



The role of omega-3 polyunsaturated fatty acids in mental disorders | Review

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Abstract: While the role of omega-3 polyunsaturated fatty acids (PUFAs) in physical health is well established, it is becoming increasingly evident that they are also important for mental health. A decrease in the intake of omega-3 PUFAs in Western countries over recent decades may have affected the prevalence of mental disorders. Omega-3 PUFAs play fundamental roles in the development, functioning and aging of the brain. In humans, dietary deficiencies of omega-3 PUFAs, such as docosahexaenoic acid and eicosapentaenoic acid, have been associated with an increased risk of various mental disorders. However, the findings of randomised clinical trials investigating therapeutic effects of omega-3 PUFAs in psychiatric disorders are inconclusive, which limits their use in clinical practice. High-quality clinical trials need to be conducted in order to assess the efficacy of omega-3 PUFAs in the prevention and treatment of mental disorders. Unwanted side effects of omega-3 PUFA supplementation should be considered. These may become apparent many years after administration and therefore elude detection.

Keywords: Omega-3 polyunsaturated fatty acids; brain; mental health; psychiatric disorders.

1. Introduction

Homo sapiens evolved in an environment rich in nutritional omega-3 polyunsaturated fatty acids (PUFAs) [1]. Palaeontological evidence suggests a link between access to food and brain size [2]. The interaction between dietary intake of omega-3 PUFAs and brain evolution is particularly well documented. Docosahexaenoic acid (DHA), the most abundant omega-3 PUFA in brain cell membranes [3], cannot be synthesised efficiently by the human body and therefore needs to be provided largely by the diet [4]. Access to DHA during the evolution of hominids has been proposed to have played an essential role the increase in the ratio of brain to body mass (encephalisation) [4]. Seafood is rich in omega-3 PUFAs that are crucial to brain development, so this source of food may have been nutritionally important in hominid evolution. A shore-based diet including the consumption of fish and shellfish with its high DHA content may have been necessary for encephalisation in hominids [2].

PUFAs constitute approximately 20% of brain weight [5] and comprise about 80% of total membrane phospholipids. More than 90% of PUFAs in the mammalian brain are composed of the long-chain PUFAs arachidonic acid (AA) and docosahexaenoic acid (DHA) [6]. PUFAs influence brain functions by altering the biophysical properties of cell membranes. Alterations in the lipid environment of the phospholipid bilayer cause functional changes in the activity of receptors and other membrane proteins [7]. PUFAs are involved in maintaining normal membrane structure and function and play critical roles in brain development and neurotransmission [8,9]. PUFAs are involved in brain function through various mechanisms, including activation of receptors and cell signaling pathways as well as modulation of the endocannabinoid system [10]. AA, DHA and their metabolites act as intracellular second messengers and modulate various brain processes, such as gene transcription, neurotransmission and neuroinflammation

[11]. DHA can affect brain plasticity and cognition in rodents by increasing hippocampal levels of brain-derived neurotrophic factor [12] and through metabolic effects, such as stimulation of glucose utilisation [13] and mitochondrial function [14] as well as by a decrease of oxidative stress [12]. Moreover, diets rich in omega-3 PUFAs can help upregulate genes involved in maintaining synaptic function and plasticity in rodents [15] and can support cognitive functioning in humans [16].

