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Omega-3 fatty acids and mental health

Klaus W. Lange *

Institute of Psychology, University of Regensburg, 93040 Regensburg, Germany

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ABSTRACT

Nutrition plays a key role in brain development, mental health, and psychiatric disorders. The role of omega-3 polyunsaturated fatty acids in physical health is well established, and their role in mental health is becoming increasingly evident. Omega-3 fatty acids are involved in a wide range of physiological functions that are related to neurogenesis, neurotransmission, and neuroinflammation; therefore, they play fundamental roles in the development, functioning, and aging of the brain. In humans, dietary deficiencies of omega-3 fatty acids are associated with an increased risk of developing various psychiatric disorders, including depression, bipolar disorder, schizophrenia, dementia, attention-deficit/hyperactivity disorder, and autism. In particular, eicosapentaenoic and docosahexaenoic acid have been linked to the maintenance of mental health, and their deficits have been implicated in the pathophysiology of mental disorders. This may be mediated by the modulation of inflammatory processes and their direct effects on neuronal membrane fluidity and receptor function. However, randomized clinical trials that have investigated the therapeutic effects of omega-3 fatty acids have yielded inconclusive results, thereby limiting the use of these nutrients in psychiatric practice. High-quality clinical trials should be conducted to examine the efficacy of omega-3 fatty acids in preventing and treating mental disorders. The undesirable side effects of omega-3 fatty acid supplementation should also be considered. These effects may become apparent after many years of administration, and therefore, they may not be detected in most cases.

1. Introduction

Mental disorders have become increasingly important public health issues because they are one of the leading causes of disability worldwide and account for approximately one-fifth of years lived with disability.[1] Because of their high prevalence, mental disorders are a significant health, social, and economic burden.[2] Good nutrition is a mainstay of physical health, and its importance in mental health is gaining increasing recognition. A growing body of evidence suggests that there is a significant relationship between diet quality and mental disorders, and diet appears to be a potentially modifiable factor that influences the onset and outcomes of mental disorders.[3–5] Dietary factors may modulate mental health not only at the individual level but also at the population level.[6] The association that an unhealthy diet shares with impaired brain development, neuronal function, and mental health suggests that dietary improvement may have the potential to assist in the prevention and management of common psychiatric disorders.

The important role that lipids, particularly omega-3 fatty acids, play in physical health has long been recognized.[7] The health benefits of omega-3 fatty acids are attributable to their anti-inflammatory, hypolipidemic, antithrombotic, and antiarrhythmic effects.[7–8] Accordingly, these fatty acids are used in the prevention and treatment of a wide range of diseases, including coronary heart disease[9–11] and rheumatoid arthritis.[12–14] The decline in the consumption of omega-3 fatty acids and increase in the dietary intake of omega-6 fatty acids over the last century are believed to have resulted in detrimental health effects.[7]

Fatty acids are the organic compounds that are most abundantly present in the brain. They are classified into eight major categories—fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, polyketides, isoprenols, and sterols.[15] Glycerophospholipids, sphingolipids, and cholesterol are the major lipids that are present in the central nervous system. The highly diverse composition of the lipids in the brain[16–17] is associated with the evolution of higher cognitive abilities in primates.[16] Lipids play complex and specific physiological roles, many of which are not well understood. They are involved in the formation of cell membranes, cellular transport, and energy storage[18] and can also act as signaling molecules and modulators of transmembrane proteins (e.g., ion channels).[18–19] The composition of brain lipids varies based on age, sex,[20–21] neuronal activity,[22] stress,[23] and trauma.[24] Furthermore, changes in the concentration, organization, and metabolism of lipids are associated with a wide range of neurological diseases and mental disorders.[25–29]

Brain function is critically dependent on an adequate intake of polyunsaturated fatty acids (PUFAs). The PUFAs that are present in the human body can be classified into two main groups, namely, omega-6 and omega-3 PUFAs, which in turn are derived from two essential fatty acids, namely, linoleic acid (LA, 18:2 ω-6) and α-linolenic acid (ALA, 18:3 ω-3), respectively.[30] All omega-3 PUFAs are derived from ALA through

* Corresponding author: klaus.lange@ur.de

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desaturation, elongation, and β-oxidation.[7] In humans, ALA must be supplied through diet because it cannot be synthesized.[31–32] More than 90% of PUFAs in the mammalian brain are composed of long-chain PUFAs, arachidonic acid (AA, 20:4 ω-6), and docosahexaenoic acid (DHA, 22:6 ω-3).[33] In humans, long-chain PUFAs can either be derived from diet or synthesized from their respective shorter-chain PUFAs, namely, LA (for AA) and ALA (for DHA), in the liver. However, biological conversion is a relatively slow and inefficient process. Therefore, diet is the main source of these fatty acids in humans.[34] The typical Western diet is estimated to entail an omega-6 to omega-3 ratio of 15–20:1.[35–36] Since omega-3 and omega-6 PUFAs compete for incorporation into cell membranes,[37] a balanced intake of these different types of PUFAs is important. In addition, different PUFAs have opposing physiological functions. Specifically, omega-6 and omega-3 PUFAs promote systemic proinflammatory and anti-inflammatory states, respectively.[36] Although omega-6 PUFAs are converted to AA and subsequently to prostaglandins and leukotrienes, which have proinflammatory effects, omega-3 fatty acids—DHA and eicosapentaenoic acid (EPA, 20:5 ω-3)—act as competitive inhibitors of omega-6 PUFAs, thereby resulting in the reduced synthesis of proinflammatory mediators.[38]

Lipids constitute approximately 50%–70% of the brain's dry weight.[39] PUFAs, the most abundant of which are DHA and AA, account for approximately 20% of the brain weight.[40–41] PUFAs comprise 80% of total membrane phospholipids. They influence brain functions by altering the biophysical properties of cell membranes. Changes in the lipid environment of the phospholipid bilayer result in functional alterations of the activities of receptors and other membrane proteins.[42] PUFAs are involved in maintaining normal membrane structure and function, and they play critical roles in brain development and neurotransmission.[43–44] PUFAs are involved in brain function through various mechanisms, including the activation of receptors and cell signaling pathways as well as the modulation of the endocannabinoid system.[45] Further, AA, DHA, and their metabolites act as intracellular second messengers and modulate various brain processes such as gene transcription, neurotransmission, and neuroinflammation.[46] In rodents, DHA can affect brain plasticity and cognition by increasing hippocampal levels of the brain-derived neurotrophic factor and through metabolic effects such as the stimulation of glucose utilization and mitochondrial function as well as the reduction of oxidative stress.[47–49] Furthermore, diets that are rich in omega-3 PUFAs can help upregulate the genes that are involved in maintaining synaptic function and plasticity in rodents and enhance cognitive functioning in humans.[50–51]

