

The emerging role of omega-3 fatty acids as a therapeutic option in neuropsychiatric disorders

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Abstract: The prevalence of neurologic and psychiatric diseases has been increasing for decades and, given the moderate therapeutic efficacy and safety profile of existing pharmacological treatments, there is an urgent need for new therapeutic approaches. Nutrition has recently been recognized as an important factor for the prevention and treatment of neuropsychiatric disorders. The omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) play critical roles in neuronal cell function and neurotransmission as well as inflammatory and immune reactions that are involved in neuropsychiatric disease states. A large number of experimental and epidemiological studies provide a strong basis for interventional clinical trials that assessed the clinical efficacy of n-3 PUFAs in various neurological and psychiatric disorders. Most of these trials found beneficial effects of dietary supplementation with EPA and DHA, and no serious safety concerns have emerged. This review gives an introduction to recent findings on the clinical efficacy of n-3 PUFAs in various neuropsychiatric disorders and the underlying biochemical mechanisms. In addition, the reader will be enabled to identify common methodological weaknesses of clinical studies on n-3 PUFAs, and suggestions for the design of future studies are given.

Keywords: EPA, DHA, n-3 PUFAs, neurologic disorders, psychiatric disorders, neuropsychiatric disorders, clinical studies, n-6/n-3 ratio, n-3 index

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Introduction

Neurological and mental disorders continue to be on the rise. The Global Burden of Disease Report 2017 states that from 2007 to 2017, the number of neurological disability-adjusted life years (DALYs) increased by 20.5%, while mental health DALYs increased by 13.5%.¹ Countries with a high sociodemographic index (SDI) are significantly more affected than countries with a low SDI, which suggests a causal role of the Western lifestyle.¹ Diet, physical activity, and social structures are critical factors that have been linked to increases in neuropsychiatric and other disorders that are usually referred to as lifestyle diseases. Concerning diet, high intakes of fruit, vegetables, fish, and whole grains have been recommended to reduce such risk.²⁻⁴ The role of nutrition for preventing and treating neuropsychiatric disorders is

increasingly being recognized, and it has recently been stated that '*nutrition and nutraceuticals should now be considered as mainstream elements of psychiatric practice*'.³⁻⁵

Research on omega-3 polyunsaturated fatty acids (n-3 PUFAs) has grown exponentially since researchers from Denmark visited Greenland in 1970 to study why the cardiovascular mortality among the Inuit population was considerably lower than in the Western countries.⁶ The researchers related their findings to the diet of the Inuit, which consisted mainly of fish and meat from seals, whales, sea birds, and fur-bearing animals. These foods contain large amounts of n-3 PUFAs.⁶ In the following decades, the health effects of n-3 PUFAs were studied extensively, covering almost all medical conditions, including

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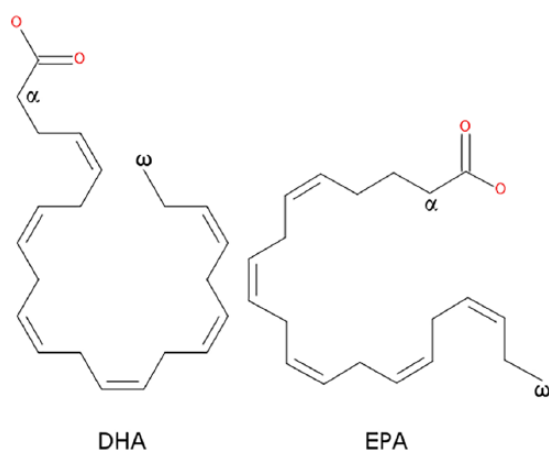


Figure 1. The chemical structure of the two most important n-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

neurological and psychiatric disorders. Such studies found that more isolated arctic populations with traditional lifestyles and diets have lower rates of depression, anxiety, and suicidality than less isolated or non-arctic populations. These findings have been associated with diet-related factors, that is, n-3 PUFA intake.⁷

Research has shown that the significance of n-3 PUFAs for neuropsychiatric disorders is based on their crucial role in neuronal cell functioning. Lipid imbalance in intracellular biochemical processes and neuronal cell membranes may lead to changes in brain functioning that can cause or aggravate neuropsychiatric disorders.⁸ The aim of this paper is to give an introduction to the clinical effects of n-3 PUFAs in various neuropsychiatric disorders and their underlying biochemical mechanisms. In addition, the reader will be enabled to identify common methodological weaknesses of clinical studies on n-3 PUFAs. For more in-depth reviews on the role of n-3 PUFAs in specific diseases, the reader is referred to the respective references.

What are n-3 PUFAs and how do they work?

Omega-3 fatty acids (FAs) are a type of PUFA. Polyunsaturated means that their carbon chain contains two or more double bonds. *Omega* (ω) is the last letter in the Greek alphabet, and omega-3 denotes that the first of these double bonds is located between the 3rd and the 4th carbon atom seen from the last (the *omega*-) atom of the carbon chain (Figure 1). Another nomenclature uses the

Latin letter *n* instead of the Greek ω . Both nomenclatures are common.

There are over 30 different PUFAs. In addition to n-3 PUFAs, there are n-5, n-6, n-7, and n-9 PUFAs. Of these, n-3 and n-6 PUFAs play the most important biological roles, and the quantitative balance between n-3 and n-6 PUFAs is believed to be a crucial factor in many disease states (discussed in the following). Table 1 gives an overview of biologically important n-3 and n-6 PUFAs.

There are several different n-3 PUFAs, the biologically most relevant ones being alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Humans cannot produce ALA and therefore ALA is one of two *essential* FAs that must be supplied by diet [the other essential FA is linoleic acid (LA), which is an n-6 PUFA]. ALA is found in seeds, nuts, and plant oils. While no major biological effects of ALA on cells or tissues have been identified so far, its biological value lies mainly in being a substrate for the synthesis of other PUFAs.⁹ The human body is not able to synthesize DHA and EPA *de novo*, but can produce them from ALA. However, this capacity is very limited and, in addition, subject to polymorphisms of the genes coding for the involved enzymes (fatty acid desaturase and elongase).¹⁰ Reported conversion rates of ALA to EPA are 0.2–6%, and 0.05% or less for DHA. Women seem to possess a higher conversion capacity than men.⁹

Since humans can convert only an insufficient proportion of ALA to EPA and DHA, the latter two are classified as *conditionally essential* FAs.⁹ Dietary sources of EPA and DHA are fish, shellfish, and meat from marine mammals, for example, seals and whales. Like humans, these animals do not produce n-3 PUFAs themselves to a relevant degree. Instead, EPA and DHA are synthesized by marine algae, which are eaten by small fish that in turn are food for larger animals.

The phospholipids of the brain's gray matter and the retina contain high concentrations of DHA and arachidonic acid (AA, which is an n-6 PUFA), which supports the notion that long-chain PUFAs play an essential role in the development and maintenance of proper central nervous system (CNS) function.^{11–14} Owing to the many double bonds, PUFAs are more bulky than saturated fatty acids (SFAs; Figure 1). When

Table 1. Biologically important n-3 and n-6 polyunsaturated fatty acids (PUFAs).

	Common name	Lipid name
n-3 PUFAs	Alpha-linolenic acid (ALA)*	18:3n3
	Eicosapentaenoic acid (EPA)**	20:5n3
	Docosahexaenoic acid (DHA)**	22:6n3
n-6 PUFAs	Linoleic acid (LA)*	18:2n6
	Gamma-linolenic acid (GLA)	18:3n6
	Arachidonic acid (AA)	20:4n6

*Essential fatty acids.
**Conditionally essential fatty acids.

PUFAs instead of SFAs are incorporated into the phospholipid layer of the cell membrane, the physicochemical properties of the membrane become altered; it becomes less rigid and more fluid. More specifically, phase behavior (how a membrane's mobility changes with temperature) is shifted to the left, that is, more fluid, while elastic compressibility (relative volume change/thickness in response to stress), permeability (passive diffusion of molecules through the membrane), fusion (two membranes merge into one), flip-flop (transverse diffusion of membrane constituents, that is, from the outer layer to the inner layer or *vice versa*), and protein activity become increased.¹⁵ Incorporation of n-3 PUFAs into cell membranes also leads to reorganization of lipid raft formation. Lipid rafts are membrane domains that contain clusters of receptors and proteins involved in signal transduction. Hence, all these mechanisms affect the function of membrane proteins, such as receptors, membrane-bound enzymes, G-proteins, and ion channels, thereby modulating intracellular and intercellular signaling pathways in neurons and other cell types.^{16,17} Of special interest for the etiology, prophylaxis, and treatment of neuropsychiatric disorders is the involvement of n-3 PUFAs in the fetal development and later maintenance of dopaminergic pathways in the brain.¹⁸

