements were seen in 9 of 14 ADHD scales \((\text{Connor’s Parent Rating Scales})\) 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 neurotransmitter synthesis and function, which are altered in several mental disorders. (Other articles in this supplement to the Journal include references 46–51.)

We thank Maureen Black for her review of the manuscript and excellent feedback.

The authors’ responsibilities were as follows—UR: participated in the data collection, review of the literature, and writing and review of the manuscript; and BI-K and AD: participated in the data collection and review of the literature, critically reviewed the manuscript, and provided feedback. None of the authors had a conflict of interest.

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