Homo sapiens evolved in an environment that was rich in nutritional omega-3 PUFAs, and paleontological evidence suggests that there is a link between access to food and brain size.[52–53] The interaction between the dietary intake of omega-3 PUFAs and brain evolution is particularly well documented. DHA, which is the most abundant omega-3 fatty acid in brain cell membranes,[54] cannot be efficiently synthesized by the human body; therefore, it must largely be derived from one's diet.[55] It has been proposed that access to DHA during the evolution of hominids plays an essential role in encephalization, which refers to the increase in brain-to-body mass ratio.[55] A shore-based diet, which entails the consumption of fish and possibly intertidal shellfish, has a high DHA content and may have therefore been necessary for hominid encephalization.[53] Over the past few decades, there has been a decline in the intake of omega-3 PUFAs and a significant increase in the consumption of saturated fatty, linoleic, and trans fatty acids in Western countries. This trend may have resulted in health effects and influenced the prevalence of mental disorders.

Omega-3 PUFAs are essential for the growth and development of the central nervous system during pregnancy, infancy, and childhood;[56] therefore, a sufficient dietary supply of these compounds is essential for normal brain development.[56–62] Omega-3 fatty acids also play an important role in the maintenance of the optimal functioning of the adult brain. Approximately 30% of the lipid fraction of the gray matter in the adult brain is made up of DHA,[33] and an increased intake of omega-3 fatty acids has beneficial effects on neurodegenerative disorders such as Alzheimer's and Parkinson's disease. It is generally assumed that an omega-3 PUFA deficiency leads to impaired learning and memory in rodents.[63–64] In contrast, in humans, a dietary deficiency of these bioactives has been linked to an elevated risk of developing various mental disorders, including depression, dementia, schizophrenia, bipolar disorder, and attention-deficit/hyperactivity disorder (ADHD).[65–69]

As early as in 1981, it was suggested that mental health problems may result from a deficiency of omega-3 PUFAs.[70] Specifically, since individuals with psychiatric disorders were successfully treated with flax oil, which is rich in ALA, it was proposed that omega-3 fatty acids may be useful in the management of mental disorders.[71] Although these findings were largely ignored, interest in the therapeutic effects of omega-3 fatty acids increased when reports underscored the reduced concentrations of these compounds in the erythrocyte membranes of individuals with schizophrenia and depression.[71–73] Furthermore, epidemiological studies have shown that there are associations between the amount of fish consumption in national diets and the prevalence of depression.[74] Moreover, other reports have also explicated the correlations that fish intake shares with the risk/prevalence of bipolar disorder,[75] postnatal depression,[76] and homicide.[77]

Consequently, pilot trials have examined the benefits of consuming fish-oil derivatives among individuals with schizophrenia[78–80] and mood disorders.[81–83] Their findings serve as preliminary evidence of the symptomatic improvement that results from the administration of omega-3 fatty acids.

The intervention trials that have examined the beneficial effects of omega-3 fatty acids on mental disorders have adopted various research designs. With regard to the examination of treatment effects, randomized controlled trials yield findings that can be situated atop the hierarchy of evidence (“gold standard”). These types of trials are currently considered to be the best means of evaluating the efficacy of an intervention and most effective basis for making evidence-based decisions about therapeutic interventions. Appropriately designed large randomized controlled trials that examine treatment effects on major clinical outcomes (rather than small inconclusive trials that assess surrogate outcomes) should be conducted. However, long-term randomized controlled trials have rarely been conducted, and they pose logistic and ethical challenges.

Unlike randomized controlled trials, observational studies are vulnerable to many threats to validity (e.g., selection effects), and they cannot account for all the possible confounding variables that are involved in the selection of participants for treatment. Differences in the indications for the administration of omega-3 PUFAs are the most significant threat because only individuals with specific characteristics may receive them (e.g., they may be more severely affected or may present with more symptoms and comorbid conditions).

2. Methods

In the present narrative review, studies that have focused on the associations that omega-3 fatty acids share with mental health and disorders are reviewed and analyzed. English articles that had been published until April 30th, 2019, were identified through keyword searches of the PubMed database and included for review. The search terms “omega-3 fatty acids” and “lipids” were paired with “ADHD,” “autism spectrum disorder,” “mood disorders,” “major depressive disorder,” “bipolar disorder,” “schizophrenia,” “dementia,” “Alzheimer's disease,” and “mild cognitive impairment.” Articles that were consistent with the focus of the present review were included; no specific quality criteria were used to include or exclude articles.

3. ADHD

ADHD is a common psychiatric condition that affects children and adolescents. It is characterized by age-inappropriate levels of hyperactivity, inattention, and impulsivity. Children and adolescents who have been diagnosed with ADHD exhibit long-term social, academic, and mental health problems.[84–86] While the etiology of ADHD appears to be multifactorial, its definite causes remain unknown. The drugs that are used to manage ADHD (e.g., psychostimulants, atomoxetine) and behavior therapy result in short-term symptom reduction but not sustained long-term improvement at

follow up.[87–88] ADHD medications can have serious adverse effects such as growth retardation and severe cardiovascular events.[88–93] The findings of randomized controlled trials suggest that pharmacotherapy for ADHD should be provided with caution or even discontinued after an administration period of 12 weeks and that alternative treatment strategies should be explored.[90]

The ratio of omega-6 to omega-3 PUFAs is higher in children with ADHD symptoms than in their counterparts without these symptoms. This may be attributable to dietary patterns, changes in gut microbiota, and abnormal PUFA metabolism.[94–97] One study examined whether an increased prenatal omega-6 to omega-3 PUFA ratio precedes the emergence of ADHD symptoms in childhood.[98] In a population-based birth cohort, omega-6 AA, omega-3 EPA, and DHA levels in the umbilical cord were measured. The ADHD symptoms of four-year-old children ($N = 580$) were assessed using teachers' reports of the extent to which they met the criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (*Fourth Edition*) for a diagnosis of ADHD.[99] Additionally, ADHD symptoms were assessed by parents using the Conners' Rating Scale-Revised Short Form ($N = 642$) when the children were 7 years old.[100] ADHD was operationalized as a continuous (i.e., scores) and dichotomous variable (i.e., diagnosis: yes/no). Whereas a higher omega-6 to omega-3 PUFA ratio in the umbilical cord plasma was associated with a higher ADHD index score at the age of 7 years, no such association had emerged at the age of 4 years. No associations emerged for the ADHD diagnostic criteria.[100] The estimated effects were small and clinically irrelevant. The results suggest that a maternal diet with a high ratio of omega-6 to omega-3 PUFAs during pregnancy can influence the offspring's risk of developing (subclinical) ADHD symptoms during childhood.