Another way in which n-3 PUFAs may positively affect CNS functions such as cognition and behavior is by affecting the gut's microbiota composition, its fatty acid composition, and by reducing intestinal inflammation, which in summary affects the gut-brain axis. This has been demonstrated in both animal and human studies.¹⁹⁻²¹

n-3 PUFAs are, apart from being building blocks in cell membranes, biotransformed to eicosanoids such as prostaglandins, thromboxanes, and leukotrienes, as well as endocannabinoids and other lipid-based signaling substances that are involved in many biochemical processes in the body, for example, inflammation and immune responses. Eicosanoids derived from n-3 PUFAs, such as prostacyclin I3 and thromboxane A3, are generally considered anti-inflammatory, antithrombotic, vasodilatory, and antineoplastic. The anti-inflammatory effects of n-3 PUFAs most probably contribute to their neuroprotective effects in various neuropsychiatric conditions (see the following). By contrast, signal substances derived from n-6 PUFAs such as AA or LA, for example, prostaglandin E2 or thromboxane A2, have mainly opposite effects. Therefore, the balance between n-6- and n-3 PUFAs has been identified as a critical biomarker for chronic disease.²² The WHO has stated that there should be an optimal balance in the dietary intake constituted by n-6 and n-3 PUFAs.²³ However, n-6 PUFAs are found in large amounts in most plant oils, and the consumption of plant oils has exploded in the past decades while fish consumption has steadily declined.²² Consequently, the Western diet is characterized by an over-supply of n-6 PUFAs, a deficiency in n-3 PUFAs, and, thus, a striking imbalance between these two.²²

All PUFAs are highly susceptible to oxidation. Accordingly, oxidative stress in the body has a large impact on lipid metabolism including PUFAs. Lipid peroxidation leads to membrane phospholipid degradation, directly affecting cell membrane

function.²⁴ Similarly, nutritional supplements that contain PUFAs must be protected by effective antioxidants. Fish and other sources of marine n-3 PUFAs contain polyphenols and other compounds that protect n-3 PUFAs from oxidation *in vivo*. However, these compounds are removed during the production of commercial n-3 preparations, mainly because they also account for the typical fishy taste and odor. Therefore, most manufacturers add vitamin E as a fat-soluble antioxidant. Despite this, studies from different countries have consistently shown that most n-3 PUFA preparations that are sold over the counter are oxidized (rancid) to varying degrees.^{25–27} Obviously, decomposed n-3 PUFAs have lost their characteristic biological properties. Even worse, peroxidation products of PUFAs may under certain conditions promote oxidative stress, a pro-inflammatory environment, DNA damage, and clinical deterioration.^{28,29} Since most interventional clinical studies use ordinary fish oil capsules, this may be a major reason why some interventional studies did not find a beneficial effect of n-3 PUFAs or even an increase in clinical symptoms.³⁰

Many authorities and professional societies recommend certain amounts of daily intake of n-3 PUFAs, but they do not provide corresponding reference ranges for n-3 PUFA blood levels.³¹ Nonetheless, free serum n-3 PUFAs, erythrocyte membrane n-3 PUFAs, and whole blood phospholipid n-3 PUFAs can be measured by many laboratories and used as biomarkers to estimate the risk for disease and to monitor the efficacy of n-3 PUFA substitution with a given commercial preparation. The two best documented biomarkers are (1) the n-3 index, which is the combined percentages of EPA plus DHA measured in erythrocyte membrane FAs, and (2) the n-6/n-3 ratio, which is the ratio of n-6 FA and n-3 FA percentages.³² A high n-6/n-3 ratio and a low n-3 index are generally associated with poorer medical condition. In Western populations, the average n-3 index varies from 2.9% to 7.7% while a value of 8–11% is required for optimal protection against cardiovascular diseases.^{33–36} The average n-6/n-3 ratio in Western countries is 15–21 while a value below 5 is generally recommended.²⁸ The predictive value of the n-6/n-3 ratio has recently been questioned and the n-3 index has been suggested as a more robust biomarker. It should be noted, however, that the author of that paper may be biased, as he has commercial interests related to n-3 index testing.^{32,37}

The reason why the PUFA status should be measured in red blood cells and not in plasma is that the plasma fatty acid profile may change within hours, depending on the type of food and time after intake, while red blood cells have a half-life of 120 days, which provides a much more stable measure of the PUFA content of cell membranes. Moreover, the PUFA content of red blood cell membranes is highly correlated to the PUFA content of major organs.^{38–40}

Effects of n-3 PUFAs in various neuropsychiatric disorders

The effects of n-3 PUFAs have been studied in a large variety of neurological and psychiatric disorders. In the following, a selection of them are discussed. Additional neuropsychiatric disorders that are not discussed in detail are summarized at the end of this section.

Depression

Numerous epidemiological and interventional studies have accumulated strong evidence for a connection between n-3 PUFA status and depression.^{41,42} Low fish consumption and a low omega-3 index are clearly correlated with a higher risk of developing a major depression.^{43–48} Accordingly, an increase in the omega-3 index reduced the risk and the severity of depressive symptoms in several clinical studies. One of them found that for each 1% increase in the n-3 index, the risk of developing depression was reduced by 28%.^{45,49,50} This correlates with findings from clinical studies in nonpsychiatric conditions.³³ Depressed patients also exhibit higher n-6/n-3 ratios than nondepressed controls.^{50–52}

Various studies found an inverse correlation between dietary intake of n-3 PUFAs and the severity of depressive symptoms including suicidality.^{28,48,52–58} Although some of these studies produced neutral results, several meta-analyses confirmed the antidepressant effects of dietary EPA and DHA.^{59–63} Daily doses between 1 and 3.5 g have produced therapeutic effects.⁴² It is unclear whether EPA and DHA differ in their antidepressant efficacy, as each of them independently has been proposed as the strongest mediator of the beneficial effects of n-3 PUFAs in depression.^{29,46,60,64,65} Interestingly, the DHA amount in blood phospholipids, but not the EPA amount, distinguished responders from nonresponders in a recent interventional study.⁶⁶

The efficacy of n-3 PUFAs in special subpopulations such as children, adolescents, elderly patients with underlying comorbidities, or in related conditions such as bipolar disorder, is only incompletely studied. Most data available so far suggest beneficial effects of supplementation with n-3 PUFAs in these patient groups.^{29,67-72}

How n-3 PUFAs exert their antidepressant action is not fully understood. At present, it appears that multiple unspecific mechanisms of action are responsible. Modulation of G-protein signaling *via* G-protein coupled receptors and effects on lipid raft formation has been suggested as one possible mechanism.⁷³ Other mechanisms such as modulation of pro-inflammatory mediators, and changes in telomerase levels may also play a role.^{48,57,65,74}

Schizophrenia

Schizophrenic patients show a marked depletion of essential FAs, particularly AA and DHA, in red blood cell membranes. These two FAs are the most abundant FAs in the human brain, which suggests that they play a crucial role in the function of the CNS.¹¹⁻¹³ Accumulating evidence from experimental and clinical studies has led to the 'membrane hypothesis', which postulates dietary-related changes in PUFA-dependent membrane function as a major pathophysiologic mechanism in schizophrenia.^{75,76} Accordingly, diet changes that lead to increased membrane levels of n-3-PUFAs can have significant effects on schizophrenic symptoms.⁷⁷

Several randomized, placebo-controlled clinical trials have studied the efficacy of n-3 PUFA supplementation in schizophrenia. While some yielded positive results,⁷⁸⁻⁸⁰ others found partial efficacy such as reduced need for antipsychotic medication,^{81,82} or no beneficial effects at all.^{30,83} However, the observation time in most studies was only 8-12 weeks and as mentioned earlier in this article, sustained changes in membrane function may take longer time to develop. The only long-term study so far, a 6-month, randomized, placebo-controlled trial in first-episode schizophrenic patients, found a significantly greater decrease in the intensity of symptoms and an improved level of functioning in the n-3 group than in the placebo group.⁸⁴

Disturbances in cortical membrane FA homeostasis have been identified as a pathological aspect of schizophrenia, which is one of several possible explanations for the efficacy of n-3 PUFAs.^{75,76,85}

Beyond membrane-related effects on neuronal cell signaling pathways, n-3 PUFAs may act through additional mechanisms, for example, modulation of dopaminergic pathways in the mesolimbic system.¹⁸ In an *in vitro* model mimicking the involvement of viral infection in the development of neuropsychiatric disorders, n-3 PUFAs showed significant neuroprotective effects.⁸⁶ In addition, clinical studies in schizophrenic patients found that n-3 PUFA substitution leads to an increase in telomerase levels as well as a reduction in oxidative stress.^{84,87,88}

ADHD

It is well established that dietary depletion of n-3 PUFAs during fetal development and early childhood may have adverse effects on brain development, neurodevelopmental outcomes, and cognitive health.^{54,89,90} For example, low maternal intake of n-3 fatty acids during pregnancy is correlated with lower verbal intelligence, attention deficit hyperactivity disorder (ADHD), dyslexia, dyspraxia, autism, and impaired social behavior in the child.^{89,91-93}

Epidemiological studies found that children with ADHD have lower blood levels of n-3 PUFAs than controls.⁹³⁻⁹⁶ Accordingly, several randomized, placebo-controlled interventional trials reported positive effects of dietary supplementation with n-3 PUFAs in ADHD.^{94,95,97-99} However, other trials found only small or no therapeutic effects. Hence, some meta-analyses stated that there is evidence for n-3 PUFAs as a supplement to established therapies while others concluded that the currently available evidence is inconclusive.^{94,100-107} Major reasons for these contradictory conclusions are different selection of studies, small sample sizes, variability of inclusion criteria, variability of the type and dosage of supplementation, short follow-up times, and different cognitive and behavioral outcome parameters.^{101,102,105} Moreover, some studies that used multiple outcome parameters observed therapeutic effects in some but not all of them.