Brain function is critically dependent on adequate PUFA consumption [17]. PUFAs in the human body include two main groups, omega-6 and omega-3 PUFAs, which are derived from two essential fatty acids, i.e. linoleic acid (LA) and α -linolenic acid (ALA), respectively [18]. All omega-3 PUFAs are derived from ALA through desaturation, elongation and β -oxidation [19]. In humans, the long-chain PUFAs can be derived from the diet or synthesised in the liver from their respective shorter-chain PUFAs, LA (for AA) and ALA (for DHA). However, biological conversion is relatively slow and inefficient. Diet is therefore the main source of these fatty acids in humans [20]. The typical diet in Western countries is estimated to contain an omega-6 to omega-3 ratio of 15–20:1 [21,22]. Since omega-3 and omega-6 PUFAs compete for incorporation into cell membranes [23], a balanced intake of these types of PUFAs is important. In addition, different PUFAs have opposing physiological functions, with omega-6 and omega-3 PUFAs promoting systemic pro-inflammatory and anti-inflammatory states, respectively [22]. While omega-6 PUFAs are converted to AA and then to prostaglandins and leukotrienes, which are responsible for the pro-inflammatory effects, the omega-3 fatty acids DHA and eicosapentaenoic acid (EPA) act as competitive inhibitors of omega-6 PUFAs, leading to a decrease in the synthesis of pro-inflammatory mediators [24].

Over recent decades, a decrease in the intake of omega-3 PUFAs has occurred, while the consumption of saturated fatty acids, linoleic acid and trans fatty acids has significantly increased in Western countries. This may be associated with health effects and may have affected the prevalence of mental disorders. It is generally assumed that an omega-3 PUFA deficiency in rodents leads to impaired learning and memory [25,26], while a dietary deficiency of these compounds in humans has been linked to an elevated risk of various mental disorders [27–31]. As early as 1981, it was suggested that mental health problems may result from a deficiency in omega-3 PUFAs [32]. Based on the successful therapy of individuals with psychiatric disorders with flax oil, which is rich in α -linolenic acid (ALA), it was proposed that omega-3 fatty

acids could be useful in the management of mental disorders [32]. While these findings were largely ignored, interest in the therapeutic effects of omega-3 PUFAs increased when reports demonstrated reduced concentrations of these compounds in the erythrocyte membranes of people with depression and schizophrenia [33–35]. Furthermore, epidemiological studies showed associations between the amount of fish consumption in national diets and the prevalence of depression [36]. Further reports also demonstrated correlations between the intake of fish and postnatal depression [37], bipolar disorder [38], and homicide [39]. Consequently, pilot trials using fish oil derivatives were conducted in individuals with mood disorders [40–42] or schizophrenia [43–45]. These studies provided preliminary evidence of symptomatic improvement following the administration of omega-3 fatty acids.

2. Omega-3 PUFAs and mental disorders

Omega-3 PUFAs are essential for the growth and development of the central nervous system during pregnancy as well as in infancy and childhood [46]; a sufficient dietary supply of these compounds is therefore essential for normal brain development [46–52]. Omega-3 PUFA deficiencies have been suggested to be implicated in the pathophysiology of neurodevelopmental disorders, such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Decreased omega-3 PUFA levels found in individuals with ASD suggest that supplementation could have the potential to improve some symptoms (see Table 1). However, in view of the available evidence, the recommendation of omega-3 fatty acids as an alternative treatment in autism spectrum disorder would be premature. At present, there is little evidence to support the efficacy of omega-3 PUFA supplementation in reducing the core symptoms or improving other outcome measures in ADHD (Table 1).

Low intake of omega-3 fatty acids may predispose certain individuals to major depression, and dietary PUFA supplementation may have preventive and therapeutic effects. However, this needs to be examined in well-designed, large-scale studies. Preliminary evidence suggests that bipolar depressive symptoms, but not manic symptoms, may be improved by adjunctive administration of omega-3 PUFAs (see Table 1).

Individuals with schizophrenia may have a potentially treatable omega-3 PUFA deficiency. However, the findings of intervention trials are inconsistent and the efficacy of omega-3 supplementation may depend on the stage of the disorder. At present, omega-3 PUFAs cannot be

recommended in the therapy of schizophrenia. However, the available findings call for high-quality studies. In particular, the effects of omega-3 PUFAs in different stages of schizophrenia should be investigated in more detail (see Table 1).