The role of omega-3 fatty acids in the etiology and management of ADHD is controversial.[101–103] A possible link between omega-3 PUFAs and ADHD has been established based on clinical observations. For example, hyperactive children have been found to exhibit the signs of fatty acid deficiency including polydipsia, polyuria, and dry skin and hair.[104] Moreover, blood plasma concentrations of DHA, EPA, and AA have been found to be significantly lower among children with ADHD than among controls.[97,105–107]

The results of a systematic review of meta-analyses of double-blind placebo-controlled trials suggested that the effect sizes for omega-3 supplementation in individuals with ADHD were small regarding symptom ratings by parents and teachers.[108] A recent randomized placebo-controlled trial investigated the effects of consuming omega-3 PUFAs for three months among children and adolescents with ADHD. The findings revealed that those who had received the placebo demonstrated a significantly greater reduction in total ADHD rating scores than those who had consumed omega-3 PUFAs.[109] When taken together with the other aforementioned results, the findings suggest that omega-3 PUFAs have no overall effect on ADHD symptoms.[109]

Numerous trials have examined the effects of omega-3 supplementation on ADHD symptoms.[110] Nevertheless, at present, there is little evidence to support the efficacy of omega-3 PUFA supplementation in reducing the core symptoms of ADHD. Efforts to delineate the role that omega-3 PUFAs play in ADHD symptom reduction have been hindered by the ill-defined nature of ADHD and a lack of biological markers that underpin the validity of a diagnosis of ADHD.[103] Moreover, substantially high rates of comorbidity with other childhood-onset neurodevelopmental and psychiatric disorders have been reported for ADHD.

4. Autism spectrum disorder

Autism spectrum disorder is a group of heterogeneous constellations that are characterized by early-appearing deficits in cognitive, communicative, and social skills and repetitive sensory-motor behaviors.[111] The increasing rates of this disorder are believed to be caused, at least in part, by a complex interaction between multiple genes and environmental risk factors.[112] Among environmental factors, nutrition has attracted growing interest, and the role of PUFAs in the development and, possibly, the prevention and treatment of autism spectrum disorder has been examined.[113–114] When compared to healthy controls, individuals with autism spectrum disorder have abnormal blood concentrations of omega-3 PUFAs.[115] This may be caused by a lower dietary intake of omega-3 PUFAs or disturbances in fatty acid metabolism and the incorporation of PUFAs into cellular membranes.[115–117] Several studies have found that there are alterations in omega-3 or omega-6 fatty acids or the ratio between omega-6 and omega-3 PUFAs in individuals with autism spectrum disorder,[117–118] but others have failed to find any such changes.[119–120] A meta-analysis of 15 case-control studies ($N = 1{,}193$) compared the blood PUFA levels of individuals with autism spectrum disorder and typically developing individuals without neurodevelopmental disorders. The results revealed that DHA, EPA, and AA levels were lower and that the total omega-6 to omega-3 PUFA ratio was higher in individuals with autism spectrum disorder.[121]

A majority of open-label trials have found that omega-3 supplementation significantly reduces the symptoms of autism spectrum disorder.[122–127] However, randomized controlled trials that have assessed the effects of omega-3 PUFAs in reducing the symptoms of autism spectrum disorder have yielded inconclusive results.[128–129] A systematic review examined the effectiveness of omega-3 PUFA interventions in reducing the core and associated symptoms of autism spectrum disorder and compared the findings of trials that varied in duration and the form and dosage of omega-3 PUFAs. The available evidence was found to be too insufficient to recommend omega-3 fatty acid supplementation.[130] A Cochrane review of two randomized controlled trials and meta-analyses that were confined to three primary outcomes (social interaction, communication, and stereotypy) and one secondary outcome (hyperactivity) arrived at the same conclusion.[131] A meta-analysis of four randomized controlled trials ($N = 107$) found that, in comparison to a placebo, omega-3 PUFA supplementation improved social interaction and the symptom of repetitive and restricted interests and behaviors among individuals with autism spectrum disorder.[121] Another meta-analysis of five randomized controlled trials ($N = 183$),[132] three of which were also included in the aforementioned study,[121] found no evidence to support the performance-enhancing effects of omega-3 PUFAs among individuals with autism spectrum disorder.[132] No serious adverse effects of omega-3 PUFA supplementation were observed in these trials.[121] The limitations of the trials that were included in these meta-analyses include very small sample sizes and short intervention durations.

In sum, the findings that individuals with autism spectrum disorder have lower levels of omega-3 PUFAs suggest that supplementation may improve some of the core symptoms of this condition. However, based on the available evidence, it would be premature to recommend the administration of omega-3 fatty acids as an alternative treatment in the management of autism spectrum disorder. High-quality investigations that use large samples and span longer durations are needed. Numerous factors such as baseline PUFA status, other dietary components, age, sex, and genotype (e.g., apolipoprotein E) may modulate the effects of omega-3 PUFAs on behavior and should, therefore, be examined in such investigations.

5. Major depressive disorder

Major depression is characterized by a depressed mood or markedly reduced interest in or the ability to derive pleasure from all activities. This disorder is highly debilitating, severely limits psychosocial functioning, and diminishes quality of life.[133] Major depressive disorder has been projected to be the leading cause of the burden of disease by 2030 worldwide.[134] Depression is difficult to treat, and the administration of omega-3 fatty acids is emerging as an approach toward its prevention and treatment.[135] Preclinical findings suggest that omega-3 fatty acids influence various neurobiological mediators that appear to be involved in the pathophysiology of depression.[136] For example, membrane lipids, including omega-3 fatty acids, play a role in the membrane's function by acting as a barrier and medium for classical transmitter signaling. Membrane lipid changes may

contribute to the pathophysiology of major depressive disorder and act as targets for lipid-based treatment approaches.[136]