While the pathophysiology of ADHD is not fully understood, it is generally accepted that brain dopaminergic and noradrenergic systems play a central role. This hypothesis is supported by the clinical effectiveness of medicines such as methylphenidate and amphetamine. In animal experiments, n-3 PUFA depletion induced symptoms that mimic ADHD in humans, while symptom

severity was inversely correlated with dietary n-3 PUFA intake. The significance of n-3 PUFAs for the regulation of dopaminergic pathways in ADHD has recently been reviewed.¹⁸

PTSD

It has long been known that both physical and psychological stress are associated with altered blood levels of free fatty acids including long-chain PUFAs.^{108,109} Cross-sectional studies reported lower n-3 PUFA blood levels in patients with PTSD than in healthy controls.^{110,111} Similarly, longitudinal studies found an inverse relation between blood levels of n-3 PUFAs and the risk of developing PTSD after accidental injury.^{112,113}

However, only a few clinical trials examined possible effects of supplementation with n-3 PUFAs on post-traumatic stress disorder (PTSD), and they produced mixed results. While one study found that EPA but not DHA reduces the risk of developing PTSD in patients with accidental injury,¹¹⁴ another study found ameliorated psychophysiological stress responses after combined supplementation with a high dose of DHA + a low dose of EPA.¹¹⁵ A study in survivors of the great earthquake in Japan 2011 found an effect of 1568 mg DHA + 157 mg EPA in women, but not in men.¹¹⁶ Further clinical research is clearly needed.

Different mechanisms could mediate possible effects of n-3 PUFAs in PTSD and other stress-related conditions. Since PTSD is associated with increased interleukin 6, interleukin 1 β , tumor necrosis factor alpha (TNF α), and interferon γ levels, it has been suggested that the expression of these cytokines may be normalized by the anti-inflammatory and neuroprotective actions of n-3 PUFAs.¹¹⁷ This hypothesis is supported by experimental findings.¹¹⁸ Another, more specific mechanism may be an increase in brain-derived neurotrophic factor (BDNF) induced by n-3 PUFAs, which leads to induction of hippocampal neurogenesis by which fear-related memory might be cleared.^{119–121} A more recent hypothesis assumes a role of the n-3 PUFA-derived endocannabinoids 2-docosahexaenoylglycerol (2-DHG) and docosahexaenylethanolamine (DHA-EA) in reducing psychological distress.¹²²

Dementia

The clinical efficacy of established medications for Alzheimer's disease (AD) and other dementias is

weak, and new treatment options are urgently warranted. A large body of evidence suggests a positive correlation between n-3 PUFAs and cognition, and most (but not all) interventional studies reported beneficial effects of n-3 PUFAs on cognitive outcome and quality of life in patients with AD, especially with early stage AD and mild cognitive impairment.^{20,123–128} While some interventional studies reported neutral results, a recent meta-analysis by Zhang *et al.* found that n-3 PUFAs from fishery products are associated with a lower risk of cognitive decline in AD patients.¹²⁹ This is supported by a study in healthy subjects where both the n-3 index and the n-6/n-3 ratio were correlated with cognitive function as well as hippocampal and total brain volume.^{130,131}

Experimental evidence implies biological plausibility for beneficial effects of n-3 PUFAs in dementia. Antioxidant actions, enhanced brain plasticity, and other mechanisms that are more directly related to the specific pathology displayed in dementia, such as anti-inflammatory, anti-amyloid and anti-tau effects, have been demonstrated.^{132–134} DHA may have stronger neuroprotective properties than EPA as DHA-deficiency is highly correlated with cortical and hippocampal atrophy.^{135,136} Experimental data also show that DHA regulates apoptotic processes and the level of A β -induced lipid peroxides, which has positive effects on the survival of neurons.¹³⁷ In addition, DHA increases dendrite density and reduces beta amyloid and tau protein load.^{138–141}

In addition to these mechanisms, n-3 PUFAs may ameliorate cognitive dysfunction via indirect effects. Both AD and vascular dementia are associated with cardiovascular events such as microinfarctions in the brain, and it has been shown that prevention of cardiovascular morbidity with n-3 PUFAs has beneficial effects on cognitive function.^{142,143}

Factors that might explain the mixed results of clinical studies on n-3 PUFAs in dementia are the large variations in study design (e.g. RCTs *versus* epidemiological studies), study populations, observation times and follow-up periods, variations in n-3 dosages, different biomarkers for fatty acid status, different cognitive outcome parameters as well as different (and partly low) sensitivity in the neuropsychological tests. Notably, it has been suggested that n-3 PUFAs may exert their most significant effects on cognition before disease onset. This is of special importance in AD

which is a disease that probably starts decades before clinical symptoms become overt.^{131,144}

Parkinson's disease

After AD, Parkinson's disease (PD) is the second most common neurodegenerative disorder with a prevalence of about 2% in people over 65 years.¹⁴⁵ While the etiology of PD is still not fully understood, its pathophysiology is well studied and involves dysfunction of the mitochondria and inflammatory and oxidative stress reactions.^{146–148} Despite this knowledge, the standard pharmacological approach to treat PD is still more or less limited to enhancing dopaminergic signaling. However, dopaminergic medications may lose effect over time and can induce serious side effects.^{149,150}

Only few clinical studies examined n-3 PUFAs in PD. All but one reported beneficial effect. Observational studies found a correlation between higher intake of n-3 PUFAs from fish and lower prevalence of PD.^{151,152} In the Rotterdam Study, a prospective population-based cohort study of 5289 subjects, each SD increase of energy-adjusted intake of PUFAs reduced the risk of developing PD by 34%.¹⁵³ A randomized, double-blind placebo-controlled trial found that supplementation with n-3 PUFAs improved clinical symptomatology in PD patients, as indicated by a decrease in the average Unified Parkinson's Disease Rating Scale score.¹⁵⁴ A case-control study, however, found that dietary intake of n-3 PUFAs was not predictive for the risk of developing PD.¹⁵⁵

Part of the positive effects of n-3 PUFAs on PD is probably due to their neuroprotective properties, since oxidative stress and neuroinflammation are ameliorated by n-3 PUFAs.¹⁵⁶ Indeed, a clinical study found that supplementation with n-3 PUFAs decreased C-reactive protein and increased glutathione concentrations as well as total antioxidant capacity.¹⁵⁴ These results are supported by experimental findings demonstrating a reduction of inducible nitric oxide synthase activity in the CNS and increased levels of BDNF after supplementation with n-3 PUFAs.^{120,157,158} Apart from neuroprotective effects, n-3 PUFAs may enhance dopaminergic signal transduction through different mechanisms.¹⁸

Other neurological and psychiatric disorders

In addition to the conditions discussed above, the effects of supplementation with n-3 PUFAs have

been clinically studied in other neuropsychiatric disorders, such as epilepsy,^{159–162} multiple sclerosis,^{163–167} bipolar disorder,^{168–170} anorexia nervosa,^{171–173} borderline personality disorder,^{174–176} and autism spectrum disorders.^{177–181} Apart from these systematic clinical trials, numerous case reports have been published for these and even more neuropsychiatric conditions including rare metabolic diseases such as Zellweger syndrome.³⁹ The majority of these interventions reported beneficial effects of supplementation with n-3 PUFAs. These findings are supported by numerous epidemiological studies that found strong evidence for an inverse relation between dietary n-3 PUFA intake/blood n-3 status and the prevalence and severity of the conditions mentioned above.^{182–189}

Safety of n-3 PUFAs

Most of the clinical studies cited in this paper did either not report any clinically significant adverse effects or no difference *versus* placebo. Few studies reported mild to moderate adverse reactions, mainly nausea or loose stools, especially with high doses.

A much-debated study in men with prostate cancer, the SELECT trial, reported that higher plasma omega-3 fatty acid levels were associated with increased risk for developing prostate cancer.¹⁹⁰ However, several comments on that study pointed out that this conclusion was inappropriate and not supported by study data. Moreover, other studies found opposite effects of n-3 PUFAs on prostate cancer.^{191–193}

Although it has been postulated that n-3 PUFAs may increase LDL cholesterol, affect glucose metabolism and prolong bleeding time, recent studies as well as reviews and meta-analyses do not support this.^{194–196} Given the widespread use of n-3 supplements and the experience from a large number of clinical studies, it must be concluded that these potential effects may gain clinical significance only in rare cases. Accordingly, the United States FDA has ruled that the daily intake of up to 3 g of n-3 PUFAs is generally recognized as safe (GRAS).¹⁹⁷ This ruling took into consideration the postulated effects on glucose metabolism, bleeding, and low-density lipoprotein (LDL) cholesterol. Similarly, the European Union's EFSA Panel on Dietetic Products Nutrition and Allergies concluded that supplemental intake of EPA and DHA at combined doses up to 5 g per day, and supplemental intakes

of EPA alone up to 1.8 g per day, do not raise safety concerns for adults.¹⁹⁸

Recommendations for future research

Most clinical trials that assessed the effect of dietary supplementation with n-3 PUFAs in neuropsychiatric conditions yielded positive results. However, a considerable number of studies produced neutral or even negative results. The conflicting findings may be attributed to several reasons.