Omega-3 fatty acids are often considered to be a promising approach to improving brain functions and retarding the progression of cognitive decline and dementia syndromes, such as Alzheimer's disease and vascular dementia. This assumption is based largely on findings of preclinical and epidemiological studies. Preliminary findings of a randomised controlled trial showed that omega-3 PUFA monotherapy improved cognition scores in people with mild cognitive impairment [53]. The promising findings of epidemiological studies suggest that omega-3 PUFAs may represent a potentially useful strategy in the prevention of Alzheimer's disease. However, clinical intervention trials have revealed little influence of omega-3 PUFAs on Alzheimer's disease (see Table 1). Omega-3 fatty acid supplementation has been suggested to have beneficial effects only in premorbid or early disease stages, particularly in non-carriers of the apolipoprotein E-ε4 risk gene [54]. The effects of omega-3 fatty acids in other types of dementia, such as vascular dementia, remain unclear [55].

The evidence for therapeutic effects of omega-3 PUFAs in obsessive-compulsive disorder, post-traumatic stress disorder or borderline personality disorder is insufficient (see Table 1).

To sum up, the evidence for preventive or therapeutic efficacy of omega-3 PUFAs in mental disorders is insufficient (Table 1). High-quality randomised controlled trials with large samples and long durations are needed. Numerous factors possibly modulating the effects of omega-3 PUFAs on behaviour, such as baseline PUFA status, other dietary components, sex, age and genotype (e.g. apolipoprotein E), should be taken into account.

3. Adverse effects of omega-3 PUFAs

Intervention trials with omega-3 fatty acids have reported no serious adverse reactions at the doses administered [56]. The more common adverse effects of fish oil preparations, particularly in higher dosages, include nausea, fishy belching and loose stools [57]. High doses of omega-3 PUFAs have been shown to prolong bleeding time [44,58]. The supplementation of supra-physiological doses of omega-3 PUFAs for extended periods of time may be associated with serious side effects, such as various kinds of cancer [59]. These may become apparent many years following supplementation and elude detection.

Fish oil supplements commonly contain antioxidants and oxidation products of omega-3 PUFAs, both of which may lead to adverse reactions. Omega-3 fatty acids are highly prone to oxidative degradation, and a substantial proportion of omega-3 fish oil preparations available in several countries have been found to significantly exceed the international voluntary safety recommendations for total oxidation [60]. Potentially negative health effects resulting from the consumption of oxidised lipids are a cause for concern [59]. Omega-3 PUFAs oxidise easily during storage, with the result that PUFA supplements contain lipid peroxides and secondary oxidation products, while the levels of unoxidised fatty acids gradually diminish. PUFA oxidation can be reduced, but not prevented, by added antioxidants. The composition of a fish oil supplement in terms of PUFA levels cannot be inferred from the concentrations shown on the label. Possible adverse consequences of the long-term use of vitamin E added as an antioxidant to fish oil supplements should also be considered, since large-scale trials of α -tocopherol supplementation have suggested a link to elevated rates of prostate cancer [61,62].

4. Conclusions and future directions

Most research on omega-3 PUFAs in mental disorders has been performed in individuals with depression and schizophrenia. Pilot studies of omega-3 PUFA supplementation have provided promising results, although with some discrepancies. Very large, definitive randomised controlled trials are needed in order to confirm the available preliminary findings.

Optimal dosage is an important issue in omega-3 supplementation trials. The PUFA dose needed to elicit therapeutic benefits may depend on baseline levels, i.e. low concentrations of DHA at baseline may require higher initial doses than conditions with higher concentrations. Whether or not people with low omega-3 PUFA status are more responsive to PUFA administration is unknown. Future studies should therefore attempt to identify subgroups of people who are most likely to benefit from omega-3 supplementation, including those with low baseline status. There could also be a threshold in regard to omega-3 PUFAs, above which supplementation has little effect. In addition, the ratio between DHA, EPA and AA needs to be considered. Another important question to be addressed is whether there is a critical age for effective omega-3 PUFA supplementation. The findings of animal studies suggest that an optimal time frame for omega-3 PUFA supplementation exists during early brain development [63–65].