A correlation between fish consumption and a decrease in the annual prevalence of major depression was found in a study that undertook multinational comparisons. Countries such as Canada, New Zealand, and Germany were characterized by low levels of fish intake and relatively high rates of major depression. Conversely, an inverse relationship between these two variables was observed in South Korea and especially Japan.[66] The findings of this widely cited paper are commonly interpreted as evidence of the preventive effects of fish consumption on depression. However, in his article, the author has explicitly stated that the emergent correlation "does not show that fish consumption can cause differences in the prevalence of major depression or that eating fish or fish oils are useful in treatment. Various cultural, economic, social, and other factors can confound this simple correlational relation".[66] A systematic review and meta-analysis of the findings of 31 observational studies ($N = 255,076$, out of which more than 20,000 individuals had depression) on the association between fish consumption, dietary omega-3 PUFA intake, and depression found that fish consumption significantly reduced the risk of depression in a linear dose-response fashion.[137] A systematic review and meta-analysis of 10 prospective cohort studies ($N = 109,764$, out of which 6,672 individuals had depression) found that there was a modest inverse association between the intake of fish or omega-3 PUFAs and the risk of depression, especially among women.[138] The correlation between fish consumption and major depression is consistent with clinical findings that higher DHA levels in erythrocyte membranes[139] and higher ratios of EPA to AA in the plasma are predictively related to a lesser severity of depressive symptoms.[140] As mentioned earlier, these findings do not necessarily imply that there is a causal relationship between fish consumption and the prevalence of major depression or indicate that fish consumption or fish-oil supplementation is helpful in the treatment of depression. Similar negative associations between omega-3 fatty acid intake and depressive symptoms have been repeatedly demonstrated.[141–142] In clinical investigations, omega-3 PUFA concentrations have been found to be lower among individuals with a diagnosis of major depressive disorder than among controls.[143–144] In addition, continuous relationships between omega-3 PUFA status and depressive symptoms have also been reported.[143] A majority of randomized placebo-controlled trials have demonstrated support for beneficial effects of omega-3 fatty acid administration on both major depressive disorder and other depressive conditions.[73,83,145,146] However, several cross-sectional studies have shown that there is either no association between depressive symptoms and omega-3 PUFA intake or some level of association that is entirely attributable to confounders.[147–149] Other studies have also failed to find significant relationships between omega-3 PUFA concentrations and depressive symptoms,[150–152] and several randomized controlled trials have found that, when compared to a placebo, omega-3 PUFA supplementation has no beneficial effects on individuals with major depressive disorder[153–154] or other depressive conditions.[155–156] Systematic reviews and meta-analyses have shown that there is substantial variability among studies.[157–161] Meta-analyses have demonstrated support for the positive effects of omega-3 fatty acids on depressive disorders,[159–160] but these effects were found to be dependent on baseline levels of the severity of depressive symptoms.[159] Specifically, individuals with severe depressive symptoms demonstrated some positive effects, but no benefits were observed among those with mild depressive symptoms.[159] A Cochrane review summarized the findings of randomized controlled trials that had examined the effects of omega-3 PUFA intake on major depressive disorder in adults.[162] Twenty-five trials ($N = 1,373$) had compared the effects of omega-3 PUFAs and a placebo on depressive symptoms and found that the former had yielded small to modest benefits.[162] However, the evidence was considered to be biased and of very poor quality, and the reported effect was judged to be clinically irrelevant.[162] In one study that was conducted using a small sample of 40 participants, no difference in the effects of omega-3 PUFAs and antidepressant medications on depressive symptomatology was found.[162] The aforementioned Cochrane review concluded that the available evidence was too insufficient to draw conclusive statements about whether omega-3 fatty acids are effective in treating major depressive disorder. Additional adequately powered randomized controlled trials are therefore required. Moreover, differences between the different types of omega-3 PUFAs should also be examined. A meta-analysis of 35 randomized controlled trials (omega-3 fatty acids: $N = 6,665$, placebo: $N = 4,373$) examined these differences and found that, when compared to placebos, EPA-predominant formulations resulted in positive clinical effects, whereas DHA-predominant formulations did not yield any benefits among individuals with a diagnosis of depression.[163] A review of 40 studies, 31 of which were randomized placebo-controlled trials, analyzed the effectiveness of omega-3 PUFAs as an add-on to antidepressant medications in treating major depressive disorder or ongoing depression.[164] The review concluded that, when compared to placebos, adjunctive omega-3 PUFA administration had reduced depressive symptoms.[164]

A systematic review of nine studies on the efficacy of omega-3 fatty acid supplementation in improving the depressive symptoms of older adults aged 60 years and older found that it had no significant overall effects. However, omega-3 dosages that were greater than 1.5g/d resulted in statistically significant symptom reduction.[165] A systematic review and meta-analysis of six randomized controlled trials ($N = 4,605$) found that omega-3 PUFA supplementation did not have a significant effect on the depressed mood of older adults with good mental health, but a large effect was found among older adults with depression.[166] However, these benefits were significant only among individuals with mild to moderate depression.[166]

Postpartum depression is a major mood disorder that occurs within one month of childbirth and lasts for several months.[167] The risk of postpartum depression appears to be associated with neuroinflammation and reduced serotonergic neurotransmission.[168–169] Risk factors for postpartum depression include deficiencies of food bioactives, including omega-3 fatty acids, which result from inadequate intake or depletion during pregnancy and lactation.[170–172] A review of the existing literature revealed that supplementation of EPA-rich oil can reduce some depressive symptoms during pregnancy and after childbirth.[173] The long-term administration of DHA-rich oils has been found to decrease the risk of postpartum depression among healthy pregnant women but not among lactating women.[173]

In sum, a low intake of omega-3 fatty acids may predispose certain individuals to major depression, and dietary PUFA supplementation can have preventive and therapeutic effects. However, this contention needs to be tested in well-designed large-scale studies.

6. Bipolar disorder

Bipolar disorder is a chronic condition that is characterized by alternating states of depression and elevated mood (mania or hypomania) and intermittent phases of euthymia.[174] The etiology of bipolar disorder is poorly understood. Low levels of omega-3 fatty acids, particularly DHA, in erythrocyte membranes have been found in individuals with this disorder.[175–176] Furthermore, a lower incidence of bipolar disorder has been found among populations with high rates of seafood consumption.[177] Individuals with bipolar disorder consume lesser PUFAs (EPA, DHA, AA, and Docosapentaenoic acid) and more saturated fats than nonpsychiatric controls.[178] Based on these findings, intervention trials have examined whether omega-3 fatty acids influence the clinical features of bipolar disorder.