1. Almost all interventional studies used fish oil capsules. That may have seriously distorted the results from these studies since most commercial n-3 preparations are oxidized (rancid) to varying degrees.²⁵⁻²⁷ Future studies using such capsules should therefore report the degree of oxidation in the preparations used, for example, by stating the peroxide value (PV), the anisidine value (AV), or the total oxidation value (TOTOX).
2. Omega-3 preparations are manufactured from different natural sources, containing different amounts of n-3 PUFAs, different DHA:EPA-ratios and different chemical composition of these FAs (mostly as ethyl esters, but also as triglycerides, diglycerides, monoglycerides, phospholipids, or free carboxylic acids) as well as different types and amounts of antioxidants (e.g. various types of tocopherols, astaxanthin, etc.). These different formulations naturally lead to differences in bioavailability, susceptibility for oxidation, and biological activity.¹⁹⁹⁻²⁰³ Being classified as food or food supplements, commercial n-3 products are not subject to bioequivalence requirements or other stringent forms of pharmaceutical/pharmacological standardization the way licensed medical drugs are. Disregarding the fact that all these n-3 preparations are not pharmaceutically and biologically equivalent represents a major weakness of clinical trials and, particularly, meta-analyses of these trials.
3. Most clinical studies used fixed doses and did not measure blood levels of n-3 PUFAs. Owing to the uncertainties inferred by varying degrees of oxidation and varying bioavailability (see above), future clinical studies should rather use individual dosing guided by the n-3 index and the n-6/n-3 ratio.

Target ranges for these biomarkers should be defined before study start. A striking example for a failed clinical study and the necessity of defining target ranges is the recently published VITAL study.²⁰⁴ After 1 year of treatment, the average n-3 index had risen from 2.1% to 4.1% and the researchers did not find a cardioprotective effect of n-3 PUFAs. It is well documented that this index must be at least 8% to obtain a cardioprotective effect, while an index below 4% is classified as 'high risk' for cardiovascular disease.³³ Consequently, the study merely confirmed the previous knowledge that an n-3 index below 8% does not provide cardioprotection.

4. While an effect of n-3 PUFA substitution on the synthesis of lipid-based signaling substances and other cytokines usually can be seen after a few days (due to the short biological half-life of these compounds), their incorporation into cell membranes and the onset of related biological effects may take longer time, depending on the turnover rate of these cells, the phospholipid-layer of their cell membrane and of the incorporated proteins. Thus, the length of the observation period is crucial, and 8 weeks may not be enough in all cases. For the same reason, n-3 PUFAs appear less suitable as acute treatment of neuropsychiatric disorders, but more useful for long-term prevention.

Conclusion

A connection between nutritional factors and neuropsychiatric disorders should be regarded as established. Numerous epidemiological studies have shown a strong correlation between low n-3 PUFA status and higher prevalence and severity of different neuropsychiatric disorders. Accordingly, many interventional studies that assessed the efficacy of n-3 PUFA supplementation in different neuropsychiatric disorders have found positive effects. A large body of experimental data provides a solid biological and pharmacological basis for these findings. At present, n-3 PUFAs appear to be more useful in long-term preventive approaches rather than treatment of acute episodes. However, not all clinical studies found beneficial effects. Possible reasons for conflicting findings have been discussed in this review, and future clinical studies as well as meta-analyses of such studies should address them.

Measurement of n-3 PUFAs in blood for diagnostic purposes, risk assessment, and therapeutic drug monitoring is cheap and already available at many laboratories. The use of n-3 PUFAs as a therapeutic option in the treatment of neurological and psychiatric disorders may be still in its infancy, but their therapeutic potential, favorable safety profile, ease of administration, and low treatment costs are promising. The increasing number of clinical studies and other research papers suggests that supplementation with n-3 PUFAs may play a greater role in the future treatment of neuropsychiatric disorders.

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Conflict of interest statement

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Ethical Statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

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References

1. Global Burden of Disease Study. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1859–1922.
2. Lai JS, Hiles S, Bisquera A, *et al.* A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *Am J Clin Nutr* 2014; 99: 181–197.
3. Sarris J, Logan AC, Akbaraly TN, *et al.* Nutritional medicine as mainstream in psychiatry. *Lancet Psychiatry* 2015; 2: 271–274.
4. Mental Health Foundation. *Feeding Minds: The Impact of Food on Mental Health*. Mental Health Foundation, 2006.
5. Sarris J, Logan AC, Akbaraly TN, *et al.* International Society for Nutritional Psychiatry Research consensus position statement: nutritional medicine in modern psychiatry. *World Psychiatry* 2015; 14: 370–371.
6. Bang HO, Dyerberg J and Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. *Lancet* 1971; 1: 1143–1145.
7. McGrath-Hanna NK, Greene DM, Tavernier RJ, *et al.* Diet and mental health in the Arctic: is diet an important risk factor for mental health in circumpolar peoples? A review. *Int J Circumpolar Health* 2003; 62: 228–241.
8. Yehuda S. Omega-6/omega-3 ratio and brain-related functions. *World Rev Nutr Diet* 2003; 92: 37–56.
9. Burdge GC. Metabolism of alpha-linolenic acid in humans. *Prostaglandins Leukot Essent Fatty Acids* 2006; 75: 161–168.
10. Davidson MH. Omega-3 fatty acids: new insights into the pharmacology and biology of docosahexaenoic acid, docosapentaenoic acid, and eicosapentaenoic acid. *Curr Opin Lipidol* 2013; 24: 467–474.
11. Innis SM. Dietary omega 3 fatty acids and the developing brain. *Brain Res* 2008; 1237: 35–43.
12. Chalon S, Vancassel S, Zimmer L, *et al.* Polyunsaturated fatty acids and cerebral function: focus on monoaminergic neurotransmission. *Lipids* 2001; 36: 937–944.
13. Yehuda S. Omega-6/omega-3 ratio and brain-related functions. *World Rev Nutr Diet* 2003; 92: 37–56.
14. Virtanen JK, Siscovick DS, Lemaitre RN, *et al.* Circulating omega-3 polyunsaturated fatty acids and subclinical brain abnormalities on MRI in older adults: the Cardiovascular Health Study. *J Am Heart Assoc* 2013; 2: e000305.
15. Stillwell W and Wassall SR. Docosahexaenoic acid: membrane properties of a unique fatty acid. *Chem Phys Lipids* 2003; 126: 1–27.
16. Gueguinou M, Gambade A, Felix R, *et al.* Lipid rafts, KCa/ClCa/Ca²⁺ channel complexes and EGFR signaling: Novel targets to reduce tumor development by lipids? *Biochim Biophys Acta* 2015; 1848: 2603–2620.
17. Turk HF and Chapkin RS. Membrane lipid raft organization is uniquely modified by n-3 polyunsaturated fatty acids. *Prostaglandins Leukot Essent Fatty Acids* 2013; 88: 43–47.
18. Healy-Stoffel M and Levant B. N-3 (Omega-3) fatty acids: effects on brain dopamine systems and potential role in the etiology and treatment of neuropsychiatric disorders. *CNS Neurol Disord Drug Targets* 2018; 17: 216–232.