Table 1. Omega-3 PUFAs and mental disorders

ASD	<p>Decreased blood omega-3 PUFA concentrations [66–68].</p> <p>Differences in omega-3 PUFAs, omega-6 PUFAs and/or the ratio between omega-6 and omega-3 PUFAs found in some studies [68,69], but not in others [70,71].</p> <p>Decreased DHA, EPA and AA concentrations and increased omega-6 to omega-3 PUFA ratio [72].</p> <p>Significant symptom reduction following omega-3 PUFA supplementation in open-label trials [73–78].</p> <p>Inconclusive findings regarding symptom reduction following omega-3 PUFA supplementation in randomised controlled trials [79,80].</p> <ul style="list-style-type: none"> • <i>Insufficient evidence for therapeutic efficacy of omega-3 PUFAs</i> [81–83].
ADHD	<p>Increased blood ratio of omega-6 to omega-3 PUFAs [84–87].</p> <ul style="list-style-type: none"> • <i>Insufficient evidence for therapeutic efficacy of omega-3 PUFAs</i> [88–90].
Major depressive disorder	<p>Reduced risk of depression following fish consumption [91].</p> <p>Inverse association between intake of fish or omega-3 PUFAs and risk of depression [36].</p> <p>Negative association between intake of omega-3 PUFAs and depression [92,93].</p> <p>Low concentrations of omega-3 PUFAs compared to controls [94,95].</p> <p>No associations between intake of omega-3 PUFAs and depressive symptoms in cross-sectional studies [96–102].</p> <p>Beneficial effects of omega-3 PUFA supplementation compared to placebo [40,42].</p> <p>No beneficial effects of omega-3 PUFA administration compared to placebo [104,105].</p> <p>Beneficial effects of omega-3 PUFAs depend on the severity of depressive symptoms at baseline (benefits with severe depressive symptoms, no benefits with mild depressive symptoms) [106].</p> <ul style="list-style-type: none"> • <i>Insufficient evidence for therapeutic efficacy of omega-3 PUFAs</i> [107].
Bipolar disorder	<p>Lower incidence in populations with high consumption of seafood [108].</p> <p>Reduced intake of PUFAs (EPA, DHA, AA, and DPA) and increased intake of saturated fats [109].</p> <p>Reduced DHA levels in erythrocyte membranes [110,111].</p> <p>Beneficial effects of omega-3 PUFAs on depressive symptoms but less on manic symptoms [112–114].</p> <p>Beneficial effects of omega-3 PUFAs as adjunctive therapy on bipolar depression, but not on manic symptoms [115,116].</p> <ul style="list-style-type: none"> • <i>Insufficient evidence for therapeutic efficacy of omega-3 PUFAs</i>.
Schizophrenia	<p>Reduced PUFA concentrations in erythrocyte membranes [117] and brain cells [118].</p> <p>Inverse association of omega-3 PUFA intake and severity of positive symptoms [119].</p> <p>Beneficial effects of omega-3 PUFA supplementation on positive and negative symptoms in some studies [32,120–122], but not in others [123,124].</p> <ul style="list-style-type: none"> • <i>Insufficient evidence for therapeutic efficacy of omega-3 PUFAs</i> [125–128].
Mild cognitive impairment	<p>Improved cognition following omega-3 PUFA monotherapy compared to placebo [53].</p> <ul style="list-style-type: none"> • <i>Insufficient evidence for therapeutic efficacy of omega-3 PUFAs</i>.
Alzheimer's disease	<p>Reduced DHA concentrations in people with dementia compared to controls [129–131].</p> <p>Associations between the intake of fish or fish oil and improved cognition and a reduced risk of dementia [132–137].</p> <p>Association between increased intake of omega-3 PUFAs and higher total brain and hippocampal volumes in postmenopausal women [138].</p> <p>Inconclusive evidence for beneficial effects of omega-3 fish oil supplements on cognitive functioning [139].</p> <p>Reduced risk for Alzheimer's disease following higher intake of fish, but not of omega-3 PUFA supplements [104].</p> <ul style="list-style-type: none"> • <i>Insufficient evidence for preventive efficacy of omega-3 PUFAs</i>.
Other mental disorders	<ul style="list-style-type: none"> • <i>Insufficient evidence for therapeutic efficacy of omega-3 PUFAs in obsessive-compulsive disorder</i> [141], <i>post-traumatic stress disorder</i> [142,143] and <i>borderline personality disorder</i> [144–146].