Therapeutic trials on the effects of omega-3 PUFA administration on bipolar disorder have yielded variable results. The findings of open-label and controlled studies lend support to the beneficial effects of omega-3 fatty acids on depressive symptoms and, to a lesser degree, manic symptoms.[146,179–180] Omega-3 PUFAs that have been administered as an add-on to standard pharmacotherapy have been found to improve both depression and mania scores.[181] Other studies have found that omega-3 PUFAs have no effects on bipolar disorder.[182–183] The limitations of these trials include small sample sizes, the heterogeneity of PUFA doses and ratios, and trial durations that are possibly too short to result in changes in brain fatty acid composition.[184] The conclusions of systematic reviews

and meta-analyses serve as preliminary evidence for the contention that the depressive but not manic symptoms of bipolar disorder can be improved through the adjunctive administration of omega-3 PUFAs.[184–187]

7. Schizophrenia

Schizophrenia is a complex and heterogeneous behavioral and cognitive syndrome that is characterized by various symptoms such as cognitive dysfunction and positive (e.g., delusions, hallucinations) and negative symptoms (e.g., impaired motivation, social withdrawal).[188] The mainstay of therapy is antipsychotic medications, the long-term outcomes of which are poor.[189] A disruption in brain development that results from genetic and/or environmental factors has been posited as the cause of schizophrenia. The "neurodevelopmental hypothesis of schizophrenia" postulates that exposure to adverse environmental events (e.g., famine) during early brain development increases the risk of subsequent manifestations of clinical symptoms.[190–191] Deficiencies of several micronutrients, including essential fatty acids, folate, iron, and vitamin D, during prenatal development, are potential risk factors for schizophrenia.[192]

The role that omega-3 fatty acids play in schizophrenia has been supported by several lines of evidence. For example, a meta-analysis of past studies has shown that there is a PUFA deficiency in the erythrocyte membranes of individuals with schizophrenia.[193] Furthermore, postmortem examinations of individuals with schizophrenia have frequently shown that their brain cells contain lower levels of DHA and EPA than those of healthy controls.[194] This may be attributable to poor dietary habits because patients with severe schizophrenia tend to adopt an unhealthy lifestyle. A deficiency of omega-3 fatty acids may be a risk factor for schizophrenia, and the severity of positive symptoms has been found to be inversely correlated with the intake of omega-3 fatty acids.[195] A decrease in the proportion of omega-3 fatty acids in red blood and brain cells has been found to be associated with poor treatment responses and greater severity of negative symptoms.[196–197] Overall deficiencies of omega-3 fatty acids at baseline have been found to predict the development of psychosis in high-risk adolescents.[198] These findings serve as the empirical base upon which the "membrane phospholipid hypothesis" of schizophrenia is founded.[71,199,200] Specifically, it postulates that inadequate phospholipid concentrations in neuronal membranes affect neuronal functioning and can lead to schizophrenia in vulnerable individuals. A restoration of omega-3 fatty acid levels has also been proposed as a potential treatment for the reduction of psychotic-like symptoms.[201] The rate of progression to the first-episode psychotic disorder was studied across 12 months among 81 individuals with subthreshold psychosis. Following a 12-week intervention, 5% and 27.5% of those who were administered omega-3 PUFAs (1.2g/d) and placebos developed a psychotic disorder, respectively.[202]

Several randomized controlled trials have examined omega-3 fatty acid supplementation in relation to schizophrenia, and most of these studies have used PUFAs as an add-on to classical or atypical antipsychotics. In two studies that examined the effects of omega-3 PUFAs as a monotherapy, most participants needed antipsychotic medication during the course of the trials.[80,203] While some trials have documented the benefits of PUFAs on the positive and negative symptoms of schizophrenia,[70,202,204–206] others have found no significant differences in the effects that omega-3 PUFAs and placebos have on positive and negative symptoms, cognition, and mood.[207–208] The limitations of these trials include small sample sizes and heterogeneity in diagnoses, trial durations, and omega-3 dosages. Moreover, baseline levels of omega-3 PUFAs were not assessed in all the studies. An additional limitation pertains to variability in the diagnoses of the participants, which include the following: schizophrenia, schizoaffective disorder,[207] the first psychotic episode,[206,208] and treatment-resistant schizophrenia.[80] Meta-analyses have evaluated the effectiveness of omega-3 PUFAs in treating schizophrenia and other psychotic disorders. These studies have yielded inconclusive findings regarding the efficacy of omega 3 PUFAs as psychotropic agents.[68,209–211] Omega-3 PUFAs may be more effective in treating schizophrenia when they are administered during the early stages of the disorder than during the chronic phase.[212] This may be attributable to the neuroprotective effects that omega-3 PUFAs can have during the early stages of this condition. However, these compounds may be unable to reverse more advanced neurobiological changes during the later stages. The potentially preventive effects of early administration of omega-3 fatty acids to individuals with a high risk of developing full-blown psychosis should be examined. One clinical trial has already demonstrated the beneficial effects of these compounds.[202]

Omega-3 PUFAs may be able to ameliorate the motor side effects of classical antipsychotics. For example, the beneficial effects of ethyl-EPA (3g/d) as an add-on treatment on extrapyramidal symptoms were observed among 40 individuals with chronic schizophrenia who had been consuming antipsychotic medication for at least six months.[71] In one study, ethyl-EPA (2g/d) was administered to 77 individuals with schizophrenia or schizoaffective disorders and tardive dyskinesia for 12 weeks, and they demonstrated an initial improvement in dyskinesia, when compared to those who received a placebo.[213] However, this effect was not sustained beyond six weeks.

In sum, individuals with schizophrenia may have a potentially treatable omega-3 PUFA deficiency. The findings of intervention trials are inconsistent, and the efficacy of omega-3 supplementation in alleviating symptoms appears to depend on the stage of the disorder. At present, omega-3 PUFAs cannot be recommended as a therapy for schizophrenia. However, the available findings underscore the need for high-quality studies. In particular, the effects of omega-3 PUFAs on schizophrenic symptomatology should be investigated across the different stages of the condition in greater detail.

8. Dementia

Aging is commonly associated with a decline in cognitive functioning, which can range from mild cognitive impairment to dementia. Mild cognitive impairment is characterized by impaired mental processing that is significant enough to be noticed but does not interfere with independent living. Up to 50% of individuals with mild cognitive impairment will develop dementia within five years.[214] The most common type of dementia is Alzheimer's disease,[215] which is a progressive neurodegenerative disorder that is characterized by severe global impairments in cognitive functions such as memory, language, and executive functions.[216] The neuropathological hallmarks of Alzheimer's disease are extracellular amyloid-β plaques and intracellular neurofibrillary tangles.[217] Vascular dementia is the second most common type of dementia among older adults. This condition can result from a reduction in blood supply to the brain, which in turn may be caused by a blocked or diseased vascular system, thereby leading to a progressive decline in memory and other cognitive functions.[218]

Omega-3 fatty acid administration is often considered a promising approach toward improving brain functions and slowing the progression of cognitive decline and dementia syndromes such as Alzheimer's disease and vascular dementia. This assumption is largely grounded in the findings of preclinical and epidemiological studies.