19. Costantini L, Molinari R, Farinon B, *et al.* Impact of omega-3 fatty acids on the gut microbiota. *Int J Mol Sci* 2017; 18.
20. La Rosa F, Clerici M, Ratto D, *et al.* The gut-brain axis in Alzheimer's disease and omega-3. A critical overview of clinical trials. *Nutrients* 2018; 10.
21. Hooijmans CR, Pasker-de Jong PC, de Vries RB, *et al.* The effects of long-term omega-3 fatty acid supplementation on cognition and Alzheimer's pathology in animal models of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 2012; 28: 191–209.
22. Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. *Exp Biol Med (Maywood)* 2008; 233: 674–688.
23. World Health Organization. Population nutrient intake goals for preventing diet-related chronic diseases, https://www.who.int/nutrition/topics/5_population_nutrient/en/index12.html (accessed 15 January 2019).
24. Du J, Zhu M, Bao H, *et al.* The role of nutrients in protecting mitochondrial function and neurotransmitter signaling: implications for the treatment of depression, PTSD, and suicidal behaviors. *Crit Rev Food Sci Nutr* 2016; 56: 2560–2578.
25. Cameron-Smith D, Albert BB and Cutfield WS. Fishing for answers: is oxidation of fish oil supplements a problem? *J Nutr Sci* 2015; 4: e36.
26. NOFIMA. *Rapport nr. 196: Lite oksiderte omega-3 oljer og potensielle helsefordeler*; 2010. Trondheim, Norway.
27. Sullivan Ritter JC, Budge SM, Jovica F, *et al.* Oxidation rates of triacylglycerol and ethyl ester fish oils. *J Am Oil Chem Soc Journal of the American Oil Chemists' Society* 2015; 92: 561–569.
28. Clayton PR and Ladi S. From alga to omega; have we reached peak (fish) oil? *J R Soc Med* 2015; 108: 351–357.
29. Ortega RM, Rodriguez-Rodriguez E and Lopez-Sobaler AM. Effects of omega 3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders. *Br J Nutr* 2012; 107(Suppl. 2): S261–S270.
30. Bentsen H, Osnes K, Refsum H, *et al.* A randomized placebo-controlled trial of an omega-3 fatty acid and vitamins E+C in schizophrenia. *Transl Psychiatry* 2013; 3: e335.
31. Biesalski HK, Erdman JW, Hathcock J, *et al.* Nutrient reference values for bioactives: new approaches needed? A conference report. *Euro J Nut* 2013; 52: 1–9.
32. Harris WS. The Omega-6:Omega-3 ratio: a critical appraisal and possible successor. *Prostaglandins Leukot Essent Fatty Acids* 2018; 132: 34–40.
33. von Schacky C. Omega-3 index and cardiovascular health. *Nutrients* 2014; 6: 799–814.
34. Oseeva M, Paluchova V, Zacek P, *et al.* Omega-3 index in the Czech Republic: no difference between urban and rural populations. *Chem Phys Lipids* 2019; 220: 23–27.
35. Berliner D, Mattern S, Wellige M, *et al.* The omega-3 index in patients with heart failure: a prospective cohort study. *Prostaglandins Leukot Essent Fatty Acids* 2019; 140: 34–41.
36. Wagner A, Simon C, Morio B, *et al.* Omega-3 index levels and associated factors in a middle-aged French population: the MONA LISA-NUT Study. *Eur J Clin Nutr* 2015; 69: 436–441.
37. OmegaQuant Analytics, LLC, <https://omegaquant.com/about/> (accessed May 11 2019).
38. Fenton JI, Gurzell EA, Davidson EA, *et al.* Red blood cell PUFAs reflect the phospholipid PUFA composition of major organs. *Prostaglandins Leukot Essent Fatty Acids* 2016; 112: 12–23.
39. Martinez M. Polyunsaturated fatty acids in the developing human brain, erythrocytes and plasma in peroxisomal disease: therapeutic implications. *J Inherit Metab Dis* 1995; 18(Suppl. 1): 61–75.
40. Letondor A, Buaud B, Vaysse C, *et al.* Erythrocyte DHA level as a biomarker of DHA status in specific brain regions of n-3 long-chain PUFA-supplemented aged rats. *Br J Nutr* 2014; 112: 1805–1818.
41. Maes M, Smith R, Christophe A, *et al.* Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord* 1996; 38: 35–46.
42. Grosso G, Micek A, Marventano S, *et al.* Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. *J Affect Disord* 2016; 205: 269–281.
43. Hibbeln JR. Fish consumption and major depression. *Lancet* 1998; 351: 1213.
44. Ali S, Garg SK, Cohen BE, *et al.* Association between omega-3 fatty acids and depressive symptoms among patients with established coronary artery disease: data from the Heart and Soul Study. *Psychother Psychosom* 2009; 78: 125–127.

45. Amin AA, Menon RA, Reid KJ, *et al.* Acute coronary syndrome patients with depression have low blood cell membrane omega-3 fatty acid levels. *Psychosom Med* 2008; 70: 856–862.
46. Reeves JL, Otahal P, Magnussen CG, *et al.* DHA mediates the protective effect of fish consumption on new episodes of depression among women. *Br J Nutr* 2017; 118: 743–749.
47. Baghai TC, Varallo-Bedarida G, Born C, *et al.* Major depressive disorder is associated with cardiovascular risk factors and low Omega-3 Index. *J Clin Psychiatry* 2011; 72: 1242–1247.
48. Sanchez-Villegas A, Alvarez-Perez J, Toledo E, *et al.* Seafood Consumption, Omega-3 Fatty Acids Intake, and Life-Time Prevalence of Depression in the PREDIMED-Plus Trial. *Nutrients* 2018; 10.
49. Pottala JV, Talley JA, Churchill SW, *et al.* Red blood cell fatty acids are associated with depression in a case-control study of adolescents. *Prostaglandins Leukot Essent Fatty Acids* 2012; 86: 161–165.
50. Swenne I, Rosling A, Tengblad S, *et al.* Omega-3 polyunsaturated essential fatty acids are associated with depression in adolescents with eating disorders and weight loss. *Acta Paediatr* 2011; 100: 1610–1615.
51. Conklin SM, Manuck SB, Yao JK, *et al.* High omega-6 and low omega-3 fatty acids are associated with depressive symptoms and neuroticism. *Psychosom Med* 2007; 69: 932–934.
52. Lin PY, Huang SY and Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatry* 2010; 68: 140–147.
53. Edwards R, Peet M, Shay J, *et al.* Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord* 1998; 48: 149–155.
54. Gow RV and Hibbeln JR. Omega-3 fatty acid and nutrient deficits in adverse neurodevelopment and childhood behaviors. *Child Adolesc Psychiatr Clin N Am* 2014; 23: 555–590.
55. Hibbeln JR and Gow RV. The potential for military diets to reduce depression, suicide, and impulsive aggression: a review of current evidence for omega-3 and omega-6 fatty acids. *Mil Med* 2014; 179: 117–128.
56. Park Y, Kim M, Baek D, *et al.* Erythrocyte n-3 polyunsaturated fatty acid and seafood intake decrease the risk of depression: case-control study in Korea. *Ann Nutr Metab* 2012; 61: 25–31.
57. Colin A, Reggers J, Castronovo V, *et al.* Lipids, depression and suicide. *Encephale* 2003; 29: 49–58.
58. Peet M and Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* 2002; 59: 913–919.
59. Carney RM, Freedland KE, Rubin EH, *et al.* Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. *JAMA* 2009; 302: 1651–1657.
60. Sublette ME, Ellis SP, Geant AL, *et al.* Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. *J Clin Psychiatry* 2011; 72: 1577–1584.
61. Grosso G, Pajak A, Marventano S, *et al.* Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One* 2014; 9: e96905.
62. Sarris J, Murphy J, Mischoulon D, *et al.* Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. *Am J Psychiatry* 2016; 173: 575–587.
63. Yang Y, Kim Y and Je Y. Fish consumption and risk of depression: Epidemiological evidence from prospective studies. *Asia Pac Psychiatry* 2018; 10: e12335.
64. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Nutr* 2009; 28: 525–542.
65. Su KP, Yang HT, Chang JP, *et al.* Eicosapentaenoic and docosahexaenoic acids have different effects on peripheral phospholipase A2 gene expressions in acute depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 80: 227–233.
66. Gnanca L, Galfalvy HC, Oquendo MA, *et al.* Lipid correlates of antidepressant response to omega-3 polyunsaturated fatty acid supplementation: A pilot study. *Prostaglandins Leukot Essent Fatty Acids* 2017; 119: 38–44.
67. Noaghiul S and Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am J Psychiatry* 2003; 160: 2222–2227.
68. Tiemeier H, van Tuijl HR, Hofman A, *et al.* Plasma fatty acid composition and depression are