The findings of studies on PUFA supplementation in mental disorders may have been influenced by numerous factors, such as heterogeneous design types, trial duration, dosage of omega-3 PUFAs, mode of administration, type of PUFA used (omega-3 and/or omega-6 PUFAs) or response assessment. When intervention trials use natural foods for omega-3 PUFA supplementation, such as omega-3 PUFA-rich vegetables or fish, the effects observed may be explained, at least partly, by other constituents contained in these foods (e.g. biologically active peptides or antioxidants). Many participants included in the studies of PUFA supplementation may have had comorbidities, which could have affected the treatment response. Beneficial effects of omega-3 PUFAs in the treatment of mental disorder may be confined to individuals with respective deficiencies. In particular, the role of perinatal deficits in DHA accrual in the brain as a preventable neuro-developmental risk factor for the subsequent emergence of psychopathological alterations requires further research. Since reduced concentrations of other food bioactives have also been observed in mental disorders, multi-ingredient supplementation may be needed to achieve benefits.

The available results regarding dietary supplementation of omega-3 PUFAs in individuals with mental disorders should be interpreted with care. A consideration in this context is the impact of mental disorders on lifestyle factors. For example, people with bipolar disorder show higher rates of familial conflicts, divorce, unemployment, and poor dietary habits [147]. Therefore, an improved lifestyle structure as a consequence of adherence to a trial could have beneficial effects. In addition, omega-3 PUFA administration may have positive effects on overall health. Omega-3 fatty acids, for example, may be beneficial for cardiovascular health and metabolic alterations [148,149]. The supplementation of omega-3 PUFAs may improve bipolar symptoms through their effects on brain functioning and general improvements in wellbeing and health.

Omega-3 PUFA supplements constitute a mixture of DHA, EPA, other fatty acids, additives (vitamin E) and unspecified concentrations of potentially harmful lipid peroxides and secondary oxidation products. Vitamin E added as an antioxidant could elevate the risk of prostate carcinoma in men. The biological effects and health consequences of the intake of oxidised fish oils remain largely unknown. Given the harmful effects of oxidised lipid products demonstrated in animal experiments and the paucity of available data in humans, it is not, at

present, possible to draw a definitive conclusion as to whether fish oils are safe following oxidation.

In summary, the many problems in assessing the effects of omega-3 fatty acids, such as identifying useful compounds, combining them at optimal dosages, examining the necessary durations of supplementation, and determining the critical phases of brain development for effective administration of omega-3 PUFAs, present an extraordinary challenge. One obstacle in the investigation is the heterogeneous nature of common mental disorders. Furthermore, unwanted side effects of omega-3 fatty acid supplementation should be considered. Short-term side effects of omega-3 PUFAs at the doses administered in past studies do not appear to give cause for concern. However, increased cancer risks may be associated with omega-3 supplementation, possibly due to the effects of PUFAs, PUFA oxidation products or added vitamin E. These adverse effects may become apparent many years after administration and may therefore fail to be detected. Great caution is advised in the recommendation of PUFA supplementation over extended periods of time. Deleterious effects of omega-3 PUFA supplements may be particularly relevant when administered during vulnerable phases of life, such as prenatal development, childhood and adolescence.

Conflict of interest

The author declares no conflict of interest.

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