Several lines of evidence underscore the preventive effects of omega-3 PUFAs on dementia. For example, in animals, the long-term administration of omega-3 fatty acids for more than 10% of their lifespan can improve cognitive function and reduce amyloid-β.[219] Other preclinical studies have found that omega-3 PUFA intake is associated with reductions in cognitive decline,[220–222] neuroinflammation,[223–226] and amyloid-β42 blood concentrations.[227–228] Furthermore, the neuroprotective effects of omega-3 PUFA intake on the aging brain have been delineated.[228–230] Omega-3 PUFA levels, particularly DHA levels, in the plasma and brain are lower among individuals with Alzheimer's disease than among controls without dementia.[231–233] Postmortem examinations of individuals with Alzheimer's disease have revealed that they have reduced concentrations of DHA[234] and that reduced DHA levels are associated with higher amyloid-β42 blood levels[228] and smaller amygdala volumes.[235]

The administration of omega-3 PUFAs through fish or fish-oil supplements may have beneficial effects on brain health and cognition among older adults. Epidemiological studies have shown that there are

associations between the consumption of fish[236–237] or fish oil[6,51] and improved cognitive functioning and a decreased risk of developing dementia.[238] In France, fish consumption has been found to have protective effects against dementia, whereas meat intake has been found to be associated, albeit poorly, with an increase in dementia risk.[239] Fish consumption at least once a week reduced the risk of developing any type of dementia and Alzheimer's disease by 34% and 31%, respectively.[239] In Chicago, the consumption of fish was found to be associated with a decrease in age-related cognitive decline, which was operationalized in terms of a global cognitive score, in a prospective community-based cohort study with 6158 participants aged 65 years and older.[237] Alzheimer's disease was 60% less common among individuals with a daily intake of approximately 60 mg of DHA (i.e., at least one fish meal a week) than among those who consumed very low quantities of fish.[240] Similar results were found in Japan,[241] where larger quantities of fish are consumed than in the West. In a 2-year double-blind randomized placebo-controlled trial that was conducted among 111 Japanese older adults with very mild dementia, the long-term administration of DHA (1,720mg/d) and EPA (407mg/d) produced beneficial effects against age-related cognitive decline.[242] Increased consumption of omega-3 fatty acids was found to be associated with greater total brain and hippocampal volumes in a cross-sectional study that was conducted among 1,111 postmenopausal women.[243] In another cross-sectional study that was conducted among 1,575 older adults, DHA levels were correlated with scores on tests of executive functioning and abstract thinking.[244]

Low plasma concentrations of omega-3 fatty acids, including DHA, appear to be associated with an increased risk of developing cognitive deficits and dementia.[245] Alzheimer's disease and vascular dementia share certain nutritional features, including insufficient intake of omega-3 fatty acids and excessive consumption of omega-6 PUFAs, which can result in chronic inflammation, changes in the microvasculature, platelet aggregation, and endothelial dysfunction.[241] Several randomized controlled trials have examined the effects of the administration of omega-3 fatty acids through fish-oil supplements on cognitive functioning among older adults. Forty individuals with Alzheimer's disease received DHA and EPA daily for 6 months but showed no significant decrease in oxidative stress.[246] Similarly, no benefits of omega-3 fatty acid supplementation for 6 months were observed among 204 patients with mild Alzheimer's disease.[247] In another randomized placebo-controlled trial that examined the effects of omega-3 fatty acid supplementation on Alzheimer's disease across 12 months, no significant differences in oxidative stress markers were found, but there was a significant reduction in the rate of decline in the Mini-Mental State Examination and activities of daily living test scores.[248] In one study, omega-3 PUFA monotherapy was provided to 46 participants for 24 weeks, and it improved the clinical functioning of individuals with mild and moderate Alzheimer's disease and mild cognitive impairment.[249] Furthermore, the administration of omega-3 fatty acids for 26 weeks improved the executive functions, gray matter volume, and white matter microstructure in healthy older adults.[250] DHA supplementation for 24 weeks improved learning and memory among 485 healthy individuals aged 55 years and older.[251] In contrast, the intake of fish oil was found to have no beneficial effects on the cognitive health of healthy older adults[252–253] or patients with Alzheimer's disease.[254] Moreover, a Cochrane review found that omega-3 fatty acid supplementation has no beneficial effects on the cognition of older adults.[255]

A more recent Cochrane review included three randomized placebo-controlled trials of high methodological quality[247–248,254] that had examined the effects of omega-3 PUFA supplementation (dosages of EPA and DHA ranged between 1,750mg/d and 2,300mg/d) among 632 participants with mild to moderate Alzheimer's disease across 6, 12, and 18 months.[256] The administration of omega-3 fatty acids for 6 months had no effect on cognition (learning and understanding), everyday functioning, quality of life, or mental health.[256] In another very small study, the long-term administration of omega-3 fatty acids improved the execution of cognitively complex daily activities (e.g., shopping).[248] Taken together, the findings of the Cochrane reviews do not offer any evidence of either the benefits or risks of the consumption of omega-3 PUFA supplements by individuals with mild to moderate Alzheimer's disease.[256]

The inconsistent results of trials that have examined the effects of omega-3 fatty acid supplementation on cognitive decline and Alzheimer's disease[257] may be attributable to variability in cohort characteristics (e.g., genetics, stage of the disease, environmental background), dosages, treatment durations, and outcome measures among the included studies. In addition, the overall composition of fatty acid intake may be more important to cognitive aging than the amount of omega-3 fatty acids consumed[250] or total fat intake.[258] For example, the consumption of saturated and trans fatty acids may affect cognition[259] and increase the risk of developing Alzheimer's disease[260–262] and consequently mask the benefits of dietary PUFAs. The mixed results regarding the potentially beneficial effects of consuming omega-3 fatty acids on Alzheimer's disease may also be attributable to high levels of oxidation of the supplements.[263] Omega-3 fatty acids are highly oxidizable, and the oxidization of omega-3 PUFAs may alter their biological function and even result in harmful effects. High levels of oxidation of omega-3 supplements have been observed, and more than 80% of evaluated omega-3 supplements were found to exceed the recommended concentrations of oxidation markers.[264] In addition to the possibility that different levels of oxidation of supplemental omega-3 oils may have led to discrepant study results, these varying levels of oxidation may also explain the differential outcomes that fish intake and omega-3 supplementation have resulted in. The results of one meta-analysis revealed that higher consumption of fish was associated with a reduction in the risk of developing Alzheimer's disease by 36%, but omega-3 fatty acid supplementation did not significantly influence this risk.[265] Differences in the protective effects of fish consumption and omega-3 fatty acid supplementation may correspond to potential differences in their rates of oxidation of omega-3 fatty acids.