- associated in the elderly: the Rotterdam Study. *Am J Clin Nutr* 2003; 78: 40–46.
69. Sarris J, Mischoulon D and Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J Clin Psychiatry* 2012; 73: 81–86.
 70. Stoll AL, Severus WE, Freeman MP, *et al.* Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999; 56: 407–412.
 71. Nemets H, Nemets B, Apter A, *et al.* Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry* 2006; 163: 1098–1100.
 72. Berger ME, Smesny S, Kim SW, *et al.* Omega-6 to omega-3 polyunsaturated fatty acid ratio and subsequent mood disorders in young people with at-risk mental states: a 7-year longitudinal study. *Transl Psychiatry* 2017; 7: e1220.
 73. Czysz AH and Rasenick MM. G-protein signaling, lipid rafts and the possible sites of action for the antidepressant effects of n-3 polyunsaturated fatty acids. *CNS Neurol Disord Drug Targets* 2013; 12: 466–473.
 74. Su KP, Huang SY, Peng CY, *et al.* Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels. *Biol Psychiatry* 2010; 67: 550–557.
 75. Horrobin DF. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. *Schizophr Res* 1998; 30: 193–208.
 76. Horrobin DF, Glen AI and Vaddadi K. The membrane hypothesis of schizophrenia. *Schizophr Res* 1994; 13: 195–207.
 77. Peet M, Laugharne JD, Mellor J, *et al.* Essential fatty acid deficiency in erythrocyte membranes from chronic schizophrenic patients, and the clinical effects of dietary supplementation. *Prostaglandins Leukot Essent Fatty Acids* 1996; 55: 71–75.
 78. Peet M, Brind J, Ramchand CN, *et al.* Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001; 49: 243–251.
 79. Emsley R, Myburgh C, Oosthuizen P, *et al.* Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. *Am J Psychiatry* 2002; 159: 1596–1598.
 80. Jamilian H, Solhi H and Jamilian M. Randomized, placebo-controlled clinical trial of omega-3 as supplemental treatment in schizophrenia. *Glob J Health Sci* 2014; 6: 103–108.
 81. Berger GE, Proffitt TM, McConchie M, *et al.* Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2007; 68: 1867–1875.
 82. Peet M, Horrobin DF and Group EEMS. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *J Psychiatr Res* 2002; 36: 7–18.
 83. Fenton WS, Dickerson F, Boronow J, *et al.* A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Psychiatry* 2001; 158: 2071–2074.
 84. Pawelczyk T, Grancow-Grabka M, Kotlicka-Antczak M, *et al.* A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. *J Psychiatr Res* 2016; 73: 34–44.
 85. Taha AY, Cheon Y, Ma K, *et al.* Altered fatty acid concentrations in prefrontal cortex of schizophrenic patients. *J Psychiatr Res* 2013; 47: 636–643.
 86. Ribeiro BMM, Chaves Filho AJM, Costa D, *et al.* N-3 polyunsaturated fatty acids and clozapine abrogates poly I: C-induced immune alterations in primary hippocampal neurons. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; 90: 186–196.
 87. Pawelczyk T, Grancow-Grabka M, Trafalska E, *et al.* Oxidative stress reduction related to the efficacy of n-3 polyunsaturated fatty acids in first episode schizophrenia: Secondary outcome analysis of the OFFER randomized trial. *Prostaglandins Leukot Essent Fatty Acids* 2017; 121: 7–13.
 88. Berger GE, Wood SJ, Wellard RM, *et al.* Ethyl-eicosapentaenoic acid in first-episode psychosis. A 1H-MRS study. *Neuropsychopharmacology* 2008; 33: 2467–2473.
 89. Tesi A, Crippa A, Ceccarelli SB, *et al.* The potential relevance of docosahexaenoic acid and eicosapentaenoic acid to the etiopathogenesis of childhood neuropsychiatric disorders. *Eur Child Adolesc Psychiatry* 2017; 26: 1011–1030.
 90. Bondi CO, Taha AY, Tock JL, *et al.* Adolescent behavior and dopamine availability are uniquely sensitive to dietary omega-3 fatty acid deficiency. *Biol Psychiatry* 2014; 75: 38–46.

91. Hibbeln JR, Davis JM, Steer C, *et al.* Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* 2007; 369: 578–585.
92. Schuchardt JP, Huss M, Stauss-Grabo M, *et al.* Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *Eur J Pediatr* 2010; 169: 149–164.
93. Montgomery P, Burton JR, Sewell RP, *et al.* Low blood long chain omega-3 fatty acids in UK children are associated with poor cognitive performance and behavior: a cross-sectional analysis from the DOLAB study. *PLoS One* 2013; 8: e66697.
94. Hawkey E and Nigg JT. Omega-3 fatty acid and ADHD: blood level analysis and meta-analytic extension of supplementation trials. *Clin Psychol Rev* 2014; 34: 496–505.
95. Widenhorn-Muller K, Schwanda S, Scholz E, *et al.* Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. *Prostaglandins Leukot Essent Fatty Acids* 2014; 91: 49–60.
96. Parletta N, Niyonsenga T and Duff J. Omega-3 and omega-6 polyunsaturated fatty acid levels and correlations with symptoms in children with attention deficit hyperactivity disorder, autistic spectrum disorder and typically developing controls. *PLoS One* 2016; 11: e0156432.
97. Long SJ and Benton D. A double-blind trial of the effect of docosahexaenoic acid and vitamin and mineral supplementation on aggression, impulsivity, and stress. *Hum Psychopharmacol* 2013; 28: 238–247.
98. Raine A, Portnoy J, Liu J, *et al.* Reduction in behavior problems with omega-3 supplementation in children aged 8–16 years: a randomized, double-blind, placebo-controlled, stratified, parallel-group trial. *J Child Psychol Psychiatry* 2015; 56: 509–520.
99. Checa-Ros A, Haro-Garcia A, Seiquer I, *et al.* Early monitoring of fatty acid profile in children with attention deficit and/or hyperactivity disorder under treatment with omega-3 polyunsaturated fatty acids. *Minerva Pediatr.* Epub ahead of print 7 November 2018. DOI: 10.23736/S0026-4946.18.04975-7.
100. Gillies D, Sinn J, Lad SS, *et al.* Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev* 2012: CD007986.
101. Rangel-Huerta OD and Gil A. Effect of omega-3 fatty acids on cognition: an updated systematic review of randomized clinical trials. *Nutr Rev* 2018; 76: 1–20.
102. Bloch MH and Qawasmi A. Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2011; 50: 991–1000.
103. Chang JP, Su KP, Mondelli V, *et al.* Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder: a systematic review and meta-analysis of clinical trials and biological studies. *Neuropsychopharmacology* 2018; 43: 534–545.
104. Abdullah M, Jowett B, Whittaker PJ, *et al.* The effectiveness of omega-3 supplementation in reducing ADHD associated symptoms in children as measured by the Conners' rating scales: a systematic review of randomized controlled trials. *J Psychiatr Res* 2018; 110: 64–73.
105. Artukoglu BB and Bloch MH. Editorial: can omega-3 fatty acids improve executive functioning? Will this reduce ADHD and depression? *J Child Psychol Psychiatry* 2018; 59: 615–617.
106. Ramalho R, Pereira AC, Vicente F, *et al.* Docosahexaenoic acid supplementation for children with attention deficit hyperactivity disorder: a comprehensive review of the evidence. *Clin Nutr ESPEN* 2018; 25: 1–7.
107. Konigs A and Kiliaan AJ. Critical appraisal of omega-3 fatty acids in attention-deficit/hyperactivity disorder treatment. *Neuropsychiatr Dis Treat* 2016; 12: 1869–1882.
108. Williams LL, Kiecolt-Glaser JK, Horrocks LA, *et al.* Quantitative association between altered plasma esterified omega-6 fatty acid proportions and psychological stress. *Prostaglandins Leukot Essent Fatty Acids* 1992; 47: 165–170.
109. Alden PB, Svingen BA, Johnson SB, *et al.* Partial correction by exogenous lipid of abnormal patterns of polyunsaturated fatty acids in plasma phospholipids of stressed and septic surgical patients. *Surgery* 1986; 100: 671–678.
110. de Vries GJ, Mocking R, Lok A, *et al.* Fatty acid concentrations in patients with posttraumatic stress disorder compared to healthy controls. *J Affect Disord* 2016; 205: 351–359.
111. Kalinic D, Borovac Stefanovic L, Jeroncic A, *et al.* Eicosapentaenoic acid in serum lipids could

- be inversely correlated with severity of clinical symptomatology in Croatian war veterans with posttraumatic stress disorder. *Croat Med J* 2014; 55: 27–37.
112. Matsuoka Y, Nishi D and Hamazaki K. Serum levels of polyunsaturated fatty acids and the risk of posttraumatic stress disorder. *Psychother Psychosom* 2013; 82: 408–410.
 113. Matsuoka Y, Nishi D, Yonemoto N, *et al.* Omega-3 fatty acids for secondary prevention of posttraumatic stress disorder after accidental injury: an open-label pilot study. *J Clin Psychopharmacol* 2010; 30: 217–219.
 114. Matsuoka Y, Nishi D, Hamazaki K, *et al.* Docosahexaenoic acid for selective prevention of posttraumatic stress disorder among severely injured patients: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2015; 76: e1015–1022.
 115. Matsumura K, Noguchi H, Nishi D, *et al.* Effects of omega-3 polyunsaturated fatty acids on psychophysiological symptoms of post-traumatic stress disorder in accident survivors: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 2017; 224: 27–31.
 116. Nishi D, Koido Y, Nakaya N, *et al.* Fish oil for attenuating posttraumatic stress symptoms among rescue workers after the great east Japan earthquake: a randomized controlled trial. *Psychother Psychosom* 2012; 81: 315–317.
 117. Passos IC, Vasconcelos-Moreno MP, Costa LG, *et al.* Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry* 2015; 2: 1002–1012.
 118. Tyagi E, Agrawal R, Zhuang Y, *et al.* Vulnerability imposed by diet and brain trauma for anxiety-like phenotype: implications for post-traumatic stress disorders. *PLoS One* 2013; 8: e57945.
 119. Matsuoka Y, Nishi D, Yonemoto N, *et al.* Potential role of brain-derived neurotrophic factor in omega-3 Fatty Acid supplementation to prevent posttraumatic distress after accidental injury: an open-label pilot study. *Psychother Psychosom* 2011; 80: 310–312.
 120. Dong Y, Xu M, Kalueff AV, *et al.* Dietary eicosapentaenoic acid normalizes hippocampal omega-3 and 6 polyunsaturated fatty acid profile, attenuates glial activation and regulates BDNF function in a rodent model of neuroinflammation induced by central interleukin-1beta administration. *Eur J Nutr* 2018; 57: 1781–1791.
 121. Okubo R, Chen C, Sekiguchi M, *et al.* Mechanisms underlying the effects of n-3 polyunsaturated fatty acids on fear memory processing and their hypothetical effects on fear of cancer recurrence in cancer survivors. *Prostaglandins Leukot Essent Fatty Acids* 2018; 131: 14–23.
 122. Ramsden CE, Zamora D, Makriyannis A, *et al.* Diet-induced changes in n-3- and n-6-derived endocannabinoids and reductions in headache pain and psychological distress. *J Pain* 2015; 16: 707–716.
 123. Ajith TA. A recent update on the effects of omega-3 fatty acids in Alzheimer's disease. *Curr Clin Pharmacol* 2018; 13: 252–260.
 124. Burckhardt M, Herke M, Wustmann T, *et al.* Omega-3 fatty acids for the treatment of dementia. *Cochrane Database Syst Rev* 2016; 4: CD009002.
 125. Canhada S, Castro K, Perry IS, *et al.* Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review. *Nutr Neurosci* 2018; 21: 529–538.
 126. Andruchow ND, Konishi K, Shatenstein B, *et al.* A lower ratio of omega-6 to omega-3 fatty acids predicts better hippocampus-dependent spatial memory and cognitive status in older adults. *Neuropsychology* 2017; 31: 724–734.
 127. Hooper C, De Souto Barreto P, Coley N, *et al.* Cognitive changes with omega-3 polyunsaturated fatty acids in non-demented older adults with low omega-3 index. *J Nutr Health Aging* 2017; 21: 988–993.
 128. Lukaschek K, von Schacky C, Kruse J, *et al.* Cognitive Impairment Is Associated with a Low Omega-3 Index in the Elderly: Results from the KORA-Age Study. *Dement Geriatr Cogn Disord* 2016; 42: 236–245.
 129. Zhang Y, Chen J, Qiu J, *et al.* Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. *Am J Clin Nutr* 2016; 103: 330–340.
 130. Nunes B, Pinho C, Sousa C, *et al.* Relevance of omega-3 and omega-6/omega-3 ratio in preventing cognitive impairment. *Acta Med Port* 2017; 30: 213–223.
 131. Pottala JV, Yaffe K, Robinson JG, *et al.* Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI study. *Neurology* 2014; 82: 435–442.
 132. Belkouch M, Hachem M, Elgot A, *et al.* The pleiotropic effects of omega-3 docosahexaenoic

- acid on the hallmarks of Alzheimer's disease. *J Nutr Biochem* 2016; 38: 1–11.
133. Cansev M, Wurtman RJ, Sakamoto T, *et al.* Oral administration of circulating precursors for membrane phosphatides can promote the synthesis of new brain synapses. *Alzheimers Dement* 2008; 4: S153–S168.
 134. Phillips MA, Childs CE, Calder PC, *et al.* Lower omega-3 fatty acid intake and status are associated with poorer cognitive function in older age: a comparison of individuals with and without cognitive impairment and Alzheimer's disease. *Nutr Neurosci* 2012; 15: 271–277.
 135. Huang TL. Omega-3 fatty acids, cognitive decline, and Alzheimer's disease: a critical review and evaluation of the literature. *J Alzheimers Dis* 2010; 21: 673–690.
 136. Hashimoto M and Hossain S. Neuroprotective and ameliorative actions of polyunsaturated fatty acids against neuronal diseases: beneficial effect of docosahexaenoic acid on cognitive decline in Alzheimer's disease. *J Pharmacol Sci* 2011; 116: 150–162.
 137. Zhao Y, Calon F, Julien C, *et al.* Docosahexaenoic acid-derived neuroprotectin D1 induces neuronal survival via secretase- and PPARgamma-mediated mechanisms in Alzheimer's disease models. *PLoS One* 2011; 6: e15816.
 138. Green KN, Martinez-Coria H, Khashwji H, *et al.* Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels. *J Neurosci* 2007; 27: 4385–4395.
 139. Hashimoto M, Hossain S, Agdul H, *et al.* Docosahexaenoic acid-induced amelioration on impairment of memory learning in amyloid beta-infused rats relates to the decreases of amyloid beta and cholesterol levels in detergent-insoluble membrane fractions. *Biochim Biophys Acta* 2005; 1738: 91–98.
 140. Lim GP, Calon F, Morihara T, *et al.* A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *J Neurosci* 2005; 25: 3032–3040.
 141. Sakamoto T, Cansev M and Wurtman RJ. Oral supplementation with docosahexaenoic acid and uridine-5'-monophosphate increases dendritic spine density in adult gerbil hippocampus. *Brain Res* 2007; 1182: 50–59.
 142. Luo C, Ren H, Yao X, *et al.* Enriched brain omega-3 polyunsaturated fatty acids confer neuroprotection against microinfarction. *EBioMedicine* 2018; 32: 50–61.
 143. Zheng J, Huang T, Yu Y, *et al.* Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. *Public Health Nutr* 2012; 15: 725–737.
 144. Kulzow N, Witte AV, Kerti L, *et al.* Impact of omega-3 fatty acid supplementation on memory functions in healthy older adults. *J Alzheimers Dis* 2016; 51: 713–725.
 145. Clarke CE. Parkinson's disease. *BMJ* 2007; 335: 441–445.
 146. Boyko AA, Troyanova NI, Kovalenko EI, *et al.* Similarity and differences in inflammation-related characteristics of the peripheral immune system of patients with Parkinson's and Alzheimer's diseases. *Int J Mol Sci* 2017; 18.
 147. Schapira AH. Mitochondria in the aetiology and pathogenesis of Parkinson's disease. *Parkinsonism Relat Disord* 1999; 5: 139–143.
 148. Dias V, Junn E and Mouradian MM. The role of oxidative stress in Parkinson's disease. *J Parkinsons Dis* 2013; 3: 461–491.
 149. Connolly BS and Lang AE. Pharmacological treatment of Parkinson disease: a review. *JAMA* 2014; 311: 1670–1683.
 150. Kalinderi K, Papaliagkas V and Fidani L. Pharmacogenetics and levodopa induced motor complications. *Int J Neurosci* 2018: 1–31.
 151. Gao X, Chen H, Fung TT, *et al.* Prospective study of dietary pattern and risk of Parkinson disease. *Am J Clin Nutr* 2007; 86: 1486–1494.
 152. Okubo H, Miyake Y, Sasaki S, *et al.* Dietary patterns and risk of Parkinson's disease: a case-control study in Japan. *Eur J Neurol* 2012; 19: 681–688.
 153. de Lau LM, Bornebroek M, Witteman JC, *et al.* Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. *Neurology* 2005; 64: 2040–2045.
 154. Taghizadeh M, Tamtaji OR, Dadgostar E, *et al.* The effects of omega-3 fatty acids and vitamin E co-supplementation on clinical and metabolic status in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Neurochem Int* 2017; 108: 183–189.
 155. Miyake Y, Sasaki S, Tanaka K, *et al.* Dietary fat intake and risk of Parkinson's disease: a case-control study in Japan. *J Neurol Sci* 2010; 288: 117–122.
 156. Orr SK, Trepanier MO and Bazinet RP. n-3 Polyunsaturated fatty acids in animal models