In sum, the promising findings of epidemiological studies suggest that omega-3 PUFAs are a potentially useful strategy to prevent Alzheimer's disease. However, clinical intervention trials have revealed that omega-3 fatty acids only have limited beneficial effects on Alzheimer's disease. Additional large-scale randomized controlled trials are therefore needed before omega-3 fatty acid supplementation can be recommended as a preventive measure. In addition, omega-3 fatty acid supplementation may have beneficial effects only during the premorbid or early stages of the disease, particularly among noncarriers of the apolipoprotein *E*-ε4 risk gene.[266]

The effects of omega-3 fatty acid supplementation on other types of dementia (e.g., vascular dementia) remain unclear.[256]

9. Mild cognitive impairment

The aging of the brain is associated with a reduction in volume, neuronal density, and neurotransmitter levels, which in turn can lead to impaired synaptic activity and reduced signal efficiency. These neurodegenerative changes are a consequence of decreased membrane fluidity, which results from high cholesterol levels, reduced desaturase activity, and an increase in oxidative and inflammatory activities.[267] Interventions that increase membrane fluidity and decrease inflammatory processes are therefore likely to lead to improved brain function. Increases in the levels of omega-3 fatty acids in the brain have various beneficial effects on the brain physiology of individuals with mild cognitive impairments; these include improvements in membrane fluidity and inflammation and a decrease in oxidative damage.[268–270] The preliminary findings of a randomized controlled trial showed that an omega-3 fatty acid monotherapy that was provided for 24 weeks improved the cognition scores of individuals with mild cognitive impairment,[249] and the administration of either DHA or EPA for 6 months also improved depressive symptoms. However, verbal fluency scores improved only after DHA supplementation.[271] Furthermore, omega-3 fatty acid supplementation has been found to increase amyloid-β phagocytosis in individuals with mild cognitive impairment.[272] Further studies are needed to examine the beneficial effects of omega-3 fatty acids on mild cognitive impairment.

10. Other mental disorders

Low levels of omega-3 fatty acids are present in the erythrocyte membranes of individuals with anxiety disorders.[273–275] With regard to therapeutic efficacy, the effects of the intake of omega-3 PUFAs on anxiety disorders have not been systematically analyzed in randomized controlled trials. Conclusions about the symptomatic efficacy of PUFAs in managing obsessive-compulsive disorder cannot be drawn because, even though a randomized controlled trial investigated the efficacy of EPA in the augmentation of medication, it used a small sample.[276] Preliminary evidence suggests that omega-3 PUFAs can alleviate the symptoms of posttraumatic stress disorder.[277–278] However, the designs that have been used in past trials disallow the drawing of concrete conclusions about the efficacy of omega-3 PUFAs in treating this condition. The effects of omega-3 PUFA supplementation have also been examined among individuals with personality disorders who frequently exhibit high levels of aggressiveness and impulsive-behavioral dyscontrol. The findings of randomized placebo-controlled trials suggest that PUFAs can have beneficial effects on the core symptoms of borderline personality disorder.[279–281] However, it is difficult to draw concrete conclusions about their effects because these studies have used different diagnostic criteria, doses and ratios of omega-3 fatty acids, and methods of administrations of conventional medications.

11. Adverse effects of omega-3 PUFA supplementation

The supplementation of omega-3 PUFAs, particularly long-term supraphysiological doses, can lead to unwanted side effects. Serious adverse effects have been observed following the administration of other natural and seemingly healthy nutrients. For example, vitamin E supplementation resulted in a trend that was indicative of an elevated risk of prostate carcinoma,[282] whereas the intake of selenium elevated the risk of diabetes.[283]

Intervention trials that have administered omega-3 fatty acids have reported no serious adverse reactions at the administered doses.[255] The more common adverse effects of fish-oil preparations, particularly at higher dosage levels, include nausea, fishy belching, and loose stools.[284] Because of these effects, the effectiveness of the blinding procedure of some of the aforementioned studies that have examined the effectiveness of fish oils in treating mental health problems has been questioned.[285] Further, in general, omega-3 PUFAs do not seem to have clinically relevant effects on bleeding time.[286] Nevertheless, caution must be exercised when high doses of these compounds are administered because they have been found to affect bleeding time.[71,213]

With regard to the undesired side effects of omega-3 PUFAs, the form in which these nutrients are consumed also needs to be considered. Both fish consumption and supplement intake can be problematic. Several potential risks need to be considered when natural omega-3 PUFAs are administered. An important natural source of these bioactives is fish and seafood, which may be contaminated with methylmercury, dioxins, and polychlorinated biphenyls. These compounds can increase the risk of some cancers or harm an unborn child when they are consumed by a pregnant mother. However, the consumption of fish once or twice a week has been found to be unproblematic in this regard.[287] The issue of contamination also applies to omega-3 fatty acid supplements. Therefore, commercially available fish-oil capsules should be examined for contamination by pollutants and certified by health agencies.

Fish-oil supplements may contain antioxidants and omega-3 PUFAs oxidation products, both of which can lead to adverse reactions. Omega-3 fatty acids are highly prone to oxidative degradation, and a substantial proportion of the omega-3 fish-oil preparations that are available in several countries significantly exceed international voluntary safety recommendations for total oxidation.[288] The omega-3 fatty acid supplements that have been used in clinical studies may have been partially oxidized, and the results of these trials may have been confounded by the administration of oxidized oils. Differences in omega-3 oxidation concentrations also explain the differential effects of omega-3 supplementation and fish intake. The effects of oxidized oils on human health should be further examined. The possible adverse consequences of the long-term use of vitamin E, which is added as an antioxidant to fish-oil supplements, should also be examined because large-scale trials have linked α-tocopherol supplementation to elevated rates of prostate cancer.[289] Similar rates of adverse events between groups that have received omega-3 fatty acids and placebos indicate that they are short-term effects.

12. Future directions

Most research studies on the role of omega-3 PUFAs in mental disorders have been conducted among individuals with depression and schizophrenia. These pilot studies have yielded promising results albeit with some discrepancies. Therefore, very large definitive randomized controlled trials are needed to establish the validity of the available preliminary findings. The limitations of past long-term studies that have examined the efficacy of omega-3 fatty acids in treating mental disorders include the following: substantial variability in outcome measures, the use of study designs that are unamenable to a meta-analytic evaluation, and a focus on symptoms as a measure of efficacy rather than on the functional implications of omega-3 administration. To comprehensively investigate the long-term effects of omega-3 PUFAs, future research studies should utilize meaningful measures of functional impairment and evaluate the degree to which the patient behaviors have been optimized.

Choosing an optimal dosage is an important issue in omega-3 fatty acid supplementation trials. The PUFA dose that is needed to elicit therapeutic benefits may depend on baseline levels (i.e., low concentrations of DHA at baseline may require higher initial doses than higher concentrations). The question of whether individuals with a low omega-3 PUFA status are more responsive to PUFA administration has not yet been explored. Therefore, future studies should aim to identify subgroups of individuals who are most likely to benefit from omega-3 supplementation, including those with low baseline status. Indeed, there may be a threshold beyond which omega-3 PUFA supplementation has little effect. In addition, the ratios of varying combinations of DHA, EPA, and AA levels should also be examined. A relative reduction in omega-3 fatty acids may also characterize medical conditions that are characterized by high levels of inflammatory activity (e.g., rheumatoid arthritis).[290] The findings of clinical studies that have been conducted among healthy individuals suggest that the administration of moderate doses of omega-3 PUFAs is sufficient to produce significant anti-inflammatory effects and that higher doses do not confer further benefits in this regard.[291] This observation explains why trials that have used higher doses of omega-3 fatty acids did not result in greater improvements in psychiatric symptoms and sometimes even produced worse effects, when compared to studies that had used lower doses. For example, low doses of omega-3 PUFAs (600mg/d–2,000mg/d of DHA and EPA combined) had significant beneficial effects on depression scores,[292] but no such benefit was observed following the administration of a high dose (6g/d).[155] High doses of supplementary omega-3 PUFAs for the management of mental disorders should be administered with caution, and they may only be needed when individuals have highly active inflammatory and autoimmune diseases. In addition, the composition of omega-3 PUFA supplements (DHA, EPA, or ALA) that are used in intervention studies requires special attention because different omega-3 PUFAs can have differential physiological and pharmacological effects.[70] Further research is needed to examine the effects of omega-3 fatty acids on the uptake, plasma binding, and metabolism of psychiatric medications.[293]

The results of studies that have examined the effects of dietary supplementation of omega-3 PUFAs on individuals with mental disorders should be interpreted with caution. In this regard, it is important to consider the interrelatedness of lifestyle factors and mental disorders. For example, the rates of familial conflicts, divorce, unemployment, and poor dietary habits are higher among individuals with bipolar disorder.[294] Therefore, improvements in lifestyle structure that result from adherence to a trial may yield beneficial effects. In addition, omega-3 PUFA administration may have positive effects on overall health. For example, omega-3 fatty acids may have

beneficial effects on cardiovascular health and metabolic alterations.[295–296] The supplementation of omega-3 PUFAs may improve bipolar symptoms by influencing brain functioning and improving general wellbeing and health.

Individuals with schizophrenia and depression have a substantially higher risk of developing coronary artery disease.[297–298] Omega-3 fatty acids can improve the physical health of individuals with depression and psychotic disorders[299] and have beneficial effects on common comorbidities that accompany these disorders (e.g., cardiovascular diseases, metabolic syndromes, and inflammatory diseases). This is particularly important because schizophrenia, schizoaffective disorder, bipolar affective disorder, and depression with psychotic features are associated with premature mortality[300] and a mortality gap of 15–20 years, when compared to the general population.[301] The major factors that underlie these markedly elevated death rates include preventable cardiometabolic complications, which in turn are attributable to high rates of being overweight and obese.[302–304] Furthermore, some antipsychotic medications such as clozapine and olanzapine are associated with increased concentrations of plasma triglycerides, which are normalized during the administration of omega-3 PUFAs.[72]

An important question that must be addressed pertains to whether there is a critical age at which omega-3 fatty acid supplementation is effective. The findings of animal studies suggest that decreased levels of DHA in the perinatal brain are associated with deficits in neuronal arborization, synaptic pathology (including deficient serotonin and dopamine neurotransmission), neurocognitive deficits, and increased anxiety, aggression, and depression.[305] In a rat model of chronic omega-3 deficiency, the administration of an equilibrated diet through the mother during the prenatal and postnatal periods restored the monoaminergic functions that were influenced by the deficiency, only if it was administered prior to the twenty-first day of life.[306–307] These findings suggest that the optimal period for omega-3 fatty acid supplementation is during brain development. For example, ADHD is often diagnosed only when a child reaches school-going age, and it may be too late to treat this condition using omega-3 PUFAs at this developmental stage. Future studies should examine whether maternal prenatal omega-3 PUFA supplementation or dietary omega-3 PUFA administration during infancy can prevent ADHD or other psychiatric disorders or reduce symptom severity.

The findings of studies on the effectiveness of PUFA supplementation in treating mental disorders may have been influenced by numerous factors such as the following: variability in study designs, trial durations, dosages of omega-3 PUFAs, modes of administration, types of PUFAs used (omega-3 and/or omega-6 PUFAs), and response assessments. When intervention trials use natural foods for omega-3 PUFA supplementation (e.g., omega-3 fatty acid-rich vegetables or fish), the observed effects may be attributable, at least in part, to other constituents of these foods (e.g., biologically active peptides or antioxidants). Many participants who were included in the studies that had used PUFA supplementation may have had comorbidities, which could have affected their treatment responses. The beneficial effects of omega-3 fatty acids on mental disorders may be specific to individuals with the corresponding deficiencies. In particular, the role of perinatal deficits in DHA accrual in the brain as a preventable neurodevelopmental risk factor for the subsequent emergence of psychopathological alterations should be further researched. Since reduced levels of other food bioactives have also been linked to mental disorders, multi-ingredient supplementation may be needed to elicit their beneficial effects.

13. Conclusions

In humans, dietary deficiencies of omega-3 fatty acids are associated with an increased risk of developing various psychiatric disorders. In particular, EPA and DHA have been linked to the maintenance of mental health, and their deficits have been implicated in the pathophysiology of mental disorders. However, randomized clinical trials that have investigated the therapeutic effects of omega-3 fatty acids have yielded inconclusive results, which limit the use of these nutrients in psychiatric practice. Therefore, high-quality clinical trials that examine the efficacy of omega-3 fatty acids in preventing and treating mental disorders are needed. Efforts to examine the effects of omega-3 fatty acids entail extraordinary challenges such as the following: identifying useful compounds, combining them at optimal dosages, examining the necessary duration of supplementation, and determining the critical phases of brain development during which the administration of omega-3 PUFAs will be effective. One obstacle that impedes such efforts is the heterogeneity of common mental disorders.

The undesirable side effects of omega-3 fatty acid supplementation should be examined. The short-term side effects of omega-3 PUFAs at the doses used in past studies do not appear to be a cause for concern. However, increased cancer risks may be associated with omega-3 supplementation, possibly because of the effects of PUFAs, PUFA oxidation products, or added vitamin E. The adverse effects of administration may become apparent after many years of administration, and therefore, they may not be detected in most cases. Recommendations for the supplementation of omega-3 PUFAs over extended periods of time should be provided with due caution. The deleterious effects of omega-3 PUFA supplements may be particularly relevant when they are administered during vulnerable life stages (e.g., prenatal development, childhood, and adolescence).[308]

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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