- with neuroinflammation. *Prostaglandins Leukot Essent Fatty Acids* 2013; 88: 97–103.
157. Cardoso HD, dos Santos Junior EF, de Santana DF, *et al.* Omega-3 deficiency and neurodegeneration in the substantia nigra: involvement of increased nitric oxide production and reduced BDNF expression. *Biochim Biophys Acta* 2014; 1840: 1902–1912.
 158. Mori MA, Delattre AM, Carabelli B, *et al.* Neuroprotective effect of omega-3 polyunsaturated fatty acids in the 6-OHDA model of Parkinson's disease is mediated by a reduction of inducible nitric oxide synthase. *Nutr Neurosci* 2018; 21: 341–351.
 159. DeGiorgio CM, Miller PR, Harper R, *et al.* Fish oil (n-3 fatty acids) in drug resistant epilepsy: a randomised placebo-controlled crossover study. *J Neurol Neurosurg Psychiatry* 2015; 86: 65–70.
 160. Ibrahim FAS, Ghebremeskel K, Abdel-Rahman ME, *et al.* The differential effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on seizure frequency in patients with drug-resistant epilepsy - A randomized, double-blind, placebo-controlled trial. *Epilepsy Behav* 2018; 87: 32–38.
 161. Omrani S, Taheri M, Omrani MD, *et al.* The effect of omega-3 fatty acids on clinical and paraclinical features of intractable epileptic patients: a triple blind randomized clinical trial. *Clin Transl Med* 2019; 8: 3.
 162. Yuen AW, Flugel D, Poepel A, *et al.* Non-randomized open trial of eicosapentaenoic acid (EPA), an omega-3 fatty acid, in ten people with chronic epilepsy. *Epilepsy Behav* 2012; 23: 370–372.
 163. Kouchaki E, Afarini M, Abolhassani J, *et al.* High-dose omega-3 fatty acid plus vitamin D3 supplementation affects clinical symptoms and metabolic status of patients with multiple sclerosis: a randomized controlled clinical trial. *J Nutr* 2018; 148: 1380–1386.
 164. Marck CH, De Livera AM, Brown CR, *et al.* Health outcomes and adherence to a healthy lifestyle after a multimodal intervention in people with multiple sclerosis: three year follow-up. *PLoS One* 2018; 13: e0197759.
 165. Mousavi Nasl-Khameneh A, Mirshafiey A, Naser Moghadasi A, *et al.* Combination treatment of docosahexaenoic acid (DHA) and all-trans-retinoic acid (ATRA) inhibit IL-17 and ROR γ gene expression in PBMCs of patients with relapsing-remitting multiple sclerosis. *Neurol Res* 2018; 40: 11–17.
 166. Pantzaris MC, Loukaides GN, Ntzani EE, *et al.* A novel oral nutraceutical formula of omega-3 and omega-6 fatty acids with vitamins (PLP10) in relapsing remitting multiple sclerosis: a randomised, double-blind, placebo-controlled proof-of-concept clinical trial. *BMJ Open* 2013; 3.
 167. Riccio P, Rossano R, Larocca M, *et al.* Anti-inflammatory nutritional intervention in patients with relapsing-remitting and primary-progressive multiple sclerosis: a pilot study. *Exp Biol Med (Maywood)* 2016; 241: 620–635.
 168. Arnold LE, Young AS, Belury MA, *et al.* Omega-3 fatty acid plasma levels before and after supplementation: correlations with mood and clinical outcomes in the omega-3 and therapy studies. *J Child Adolesc Psychopharmacol* 2017; 27: 223–233.
 169. Fristad MA, Young AS, Vesco AT, *et al.* A randomized controlled trial of individual family psychoeducational psychotherapy and omega-3 fatty acids in youth with subsyndromal bipolar disorder. *J Child Adolesc Psychopharmacol* 2015; 25: 764–774.
 170. Wozniak J, Faraone SV, Chan J, *et al.* A randomized clinical trial of high eicosapentaenoic acid omega-3 fatty acids and inositol as monotherapy and in combination in the treatment of pediatric bipolar spectrum disorders: a pilot study. *J Clin Psychiatry* 2015; 76: 1548–1555.
 171. Ayton AK, Azaz A and Horrobin DF. A pilot open case series of ethyl-EPA supplementation in the treatment of anorexia nervosa. *Prostaglandins Leukot Essent Fatty Acids* 2004; 71: 205–209.
 172. Barbarich NC, McConaha CW, Halmi KA, *et al.* Use of nutritional supplements to increase the efficacy of fluoxetine in the treatment of anorexia nervosa. *Int J Eat Disord* 2004; 35: 10–15.
 173. Manos BE, Bravender TD, Harrison TM, *et al.* A pilot randomized controlled trial of omega-3 fatty acid supplementation for the treatment of anxiety in adolescents with anorexia nervosa. *Int J Eat Disord* 2018; 51: 1367–1372.
 174. Bozzatello P, Rocca P and Bellino S. Combination of omega-3 fatty acids and valproic acid in treatment of borderline personality disorder: a follow-up study. *Clin Drug Investig* 2018; 38: 367–372.
 175. Amminger GP, Chanen AM, Ohmann S, *et al.* Omega-3 fatty acid supplementation in adolescents with borderline personality disorder and ultra-high risk criteria for psychosis: a post hoc subgroup analysis of a double-blind, randomized controlled trial. *Can J Psychiatry* 2013; 58: 402–408.

176. Zanarini MC and Frankenburg FR. omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* 2003; 160: 167–169.
177. Amminger GP, Berger GE, Schafer MR, *et al.* Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biol Psychiatry* 2007; 61: 551–553.
178. Mazahery H, Conlon CA, Beck KL, *et al.* A randomised controlled trial of vitamin D and omega-3 long chain polyunsaturated fatty acids in the treatment of irritability and hyperactivity among children with autism spectrum disorder. *J Steroid Biochem Mol Biol* 2019; 187: 9–16.
179. Mazahery H, Conlon CA, Beck KL, *et al.* A randomised-controlled trial of vitamin d and omega-3 long chain polyunsaturated fatty acids in the treatment of core symptoms of autism spectrum disorder in children. *J Autism Dev Disord* 2019; 49: 1778–1794.
180. Keim SA, Gracious B, Boone KM, *et al.* omega-3 and omega-6 fatty acid supplementation may reduce autism symptoms based on parent report in preterm toddlers. *J Nutr* 2018; 148: 227–235.
181. Cheng YS, Tseng PT, Chen YW, *et al.* Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: a meta-analysis of randomized controlled trials. *Neuropsychiatr Dis Treat* 2017; 13: 2531–2543.
182. Caspar-Bauguil S, Montastier E, Galinon F, *et al.* Anorexia nervosa patients display a deficit in membrane long chain poly-unsaturated fatty acids. *Clin Nutr* 2012; 31: 386–390.
183. Bahagat KA, Elhady M, Aziz AA, *et al.* Omega-6/omega-3 ratio and cognition in children with epilepsy. *An Pediatr (Barc)* 2019. pii: S1695-4033(18)30544-7.
184. Yuen AW, Sander JW, Flugel D, *et al.* Erythrocyte and plasma fatty acid profiles in patients with epilepsy: does carbamazepine affect omega-3 fatty acid concentrations? *Epilepsy Behav* 2008; 12: 317–323.
185. Bjornevik K, Chitnis T, Ascherio A, *et al.* Polyunsaturated fatty acids and the risk of multiple sclerosis. *Mult Scler* 2017; 23: 1830–1838.
186. Wulsin LR, Blom TJ, Durling M, *et al.* Cardiometabolic risks and omega-3 index in recent-onset bipolar I disorder. *Bipolar Disord* 2018; 20: 658–665.
187. McNamara RK and Welge JA. Meta-analysis of erythrocyte polyunsaturated fatty acid biostatus in bipolar disorder. *Bipolar Disord* 2016; 18: 300–306.
188. Saunders EF, Reider A, Singh G, *et al.* Low unesterified:esterified eicosapentaenoic acid (EPA) plasma concentration ratio is associated with bipolar disorder episodes, and omega-3 plasma concentrations are altered by treatment. *Bipolar Disord* 2015; 17: 729–742.
189. Esteban-Figuerola P, Canals J, Fernandez-Cao JC, *et al.* Differences in food consumption and nutritional intake between children with autism spectrum disorders and typically developing children: A meta-analysis. *Autism* 2018; 1362361318794179.
190. Brasky TM, Darke AK, Song X, *et al.* Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2013; 105: 1132–1141.
191. Brenna JT, Burdige GC, Crawford MA, *et al.* RE: Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2014; 106: dju015.
192. Harris WS and Davidson MH. RE: Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2014; 106: dju019.
193. McCarty MF, Dinicolantonio JJ, Lavie CJ, *et al.* RE: Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2014; 106: dju014.
194. Backes J, Anzalone D, Hilleman D, *et al.* The clinical relevance of omega-3 fatty acids in the management of hypertriglyceridemia. *Lipids Health Dis* 2016; 15: 118.
195. Chen C, Yu X and Shao S. Effects of omega-3 fatty acid supplementation on glucose control and lipid levels in type 2 diabetes: a meta-analysis. *PLoS One* 2015; 10: e0139565.
196. Jeansen S, Witkamp RF, Garthoff JA, *et al.* Fish oil LC-PUFAs do not affect blood coagulation parameters and bleeding manifestations: analysis of 8 clinical studies with selected patient groups on omega-3-enriched medical nutrition. *Clin Nutr* 2018; 37: 948–957.
197. FDA. Substances affirmed as generally recognized as safe: menhaden oil. *Federal Register* 2004; 69: 2313.
198. EFSA Panel on Dietetic Products Nutrition and Allergies (NDA). Scientific Opinion related to the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic

- acid (DHA) and docosapentaenoic acid (DPA). *EFSA Journal* 2012; 10: 2815.
199. Carlier H, Bernard A and Caselli C. Digestion and absorption of polyunsaturated fatty acids. *Reprod Nutr Dev* 1991; 31: 475–500.
200. Dyerberg J, Madsen P, Moller JM, *et al.* Bioavailability of marine n-3 fatty acid formulations. *Prostaglandins Leukot Essent Fatty Acids* 2010; 83: 137–141.
201. Lawson LD and Hughes BG. Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters. *Biochem Biophys Res Commun* 1988; 152: 328–335.
202. Neubronner J, Schuchardt JP, Kressel G, *et al.* Enhanced increase of omega-3 index in response to long-term n-3 fatty acid supplementation from triacylglycerides versus ethyl esters. *Eur J Clin Nutr* 2011; 65: 247–254.
203. Hong DD, Takahashi Y, Kushiro M, *et al.* Divergent effects of eicosapentaenoic and docosahexaenoic acid ethyl esters, and fish oil on hepatic fatty acid oxidation in the rat. *Biochim Biophys Acta* 2003; 1635: 29–36.
204. Manson JE, Cook NR, Lee IM, *et al.* Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med* 2019; 380: 23–32.

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